

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1734 – Intravascular lithotripsy for the treatment of moderately or severely calcified peripheral artery disease

Applicant: Shockwave Medical Inc (Manufacturer) and
Diverse Devices Pty Ltd (Distributor)

Date of MSAC consideration: 23-24 November 2023

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing for providing intravascular lithotripsy (IVL), as a stand-alone treatment or as a vessel preparation strategy prior to stent insertion or treatment with a drug-coated balloon (DCB), in patients with moderately or severely calcified peripheral arterial disease (PAD) in lower limbs and 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 and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC deferred its advice for public funding of IVL for the treatment of moderately or severely calcified peripheral artery disease. MSAC considered there is likely superior procedural effectiveness and non-inferior safety for IVL compared to standard balloon angioplasty when used as a vessel preparation strategy for drug coated balloon or stent. MSAC considered that there was weak evidence for superior effectiveness and non-inferior safety to SBA when IVL is employed as a stand-alone therapy.

MSAC considered the cost utility analysis for the economic model was inappropriate due to the lack of evidence demonstrating an increase in health-related quality of life (HRQoL) or other patient related outcome gains. MSAC considered that a resubmission to address these problems would require a revised clinical care pathway to better capture the decision pathway used by proceduralists to determine use of IVL as a stand-alone or adjunct intervention. This information should serve as the basis for a revised economic model (inclusive of both uses) which is more appropriately a cost consequence analysis rather than a cost utility analysis. MSAC considered that a cost consequence analysis focussing on costs of the procedure, costs of changes in resource use (i.e stents and balloons used) with the outcomes being procedural outcomes would be useful. MSAC considered that the costs of IVL, including potential out of pocket costs, needed to be confirmed and benchmarked against relevant stents. MSAC considered the appropriate pathway for the revised application to be a direct pathway to MSAC.

Consumer summary

This is an application from Shockwave Medical requesting Medicare Benefits Schedule (MBS) listing of intravascular lithotripsy (IVL) in patients who have moderately or severely calcified peripheral arterial disease (PAD) in lower limbs.

PAD is a condition in which the build-up of fatty deposits (plaque) in arteries results in narrowing of the arteries in the arms or legs. This in turn reduces blood flow. The plaque build-up can cause arteries to stiffen and hard calcium crystals can form within the plaque which makes the stiffening worse. Stiff arteries can cause a number of problems including reduced blood flow to the body's tissues and making the heart work harder. PAD most commonly affects the arteries supplying the legs or feet, causing the circulation to be partially cut off which can cause pain and difficulties with walking. People with PAD are at higher risk of cardiovascular disease, stroke and death.

IVL involves inserting a tiny device into the affected arteries in the lower legs. The device gives off high pressure shockwaves which help to break up plaques and improve blood flow.

The application was for two different groups of patients: 1. for people with PAD who would receive IVL and no further treatment, and 2. for people with PAD who would receive IVL plus some further treatment such as the insertion of a stent (small metal tube) or balloon to widen the arteries.

MSAC considered that IVL appears to be safe and effective. MSAC also acknowledged the clinical need for this device for patients with moderate or severe calcification in their arteries. The alternative treatment, standard balloon angioplasty (SBA), can sometimes be associated with damage to the arteries, which may require further treatment. IVL does not appear to have these same adverse events as SBA.

However, MSAC had many concerns about how the application calculated the value for money for the two groups of patients. MSAC also considered that the categorisation of patients into these two groups did not reflect what was actually undertaken in practice, as it would be very difficult to determine before the treatment who would only need to receive IVL and who would require further treatment after IVL. Thus, MSAC requested that the applicant revisit the cost calculations based on combining the two groups of people into a single group (that is, people with moderate to severe PAD) to ensure that MSAC could be confident about the device's value for money and total budget impact. MSAC would then reconsider the application.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC deferred its decision to support IVL in patients who have moderately or severely calcified PAD in lower limbs. MSAC thought that IVL was likely safe and effective, but was very uncertain about its value for money. MSAC advised that the applicant should resubmit their application using a different economic model so that MSAC could better determine if the device was good value for money.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from Shockwave Medical requested Medicare Benefits Schedule (MBS) listing of IVL for patients who have moderately or severely calcified peripheral arterial disease (PAD) in lower limbs. This is the first time MSAC has considered this application.

MSAC noted that PAD is a manifestation of systemic atherosclerotic disease that affects the arteries supplying blood to the legs and feet. Risk factors for PAD include tobacco smoking, diabetes, abnormal blood lipids, high blood pressure, overweight or obesity and family history.

PAD is associated with a reduction in functional capacity and quality of life (QoL). Patients with PAD are at higher risk of cardiovascular morbidity, mortality and stroke.

MSAC noted that IVL is delivered via a catheter and uses a vaporising fluid to create an expanding bubble. This bubble generates sonic pressure waves that cause microfractures in arterial calcification. The device uses a generator, which is reusable, and single-use catheters. MSAC noted that vascular surgeons and interventional radiologists would perform the procedure. Because IVL is balloon-based, no additional training would be required for operators already familiar with standard balloon angioplasty (SBA) procedures.

MSAC noted that the device is listed on the Australian Register of Therapeutic Devices for use in limbs only.

MSAC noted that there was no consultation feedback received for this application.

MSAC noted that the applicant-developed assessment report (ADAR) proposed two populations, namely patients with PAD who have moderately or severely calcified lesions in their lower limb(s) who are indicated for IVL in the following situations:

1. IVL used as a standalone treatment.
2. IVL used as a vessel preparation strategy before stent insertion or treatment with a drug-coated balloon (DCB).

MSAC considered the proposed populations to be inappropriate, because predetermining beforehand which patients belong to each of the two separate populations is not reflective of Australian clinical practice. MSAC considered that the decision is made in real time and that before IVL, it would be unknown whether the patient would receive IVL as a standalone treatment or require further stenting. Additionally, MSAC noted that bare metal stents are now more commonly used in Australia as a vessel preparation strategy than DCBs.

The clinical claim for IVL is that, when sonic pressure waves are used to disrupt and fracture calcified plaque, the risk of both procedural and longer-term complications associated with high-pressure balloon angioplasty is reduced. SBA – the comparator – requires high balloon inflation pressure to achieve reduction in lesion diameter stenosis, and in heavily calcified lesions can be associated with suboptimal vessel expansion and vascular complications. These potential complications, including dissection and perforation, necessitate the use of bailout stent placement postprocedure. MSAC acknowledged that SBA can result in acute complications for PAD patients with moderate to severe calcification, and thus agreed there is a clinical need for alternative treatments for people with PAD.

MSAC noted the clinical evidence for population 1, which comprised three single-arm feasibility trials (DISRUPT PAD I, DISRUPT PAD II and DISRUPT PAD BTK) looking at patency 12 months after IVL, which had been undertaken as a standalone procedure. For population 2, DISRUPT PAD III and DISRUPT PAD III OS provided the evidence base. DISRUPT PAD III was a randomised controlled trial (RCT; $n = 306$) comparing IVL with percutaneous transluminal angioplasty (PTA) +/- post-dilatation if stenosis $>30\%$. DISRUPT PAD III OS was a single-arm, observational study ($n = 1,373$) using IVL. MSAC noted some risk of bias concerns associated with DISRUPT PAD III RCT due to the single-blinded design and the fact that almost 20% of patient data was missing from the analysis (due to death, withdrawal and loss of follow up). However MSAC noted the commentary acknowledged that the missing data were balanced between the two treatment arms and is not considered likely to be due to the intervention. MSAC noted that the commentary also identified differences between the trial population and the Australian patient population with PAD, which may affect the generalisability of the trial data to the Australian clinical setting.

For population 1, MSAC reiterated ESC's concern about the weak evidence for non-inferior safety given the lack of comparative evidence. For population 2, MSAC noted that IVL demonstrated non-inferior short- and medium-term safety in terms of major adverse events (MAEs), with 24-month follow-up in the RCT and 12-month follow-up in the single-arm study. However, MSAC considered the overall non-inferior safety claim to be uncertain because of the lack of long-term data.

In the DISRUPT PAD III RCT, which was relevant to population 2, MSAC considered that IVL appears to demonstrate superior effectiveness for procedural success (65.8% IVL v 50.4% PTA, $p=0.007$) when used for vessel preparation prior to stent insertion or DCB. Procedural success was defined as a reduction of at least 30% stenosis without flow-limiting dissection (\geq grade D) before any adjunct therapy. When considering site-reported procedural success, the differences increased to 90.1% for IVL and 64.8% for PTA ($p<0.0001$). MSAC noted that primary patency was retained after 1 year (80.5% IVL and 68.0% PTA, $p=0.017$). Freedom from provisional stenting after 1 year was 95.4% for IVL and 81.7% for PTA ($p<0.0001$). MSAC noted that primary patency was retained after 2 years (70.4% IVL and 51.3% PTA, $p=0.003$). Freedom from provisional stenting after 2 years was 95.4% for IVL and 81.7% for PTA ($p<0.0001$).

However, MSAC noted that, when looking at the endpoints of procedural success for population 2 (secondary analysis using the primary patency population) freedom from clinically driven target lesion revascularisation (CD-TLR) and freedom from restenosis, there was no statistically significant difference between IVL and PTA for freedom from CD-TLR and restenosis, post-procedure, after 1 or 2 years. MSAC noted that, overall, the treatment outcomes in the single-arm DISRUPT PAD III OS study showed similar outcomes to the RCT.

Overall, for population 1, MSAC considered that there was very limited and weak evidence for non-inferior safety of IVL and for comparable effectiveness of IVL to SBA, given alignment of single-arm trials with a comparative RCT. For population 2, MSAC considered that there was evidence of non inferior safety of IVL in terms of absence of MAEs, thrombus and distal emboli events in all patients treated with IVL, but lack of evidence on long-term safety; and evidence of superior effectiveness of IVL in terms of procedural success (although noting this was based on only one RCT and one single arm study and there were risk of bias concerns associated with the RCT evidence). MSAC also noted that the evidence did not demonstrate any patient-reported outcomes such as QoL benefit, ankle-brachial index scores or walking improvement nor any survival benefit demonstrated either directly, or from any linked evidence on avoidance of stenting.

MSAC noted that the economic evaluation included a cost-utility analysis and a cost-consequence analysis. The cost-utility analysis model replaced asymptomatic and intermittent claudication with patency and loss of patency respectively, and assumed that patency is equivalent to asymptomatic disease and loss of patency is equivalent to intermittent claudication. MSAC agreed with the commentary that patency and loss of patency were appropriate for end of procedure or follow-up for a decision-tree analysis, but not as health states as used in the ADAR's Markov model. MSAC noted expert opinion that highlighted the importance of patency when treating PAD patients because patency is mechanically related to symptoms of PAD but considered that this still did not address concerns that use of patency as a health state in Markov modelling was methodologically inappropriate. MSAC also considered the extrapolation time horizon of 30 years to be implausible, because the average patient age for PAD was 71–72 years. MSAC considered the time horizon of 15 years supplied by the applicant in the pre-ESC response to be more appropriate.

MSAC noted further issues with the model input parameters associated with the base case model (which was for population 2 with a scenario analysis for population 1):

- Rate of stenting after the intervention: the ADAR used MBS data instead of trial-based data, but the MBS items were not specific enough to be used reliably, but the ADAR still applied the relative risk data from the trial which then overestimated the percentage of stenting avoided with the use of IVL. The rate of stenting was a key driver of the incremental cost-effectiveness ratio (ICER).
- Transition probabilities for loss of patency: the model assumed the rate after 2 years would be constant, which is not clinically plausible. Mortality was also assumed to be constant regardless of the health state, which is also not plausible.
- Utility weights: these were based on a US value set and assumed that loss of patency is equivalent to the baseline utility value of symptomatic patients. Further, model states were angiographic and informed by trial data, but utilities were attributed to those from symptoms or health states.
- Healthcare resource use and cost: Drug-eluting stent (DES) costs were used, which are very expensive and not reflective of Australian practice (which uses bare metal stents).
- IVL generator costs and fluoroscopy costs were not included.

MSAC noted that the base case ICER was \$ **redacted** per quality-adjusted life year (QALY) for population 1 and \$ **redacted** /QALY for population 2, using a 30-year time horizon. MSAC considered both ICERs to be highly uncertain; the ICER for population 1 was based on weak non-comparative evidence (as previously noted), the ICER for population 2 had problematic economic modelling (for the reasons already discussed), and both were based on an implausible time horizon. However, sensitivity analysis showed that the time horizon was not a major driver of the ICER – using 15 years only increased the ICER slightly to \$ **redacted** /QALY for population 2.

For population 2, the ICER was very sensitive to the rate of stenting postprocedure, and was also influenced by the cost of the stent. A stenting rate of 23.3% for IVL increased the ICER to \$ **redacted**. MSAC considered the rate of stenting to be a major cause of uncertainty in the economic model and ICER. MSAC noted the pre-MSAC response, which advised that the Australasian Vascular Audit suggests a stenting rate of about 36.6% (compared with 4% vs 18% stenting rates used in the DISRUPT PAD III trial).

The ADAR used a market share approach for the financial impact, which was \$ **redacted** (net costs to all governments) in year 1 to \$ **redacted** in year 6. However, the uncertainties in the economic modelling (such as the use of DES costs to calculate stenting costs and overestimate of stents avoided by the intervention) flowed through to the financial impact. The assumed uptake of between 15% and 50% over time was not based on the evidence presented and resulted in an uncertain financial impact. MSAC noted that the pre-MSAC response stated that this was a minimal financial impact, and MSAC agreed.

MSAC deferred its decision regarding funding IVL on the MBS. MSAC considered that despite the weak and uncertain evidence, especially for IVL as a stand-alone procedure, its key concerns related to the inappropriate structure of the economic model did not facilitate assessment of IVL's cost effectiveness. However, MSAC acknowledged the clinical need for such a service, as the comparator has several related adverse events.

MSAC recommended that any resubmission should include a revised clinical algorithm that it is not split into two populations since this is not reflective of clinical practice where stenting is provisional depending on the outcome of the IVL as perceived by the clinician in real time. Rather, the clinical algorithm should reflect only one population, namely patients with PAD who have moderately or severely calcified lesions in their lower limb(s). This would result in one proposed MBS item and descriptor and would also serve as a basis for appropriate revisions to the structure of the economic model.

MSAC considered that since the evidence did not present any health-related QoL or other patient-related outcomes, the economic modelling should be presented as a cost-consequence analysis using a decision tree structure based on the proposed revised clinical algorithm with one patient population. It should focus on procedure costs and costs of changes in resource use (stents, balloons used, etc.), with the procedural outcome (patency vs lack of patency) as the final outcome. The model should also address and correct the problematic input parameters identified by MSAC such as the omission of generator and fluoroscopy costs and the use of bare metal stents over DES for the cost of stenting.

MSAC requested that the sponsor clarify the cost of consumables and any potential out-of-pocket costs for patients in the resubmission. The resubmission should also produce revised financial estimates which address the issues identified by MSAC. MSAC noted that there was upcoming updated NICE guidelines on IVL due in January 2024 and any implications of this could also be discussed in a resubmission.

MSAC considered that the re-entry pathway for a resubmission that addressed these concerns could be submitted for direct consideration by MSAC.

4. Background

MSAC has not previously considered IVL for the treatment of moderately or severely calcified PAD in lower limbs.

MBS items 35300 and 35303 for transluminal balloon angioplasty, MBS items 35306 and 35309 for transluminal stent insertion, including associated balloon dilatation and MBS item 35312 for peripheral arterial atherectomy were introduced on the MBS from 1 April 1992.

5. Prerequisites to implementation of any funding advice

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

The proposed TGA indication for the IVL is as follows.

ARTG ID: 320482 - "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".

ARTG ID: 388192 - "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".

There are two IVL systems in series: Shockwave S4 and M5. At the pre-PASC meeting, the applicant claimed that both S4 and M5 catheters are similar in all features, except they are indicated for different vessel diameters.

6. Proposal for public funding

The applicant proposed a single new MBS item for peripheral IVL, including associated balloon dilatation of 1 peripheral artery of 1 limb. Table 1 presents the proposed item descriptor provided in the ADAR.

Table 1: Presentation of an existing, amended or newly proposed MBS item

Category 3 – Therapeutic Procedures
MBS item *XXXX
PERIPHERAL INTRAVASCULAR LITHOTRIPSY, including associated balloon dilatation of 1 limb, percutaneous or by open exposure, in patients who have moderately or severely calcified lesions, excluding associated radiological services or preparation, and excluding aftercare
Multiple Operation Rule (Anaes.) (Assist.)
Fee: \$736.25 Benefit: 75% = \$552.18 85% = \$625.81

The proposed MBS descriptor of "1 limb" is consistent with the ratified PICO and the MBS descriptors of other relevant MBS items (35300 and 35303). However, the department sought MSAC advice on whether the proposed new item descriptor for IVL should be amended to "1 lower limb" to be more consistent with the evidence presented in the assessment report and advice from PASC.

The applicant has proposed a fee of \$736.25 for IVL based on the current fee for standard balloon angioplasty (SBA) 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.¹ That RCT reported 89.9 mins for IVL vs. 66.5 mins for balloon angioplasty. Considering an approximately 35% longer duration for IVL compared to balloon angioplasty, the application proposed a fee of \$736.25 for IVL.

In addition to the MBS fee for service provision, the proposed therapeutic intervention involves using consumables. The Shockwave S4 or M5 catheter are the single-use consumables required for this service, with the cost of these being currently covered via hospital funding (at the hospital's discretion). The IVL generator and connector cable are multi-use.

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

There are differences between the proposed descriptor and both the TGA indication and the DISRUPT III RCT¹, the main clinical trial included in the ADAR. TGA did not specify symptom or calcification severity. The DISRUPT III RCT included patients with symptomatic leg claudication and/or rest pain (Rutherford class 2-4) and moderate or severe calcification (based on Peripheral Academic Research Consortium (PARC) criteria).

At the PASC meeting, whether the Rutherford classification system should be included in the proposed MBS item descriptor to define the patient population was discussed. The applicant's clinical expert stated that the Rutherford classification system is not currently used in clinical practice to define patient eligibility for endovascular procedures. Furthermore, 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

¹ Tepe, G., Brodmann, M., Werner, M., Bachinsky, W., Holden, A., Zeller, T., Gray, W. A. (2021). Intravascular Lithotripsy for Peripheral Artery Calcification: 30-Day Outcomes From the Randomized Disrupt PAD III Trial. *JACC Cardiovasc Interv*, 14(12), 1352-1361. doi:10.1016/j.jcin.2021.04.010

there is no specific classification system to decide on the patient's eligibility for IVL treatment in clinical settings.

7. Population

The proposed population is patients with PAD in lower limbs, moderate or severe calcification and who are indicated for endovascular revascularisation.

There are two PICO sets available for this application.

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 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 ADAR stated that if the anatomic assessment reveals at least moderate calcification, the patient would be eligible for treatment with IVL in place of SBA. The proposed algorithm includes two pathways for patients with PAD in lower limbs based on the 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 stand-alone or combined 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 stand-alone or combined with DCB/stent/atherectomy). Therefore, the patient population relevant for the PICO set 1 (IVL as stand-alone treatment) will receive IVL in place of current technology (as an alternative or as a replacement). The patient population relevant for the PICO set 2 (IVL in combination with other therapy) will receive IVL in addition to current technology.

This ADAR of IVL addresses all the PICO elements that were prespecified in the Ratified PICO.

8. Comparator

The ADAR proposed SBA alone as the comparator for PICO set 1 and SBA followed by drug-coated balloon (DCB) and/or stent as the comparator for PICO set 2. This is consistent with the Ratified PICO.

The application stated that 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 for items 35300, 35303, 35306 and 35309. The remaining patients predominantly receive stent insertion (32%), atherectomy (5%), or bypass surgery (4%). ESC considered that, 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 (35306 and 35309) also include associated balloon dilatation. However, it has been reported that in Australia, 70% of peripheral artery surgeries were endovascular procedures in 2015, and this proportion is estimated to increase over the years.² Therefore, ESC considered

² Aitken, S. (2020). Peripheral artery disease in the lower limbs: The importance of secondary risk prevention for improved long-term prognosis. *Australian Journal for General Practitioners*, 49, 239-244. Retrieved from <https://www1.racgp.org.au/ajgp/2020/may/peripheral-artery-disease-in-lower-limbs>

that SBA and SBA, followed by DCB and/or stent are the relevant comparators for the PICO set 1 and 2, respectively.

There are four existing item numbers related to the comparator SBA (also referred to as percutaneous transluminal angioplasty (PTA)) or transluminal balloon angioplasty (TBA)) 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 aftercare.
- 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.

Due to their low use rates, atherectomy and bypass surgery are not considered relevant comparators.

9. Summary of public consultation input

No consultation feedback was received by the department.

10. Characteristics of the evidence base

The ADAR provided evidence for using IVL to treat moderate or severely calcified PAD based on five relevant trials identified through a systematic literature search. Of these, three were applicable to IVL as a stand-alone treatment (DISRUPT PAD I, DISRUPT PAD II and DISRUPT BTK), and two were applicable to IVL as a vessel preparation strategy followed by a DCB and/or stent insertion (DISRUPT PAD III RCT and DISRUPT PAD III OS).

The DISRUPT PAD I, DISRUPT PAD II and DISRUPT BTK are prospective, multicentre (MC), single-arm clinical trials that evaluate the safety and feasibility of IVL as a stand-alone treatment in PAD.

DISRUPT PAD III RCT is a prospective, MC, single-blind, randomised (1:1) study of IVL versus SBA for vessel preparation prior to DCB treatment or stenting in moderate or severely calcified femoropopliteal arteries. The DISRUPT PAD III OS is a prospective, MC, single-arm clinical trial for subjects who did not meet the inclusion/exclusion criteria of the PAD III RCT or for subjects recruited after enrolment once the randomised portion of the study was completed.

The ADAR presented:

- 1) Direct, randomised comparative evidence
 - Evidence based on the DISRUPT PAD III RCT for the PICO set 2. The ADAR was mainly based on the direct RCT.
- 2) Direct, single-arm studies
 - Evidence-based on the DISRUPT PAD III OS for the PICO set 2
 - Evidence-based on the DISRUPT PAD I, DISRUPT PAD II and DISRUPT BTK single-arm clinical trials for the PICO set 1

Table 2 summarises the key features of the included evidence.

Table 2: Key features of the included evidence

References	N	Design/ duration	Risk of bias ^a	Patient population	Outcome(s)	Use in modelled evaluation
Direct, randomised comparative evidence						
DISRUPT PAD III (Tepe 2022)	306	MC, R, SB	Moderate	PAD patients with Rutherford class 2-4, and angiographic evidence of ≥70% stenosis within the superficial femoral and/or popliteal artery, lesion length up to 180 mm, reference vessel diameter 4-7 mm, and moderate or severe calcification. (calcification graded using PARC criteria)	Efficacy: Procedural success ^b , change in ABI at 30 days, change in WIQ at 30 days, change in EQ-5D at 30 days, change in EQ-5D VAS at 30 days, change in Rutherford class at 30 days Efficacy at 1 year: primary patency at 1 year ^c , change in ABI at 1 year, change in WIQ at 1 year, change in EQ-5D at 1 year, Change in Rutherford class at 1 year Efficacy at 2 year: primary patency at 2 year ^c Safety: Rates of MAE ^d , TLR rates at 30 days, Post-dilation rates at 30 days, stent placement at 30 days, flow-limiting dissection rates at 30 days	TP for patency to loss of patency, HS utility for loss of patency, Annual probability of mortality, RR for rate of stent in intervention arm, MAE rate, flow limiting dissection rate and CD-TLR rate
Direct, single-arm studies						
DISRUPT PAD III OS Attachment 2.4 of the ADAR, Study CSR ^e	1,373	Prospective, single arm, MC, observational study	Moderate	PAD patients with claudication or CLI by Rutherford class 2-6 and at least moderate calcification defined as presence of fluoroscopic evidence of calcification in the iliofemoral, femoropopliteal or infrapopliteal arteries	Efficacy: Procedural success Safety: Adverse events – site-reported, Serious adverse events – site-reported	Not used
DISRUPT PAD II (Brodmann 2018a)	60	Prospective, single-arm, non- randomised, MC trial	Low to moderate	PAD patients with claudication or CLI by Rutherford class 2-4 and at least moderate calcification defined as presence of fluoroscopic evidence of calcification	Efficacy: Target lesion patency at 12 months, primary patency at 12 months, acute procedural success Safety: MAE through 30 days, secondary safety endpoint Functional outcomes: Improvement in ABI at 30 days, 6 months and 12 months and improvement in Rutherford Classification at 30 days, 6 months and 12 months	Scenario analysis - rate of flow-limiting dissections, CD-TRL in 1-year, restenosis at 1-year
DISRUPT PAD I (Brodmann 2017)	35	Prospective, single-arm, non- randomised, MC trial	Low to moderate	PAD patients with Rutherford class 2-4 and moderate to severe calcification of target lesion(s) per pre-procedure CT scan	Efficacy: Procedural success, loss of vessel patency Safety: MAEs at 30 days and 6 months Functional outcomes: Improvement in ABI, improvement in Rutherford Classification	Not used

References	N	Design/ duration	Risk of bias ^a	Patient population	Outcome(s)	Use in modelled evaluation
DISRUPT PAD BTK (Brodmann 2018b)	20	Prospective, single-arm, non- randomised, MC trial	Low to moderate	PAD patients with Rutherford class 1- 5 and moderate to severe calcification in BTK arteries	Efficacy: Acute reduction in percent diameter stenosis of the target lesion, procedural success Safety: Composite of MAE through 30 days	Not used

Abbreviations: ABI = ankle-brachial index; BTK = below-the-knee; CD-TLR= clinically driven target lesion revascularisation; CLI = critical limb ischemia; CT = computed tomography; DCB= drug-coated balloon; EQ-5D = EuroQoL-5 Dimension questionnaire; HS= Health state; IVL = intravascular lithotripsy; MAE = major adverse events; MC = multicentre; OS = overall survival; PAD = Peripheral Artery Disease; ; PARC = Peripheral Academic Research Consortium; R = randomised; RR = Relative Risk; SB = single-blind; TP = Transition probability; TLR = Target lesion revascularisation; VAS = Visual analogue scale; WIQ = Walking Impairment Questionnaire.

Notes:

^a Single-arm clinical trials used the ROBINS-1 Risk of Bias Tool, and RCT used the Cochrane Risk of Bias Tool;

^b Determined by the angiographic core laboratory as residual stenosis $\leq 30\%$ without flow-limiting dissection (\geq type D) following the randomised treatment and prior to DCB treatment and/or provisional stent placement;

^c Defined as freedom from CD-TLR and freedom from restenosis as determined by duplex ultrasound (DUS) or angiogram $\geq 50\%$ stenosis;

^d Unplanned surgical revascularisation or major (above ankle) amputation of the target limb, symptomatic thrombus or embolus requiring treatment, and perforations requiring provisional stent placement or other treatment;

^e Published studies of DISRUPT PAD III OS (Adams et al., 2020; Armstrong et al., 2020; and Adams et al., 2021 provided only the subgroup analysis of DISRUPT PAD III OS study.

Patients in the DISRUPT PAD clinical trials were predominantly male, with a mean age between 72 to 73 years. The Australian Institute of Health and Welfare (AIHW) reported a lack of epidemiological data for the PAD population. However, 20% prevalence of PAD is estimated in the population over 75 years of age. According to the AIHW, PAD-related hospitalisations were twice as high for males as females in 2020–21.³

The commentary identified differences between the trial population and the Australian patient population with PAD and/or other vascular diseases. For instance, diabetes, hypertension and current smokers were reported in 44.8%, 94.4% and 24.2% in the DISRUPT PAD III RCT compared to 16.3%, 52.7% and 22.80% in Australians with cardiac, stroke, or vascular diseases based on AIHW data. A study conducted among men aged 65–83 years with PAD living in Perth reported 16.4% diabetes, 50.5% hypertension and 18.4% current smokers in the study population.⁴ A study conducted in Townsville reported 43.8%, 93.8%, and 56.3% diabetes, hypertension and current smokers, respectively, among Indigenous patients with PAD compared to 26.8%, 75.3% and 31.4% among the non-Indigenous patients with PAD.⁵

Furthermore, the commentary noted that the DISRUPT PAD studies included patients based on the Rutherford classification. However, the Rutherford classification system is not currently used in clinical practice to define patient eligibility for endovascular procedures. Hence, the Australian clinical setting could differ from the included patient population in the DISRUPT PAD trials. Therefore, the applicability of the trial population to the Australian clinical setting is uncertain however, PASC 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 DISRUPT PAD III⁶ and a recent trial.⁷

The ADAR was mainly based on the DISRUPT PAD III RCT, which provided evidence for PICO set 2. The risk of bias for the DISRUPT PAD III RCT was assessed using the Cochrane Risk of Bias tool v2.0. The risk of bias analysis revealed that this study has some concerns, particularly the bias due to missing data and single blinding. At 24 months, almost 20% of patient data was missing from the analysis due to death (28%), withdrawal (49%) and loss to follow-up (22%). However, the commentary acknowledges that the missing data were balanced between the two treatment arms and is not considered likely to be due to the intervention. The commentary noted that the follow-up duration of this study was short, and outcomes were mainly procedure-based rather than patient-relevant outcomes.

³ Australian Institute of Health Welfare. (2023). Heart, stroke and vascular disease: Australian facts. Retrieved from Canberra: <https://www.aihw.gov.au/reports/heart-stroke-vascular-diseases/hsvd-facts/contents/heart-stroke-and-vascular-disease-subtypes/peripheral-arterial-disease>

⁴ Fowler B, Jamrozik K, Norman P, Allen Y. Prevalence of peripheral arterial disease: persistence of excess risk in former smokers. *Aust N Z J Public Health*. 2002;26(3):219-24.

⁵ Singh TP, Moxon JV, Healy GN, Cadet-James Y, Golledge J. Presentation and outcomes of indigenous Australians with peripheral artery disease. *BMC Cardiovasc Disord*. 2018 May 16;18(1):94. doi: 10.1186/s12872-018-0835-z.

⁶ Tepe, G., Brodmann, M., Bachinsky, W., Holden, A., Zeller, T., Mangalmurti, S., Nolte-Ernsting, C., Virmani, R., Parikh, S. A., & Gray, W. A. (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(4).

⁷ Shishehbor, M.H., Powell, R.J., Montero-Baker, M.F., Dua, A., Martínez-Trabal, J.L., Bunte, M.C., Lee, A.C., Mugglin, A.S., Mills, J.L., Farber, A. and Clair, D.G. (2023). Transcatheter arterialization of deep veins in chronic limb-threatening ischemia. *New England Journal of Medicine*, 388: 1171-80.

11. Comparative safety

The ADAR provided evidence of safety outcomes based on one RCT and four single-arm clinical trials. The main safety outcomes presented in the ADAR were:

- 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

These safety outcomes are presented as single or composite outcome measures (e.g., Major adverse events).

Evidence based on direct RCT

Table 3 summarises the main safety results based on the DISRUPT PAD III RCT for the proposed technology and the main comparator relevant to the PICO set 2.

In DISRUPT PAD III RCT, major adverse events (MAEs) were defined as need for emergency surgical revascularisation of target limb, unplanned target limb major amputation (above the ankle), symptomatic thrombus or distal emboli (that require surgical, mechanical, or pharmacologic means to improve flow and extend hospitalisation) and perforations that require an intervention, including bail-out stenting.

Table 3: Summary of safety results from direct, randomised comparative evidence base

	IVL (n = 153)	PTA (n = 153)	P value
Final angiographic thrombus and distal emboli events from DISRUPT PAD III RCT			
Thrombus			
Number of available patient data	146	133	
Events (%)	0 (0.0)	0 (0.0)	
Distal emboli			
Number of available patient data	145	133	
Events (%)	0 (0.0)	0 (0.0)	
Results of MAE rates from DISRUPT PAD III RCT			
MAEs at 30 days	0/152 (0.0)	2/153 (1.3)	0.1573
MAEs at 6 months	0/147 (0.0)	2/147 (1.4)	0.1559
MAEs at 12 months	0/143 (0.0)	2/140 (1.4)	0.1515
MAEs at 24 months	0/119 (0.0)	2/118 (1.7)	0.1573

Abbreviations: IVL = Intravascular lithotripsy; MAE = major adverse event; PTA = Percutaneous transluminal angioplasty

The incidence of 30-day MAE was not significantly different between the IVL arm (0.0%) and the PTA arm (1.3%, $p=0.1573$). During the 6-month follow-up period, no MAEs occurred in the IVL arm, and no new MAEs occurred in the PTA arm. The incidence of 6-month MAE was also not significantly different between the IVL arm (0.0%) and PTA arm (1.4%, $p=0.1559$).

The DISRUPT PAD III study reported 17 deaths (10 deaths in the IVL arm and 7 in the SBA arm) over the two-year trial period. However, the reasons for the deaths were not reported. The commentary considers that given the relatively short follow-up duration of 2 years, the long-term safety of IVL in this population is uncertain.

Evidence based on single-arm clinical trials

The DISRUPT PAD III OS study reported that 55.3% of the patients received adjunct therapies. However, it did not report the safety outcomes separately for the IVL as stand-alone (PICO set 1) and IVL along with adjunct therapies (PICO set 2). The DISRUPT PAD I, II and BTK studies provided safety evidence related to the PICO set 1.

Table 4 summarises the safety results from single-arm studies

Table 4: Summary of safety outcomes for single-arm study evidence base

DISRUPT PAD III OS			
Major adverse event	n/N with events (%)		
Post-IVL perforation			
Grade I	1/1118 (0.1)		
Grade II	1/1118 (0.1)		
Grade III	2/1118 (0.2)		
Post-IVL distal emboli	1/1118 (0.1)		
Post-IVL thrombus	1/1118 (0.1)		
Revascularisation	0/1118 (0.0)		
Major amputation (above the ankle)	0/1118 (0.0)		
Provisional stenting	0/1118 (0.0)		
Mortality	5/1118 (0.04)		
DISRUPT PAD II			
Major adverse events	30 days	6 months	12 months
Emergency surgical revascularisation of target limb	0/59 (0.0)	0/58 (0.0)	0/57 (0.0)
Unplanned target limb amputation	0/59 (0.0)	0/58 (0.0)	0/57 (0.0)
Symptomatic thrombus or emboli	0/59 (0.0)	0/58 (0.0)	0/57 (0.0)
Perforations or Grade D dissections w/ interventions	1/59 (1.7)	1/58 (1.7)	1/57 (1.8)
DISRUPT PAD I			
Major adverse events	Periprocedural	Discharge	30 days
Need for emergency surgical revascularisation of target limb	0/35 (0.0)	0/35 (0.0)	0/35 (0.0)
Unplanned target limb amputation (above the ankle)	0/35 (0.0)	0/35 (0.0)	0/35 (0.0)
Symptomatic thrombus or distal emboli*	0/35 (0.0)	0/35 (0.0)	0/35 (0.0)
Perforations and dissections of grade D or greater that require an intervention to resolve, including bail-out stenting	0/35 (0.0)	0/35 (0.0)	0/35 (0.0)
DISRUPT PAD BTK			
Major adverse events	Assessed at 30 days post-procedure		
Death	0/20 (0.0)		
Myocardial Infarction	0/20 (0.0)		
Emergency surgical revascularisation of target limb	0/20 (0.0)		
Unplanned target limb amputation (above the ankle)	0/20 (0.0)		

IVL = Intravascular lithotripsy

*Defined as clinical signs or symptoms of thrombus or distal emboli detected in the treated limb in the area of the treated lesion or distal to the treated lesion after the index procedure or noted angiographically, and requiring mechanical or pharmacological means to improve flow.

The DISRUPT PAD III OS study reported perforations in 0.4% of lesions treated (4/1118). No vascular reflow post-IVL occurred in 0.2% (2/1119) of the lesions, distal emboli in one lesion 0.1% (1/1118), and thrombus in one lesion 0.1% (1/1119). The DISRUPT PAD III OS study also reported five deaths. However, none were related to the device or the procedure.

The DISRUPT PAD II study reported 1.7% of MAEs at 30 days, and no further incidences of MAEs reported beyond the initial 30 days of the study. One death was reported during the study, which was determined to be cardiac-related and not associated with the study device or procedure.

In DISRUPT PAD I reported no major adverse events at the time of the procedure and through the 30-day or 6-month follow-up visit.

DISRUPT PAD BTK reported no major adverse events (defined as death, myocardial infarction, emergency surgical revascularisation, or unplanned target limb amputation) through 30 days post-procedure.

The commentary considers that DISRUPT PAD III RCT provided comparative evidence of the safety of IVL and SBA and was relevant for the PICO set 2. Nevertheless, the clinical claim of non-inferior safety in the ADAR is uncertain as the DISRUPT PAD III RCT does not provide long-term safety evidence. The commentary noted that the comparative safety evidence related to the IVL and SBA in PICO set 1 is limited as it was based on single-arm studies only.

12. Comparative effectiveness

The ADAR provided evidence of effectiveness outcomes based on one RCT and four single-arm clinical trials. Procedural success and primary patency are the main effectiveness measures evaluated in the DISRUPT PAD studies. Changes in PAD severity (measured with ankle-brachial index), walking performance measured with Walking Impairment Questionnaire (WIQ), Quality of Life (QoL), and Rutherford classification stage are the secondary effectiveness measures, including patient-relevant outcomes evaluated in the DISRUPT PAD studies.

Evidence based on direct RCT

DISRUPT PAD III RCT

The DISRUPT PAD III RCT provided comparative evidence of the effectiveness of IVL and SBA and was relevant for PICO set 2.

In DISRUPT PAD III RCT, procedural success was defined as residual stenosis $\leq 30\%$ without flow-limiting dissection (\geq grade D) prior to DCB or stenting by an angiographic core lab. Procedural success was significantly greater in the IVL arm compared to the PTA arm (IVL: 65.8% [n = 96/146]; PTA: 50.4% [n = 67/133]; RR: 1.31 [95% CI 1.06, 1.60]; RD: 0.15 [95% CI 0.04, 0.27]; p = 0.0065) as evaluated by the angiographic core laboratory.

Primary patency is defined as freedom from clinically driven target lesion revascularisation (CD-TLR) and freedom from restenosis as determined by duplex ultrasound or angiogram $\geq 50\%$ stenosis. Further, acute procedure failure requiring a stent at any time during the index procedure is counted as a loss of primary patency and therefore “freedom from provisional stenting” is also a measure of primary patency.

The results of the main efficacy outcomes of procedural success and primary patency are summarised in Table 5 for DISRUPT PAD III RCT.

Table 5: Summary of efficacy outcomes in the direct, randomised comparative evidence base

	IVL	PTA	RR (95% CI)	RD (95% CI)	p-value
	n/N with events (%)	n/N with events (%)			
Procedural success					
Procedural success	96/146 (65.8%)	67/133 (50.4%)	1.31 [1.06, 1.60]	0.15 [0.04, 0.27]	0.0065
Procedural success (Secondary analysis using PP population)	87/126 (69.0%)	57/127 (51.2%)	1.54 [1.23, 1.93]	0.24 [0.12, 0.36]	0.0027
Primary Patency					
Primary patency at Year 1	99/123 (80.5%)	87/128 (68.0%)	1.18 [1.02, 1.37]	0.13 [0.02, 0.23]	0.0167
Freedom from provisional stenting	146/153 (95.4%)	125/153 (81.7%)	1.17 [1.08, 1.27]	0.14 [0.07, 0.21]	<0.0001
Freedom from CD-TLR at Year 1	132/138 (95.7%)	114/116 (98.3%)	0.97 [0.93, 1.02]	-0.03 [-0.07, 0.02]	0.9442
Freedom from restenosis at Year 1	99/110 (90.0%)	87/98 (88.8%)	1.01 [0.92, 1.11]	0.01 [-0.07, 0.10]	0.4745
Primary patency at Year 2	81/115 (70.4%)	63/118 (51.3%)	1.32 [1.07, 1.62]	0.17 [0.05, 0.29]	0.0054
Freedom from provisional stenting	146/153 (95.4%)	125/153 (81.7%)	1.17 [1.08, 1.27]	0.14 [0.07, 0.21]	<0.0001
Freedom from CD-TLR at Year 2	108/118 (91.5%)	93/102 (91.2%)	1.00 [0.93, 1.09]	0.00 [-0.07, 0.08]	0.56
Freedom from restenosis at Year 2	78/94 (83.0%)	58/76 (76.3%)	1.09 [0.93, 1.27]	0.07 [-0.06, 0.19]	0.19

Abbreviations: CD-TLR = Clinically driven target lesion revascularisation; IVL = Intravascular lithotripsy; PTA = Percutaneous transluminal angioplasty; RR = risk ratio; RD = risk difference

Bold indicates a statistically significant difference

The freedom from provisional stent during the index procedure was included as part of the primary patency in both 1-year and 2-year effectiveness outcomes.

DISRUPT PAD III RCT reported significantly higher primary patency at Year 2 in the IVL group compared to the PTA group (IVL: 70.4%, PTA: 51.3%, RR: 1.32 [95% CI 1.07, 1.62], RD: 0.17 [95% CI 0.05, 0.29], p = 0.0054). However, there was no significant difference in freedom from CD-TLR and restenosis at 2-years. The significant difference in primary patency at 2 years between the IVL and SBA arm was driven by the freedom from provisional stent during the index procedure (Freedom from CD-TLR and restenosis were not statistically significant at 2 years). Hence, the commentary considers that the long-term effectiveness in terms of primary patency is uncertain.

Secondary effectiveness outcomes

The DISRUPT PAD III RCT reported changes in PAD severity (based on Ankle-brachial index (ABI)), walking performance, quality of life (QoL) and Rutherford classification stage as secondary effectiveness outcomes.

ABI improvement from baseline

The IVL and PTA treatment arms showed clinical improvement in ABI scores at 30 days and 12 months from baseline (IVL: 0.19 ± 0.20; PTA: 0.23 ± 0.25; p = 0.25) as both groups reported ABI

0.9 mean scores at both 30 days and 12 months. However, no significant differences were observed in the change from baseline to 12 months between the intervention and comparator groups.

Walking performance measured with walking impairment questionnaire (WIQ)

The DISRUPT PAD III study reported improvement in WIQ overall scores from baseline across both treatment arms. However, there were no statistically significant differences between patients in the IVL arm and those in the PTA arm.

Rutherford classification change from baseline

The change in Rutherford classification was comparable in both treatment arms at 30 days (IVL: -2.20 ± 1.08 ; PTA: -2.27 ± 0.99 ; $p=0.5733$), 6 months (IVL: -2.35 ± 0.91 ; PTA: -2.29 ± 1.00 ; $p=0.6323$), 12 months (IVL: -2.22 ± 1.08 ; PTA: -2.32 ± 1.04 ; $p=0.4477$) and 24 months (IVL: -2.15 ± 1.14 ; PTA: -2.12 ± 1.29 ; $p=0.8444$). However, no statistically significant differences were observed between two groups over the follow-up period.

Quality of life

QoL results using the EuroQoL-5D (EQ-5D) were comparable across both treatment arms in the change from baseline at 30 days (IVL: 0.10 ± 0.20 ; PTA: 0.12 ± 0.18 ; $p=0.60$) and at 12 months (IVL: 0.09 ± 0.20 ; PTA: 0.07 ± 0.21 ; $p=0.54$). However, no significant difference was observed between IVL and PTA arms.

DISRUPT PAD III RCT reported a statistically significant superior result in a 30-day change from baseline measurements (IVL: 9.1 ± 16.9 ; PTA: 4.3 ± 15.7 ; $p=0.01$) in the EQ-5D visual analogue scale (EQ-5D VAS) score between IVL and PTA groups. However, this difference was not significant in the 12 months (IVL: 6.7 ± 17.2 ; PTA: 2.7 ± 21.2 ; $p=0.0925$).

Evidence based on single-arm clinical trials

The results of the main efficacy outcomes of procedural success and primary patency are summarised in Table 6 for single-arm clinical trials.

Procedural success was defined as residual stenosis $\leq 30\%$ without flow-limiting dissection (\geq grade D) prior to DCB or stenting by angiographic core in DISRUPT PAD OS (This is similar to the procedural success defined in the DISRUPT PAD III RCT). DISRUPT PAD I, II, and DISRUPT PAD BTK studies did not report results of procedural success defined as $\leq 30\%$ final residual stenosis without a flow-limiting dissection (\geq grade D). Hence, the ADAR did not include the procedural success results for these studies.

Of note, the definition of procedural success varies across DISRUPT PAD studies. Due to this heterogeneity, the studies were not pooled.

However, flow-limiting dissection (\geq grade D) was one of the procedural success markers reported in the DISRUPT PAD II study and flow-limiting dissection (\geq grade D) was observed in one patient (1.7%). The ADAR stated that this value was used in the economic model for the PICO 1 scenario analysis. Hence, it is included in the summary table. The economic evaluation section will discuss the appropriateness of using this value in the economic model.

The DISRUPT PAD III OS and the DISRUPT PAD BTK studies did not report primary patency as a primary effectiveness endpoint. The primary patency in DISRUPT PAD II and DISRUPT PAD I studies is defined as freedom from CD-TLR and from $\geq 50\%$ stenosis by duplex ultrasound as in DISRUPT PAD III RCT.

Table 6: Summary of efficacy outcomes in the single-arm study evidence base

Study	Outcome	n/N with events (%)		
DISRUPT PAD III OS				
Procedural success	Procedural success by subject [residual stenosis ≤30%]	772/1112 (69.4)		
Primary patency	NR			
DISRUPT PAD II				
Procedural success	Successful IVL catheter delivery and treatment	60/60 (100)		
	Flow-limiting dissection (≥ grade D)	1/60 (1.7)		
	Final residual stenosis %, mean ± SD	24.2 ± 5.7		
Primary patency		30 days	6 months	12 months
	Target lesion patency ^a	100% (56/56)	72.7% (40/55)	69.8% (30/43)
	Freedom from TLR ^b	100% (58/58)	98.3% (57/58)	79.3% (46/58)
	Primary patency ^c	100% (56/56)	71.4% (40/56)	54.5% (30/55)
DISRUPT PAD I				
Primary patency		30 days	6 months	12 months
	Primary patency, % (95% CI)	100.0 (90.7 to 100.0)	82.1 (66.5 to 92.5)	NR
	Freedom from TLR, % (95% CI)	100.0	100.0	NR

Abbreviations: CI = confidence interval; IVL = Intravascular lithotripsy; NR = Not reported SD = Standard deviation, TLR = target lesion revascularisation

^a, Excludes any patient that had a TLR from the analysis

^b, Two patients withdrew from the study

^c, Three patients did not complete Duplex ultrasound, and two patients withdrew from the study

Secondary effectiveness outcomes

ABI improvement from baseline

ABI improvement was not reported in DISRUPT PAD III OS and DISRUPT PAD BTK studies. The DISRUPT PAD II study reported statistically significant improvement of ABI from the baseline measurement at 6 months (mean 0.3, 95% CI 0.2-0.3; p<0.001), and 12 months (mean 0.2, 95% CI 0.2-0.3; p<0.001). The DISRUPT PAD I study also reported improvement of ABI from baseline to post-discharge (mean 0.3, 95% CI 0.2-0.3; p<0.001), with the improvement reaching a plateau at both the 30-day (mean 0.3, 95% CI 0.2-0.4; p<0.001) and 6-month (mean 0.3, 95% CI 0.2-0.4; p<0.001) time points.

Rutherford classification change from baseline

Rutherford classification improvement was not reported in DISRUPT PAD III OS and DISRUPT PAD BTK studies. The DISRUPT PAD II study reported statistically significant improvement of Rutherford classification from the baseline measurement at 6 months (mean -2.0, 95% CI -2.31 to -1.76; p<0.0001), and 12 months (mean -2.1, 95% CI -2.33 to -1.78; p<0.0001). The DISRUPT PAD I study also reported statistically significant improvement of Rutherford classification from the baseline at discharge (mean -2.1, 95% CI -2.5 to -1.7; p<0.0001), 30-day (mean -2.5, 95% CI -2.7 to -2.2; p<0.0001) and 6-month (mean -2.2, 95% CI -2.5 to -2.0; p<0.0001) time points.

Quality of life

None of the single-arm clinical trials reported QoL outcomes.

Walking performance measured with WIQ

Of the four single-arm clinical trials, only the DISRUPT PAD II study reported WIQ scores. This study revealed significant improvement in WIQ scores across all domains at 30 days, 6 months and 12 months.

Pooling of the included studies may not be appropriate given the high heterogeneity in the included studies⁸.

Clinical claim

The clinical claim is that IVL results in superior effectiveness and non-inferior safety compared with SBA for treating PAD patients with moderate to severe calcification.

The clinical claim of superior effectiveness is uncertain because:

- The applicability of the trial population to the Australian clinical practice is uncertain due to differences between the eligibility criteria in the trial and the target population as well as differences in patient characteristics, e.g., comorbidities.
- There is limited comparative effectiveness evidence to support IVL use as a stand-alone intervention (PICO set 1), as the evidence provided in the ADAR is based on single-arm studies only.
- The comparative effectiveness evidence for the PICO set 2 was based on a single-blinded RCT (DISRUPT PAD III) and a single-arm clinical trial. There were some concerns regarding the risk of bias associated with the DISRUPT PAD III RCT due to missing data and single-blinded study design.
- The effectiveness evidence provided for PICO sets 1 and 2 were mainly related to procedure-related outcomes (procedural success and primary patency) rather than patient-relevant outcomes.
- The evidence related to long-term effectiveness in terms of primary patency is uncertain due to DISRUPT PAD III RCT primary patency at 2 years between IVL and SBA arm being driven by the freedom from provisional stent at the procedure.

The clinical claim of noninferiority in safety is uncertain because:

- There is limited comparative safety evidence to support IVL use as stand-alone intervention (PICO set 1) as the evidence provided in the ADAR is based on single-arm studies only.
- The DISRUPT PAD III study reported a relatively short follow-up duration of 2 years. There were 17 deaths (10 deaths in the IVL arm and 7 in the SBA arm) over the two-year trial period reported as missing data. The cause of the deaths was not reported.

13. Economic evaluation

The ADAR presented a CUA based on the clinical claim of superior effectiveness and non-inferior safety compared with SBA.

The ADAR presented a trial-based cost-consequence analysis (CCA) and a modelled cost-utility analysis (CUA) over a 30-year (i.e., lifetime) time horizon. The base case analysis in the CUA was

⁸ Wong, C. P., Chan, L. P., Au, D. M., Chan, H. W. C., & Chan, Y. C. (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(3), 446-456.

based on PICO set 2 (i.e., IVL or SBA followed by stent and/or DCB). A scenario analysis is presented for PICO set 1, comparing IVL and SBA as stand-alone treatments.

Summary of economic evaluation

Table 7 provided a summary of economic evaluation presented in the ADAR.

Table 7: Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	Patients with symptomatic PAD with moderate to severe calcification
Prior testing	Tests to determine severity of PAD and calcification
Intervention and comparator	Base case: IVL vs SBA followed by DCB or stent Scenario: IVL vs SBA as a stand-alone treatment
Type(s) of analysis	Cost consequence; cost-utility analysis
Outcomes	Provisional stents avoided, dissections avoided, flow-limiting dissections avoided, primary patency progression, major adverse events, and quality-adjusted life year.
Time horizon	30 years (lifetime) in the model base case vs. 2 years in the key trial
Computational method	Markov cohort
Generation of the base case	Trial-based and modelled.
Health states	Patency, loss of patency, critical limb ischaemia, amputation, death
Cycle length	1 month
Transition probabilities	Transition from patency to loss of patency is informed from the PAD III RCT and extrapolated beyond the 2-year trial follow-up. Transition probabilities to CLI amputation are sourced from a literature review.
Discount rate	5% base case (0%, 3.5% as sensitivity analyses)
Software	Excel

Abbreviations: CLI = critical limb ischaemia; DCB = drug-coated balloon; IVL = intravascular lithotripsy; PAD = peripheral artery disease; RCT = randomised control trial; SBA = standard balloon angioplasty

Cost consequence analysis (CCA)

The ADAR presented a CCA using outcomes based on the DISRUPT PAD III RCT. Provisional stents avoided, dissections avoided, flow-limiting dissections avoided, primary patency progression, and MAEs were the outcomes included. Costs included were the costs associated with the initial procedure, subsequent treatment and disease management costs over a 2-year time horizon.

MSAC guidelines recommend using a CCA when the proposed intervention includes a different profile of effects that are not adequately captured by a single outcome measure. The commentary noted that the outcomes presented in the CCA are the same outcome measures used in the CUA. Hence, the presented trial-based CCA may not add any new evidence to the ADAR.

The commentary also noted that the outcomes used in the CCA are focused on procedure outcomes and adverse events but did not include patient-reported outcomes. Furthermore, the DISRUPT PAD III RCT included QoL data based on EQ-5D. However, this was not included in the trial-based analysis.

Cost-utility analysis (CUA)

The CUA presented in the ADAR was a Markov cohort model, which models long-term outcomes over a 30-year (i.e., lifetime) time horizon. The model used data related to the procedure success from the 2-year follow-up of the DIRSUPT PAD III trial and extrapolated this for 30 years however, a 10-year time horizon may be more appropriate given that the starting age in the model was 72 years.

Model structure

The Markov model structure was based on the modified economic model presented by Simpson et al., 2014⁹.

The commentary noted that the final model structure (Figure 3) provided in the ADAR did not appropriately reflect the PAD disease pathways compared to the model by Simpson et al., 2014. The economic model in the ADAR replaced the asymptomatic and intermittent claudication (IC) health states in the model by Simpson et al. with the patency and loss of patency health states. In other words, the presented model assumed that patency is equivalent to asymptomatic disease and loss of patency is equivalent to IC.

The commentary noted that the ADAR used model input parameters relevant for the patent and asymptomatic for the patent health state interchangeably, as is the case for using model parameters relevant for the loss of patency and IC for the loss of patent health state.

Figure 1 illustrates the model structure presented in the ADAR.

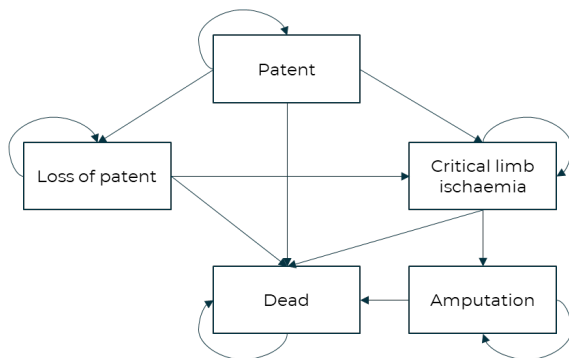


Figure 1: Model structure

Model input parameters

The commentary noted some model input parameters are irrelevant or not accurate:

- **Rate of stenting**

The ADAR assumed a 45% rate of stenting for the comparator (i.e., SBA) arm based on MBS utilisation data from 2017-2022 (MBS items 35306 and 35309). A relative risk of 0.25 was applied to 45% to calculate the rate of stenting in the IVL arm based on the rate of the stent at the procedure (18.3% in the SBA arm vs 4.6% in the IVL arm) reported in the DISRUPT PAD III RCT.

⁹ Simpson, E., Kearns, B., Stevenson, M., Cantrell, A., Littlewood, C., & Michaels, J. (2014). Enhancements to angioplasty for peripheral arterial occlusive disease: systematic review, cost-effectiveness assessment and expected value of information analysis. *Health Technology Assessment*, 18(10).

The MBS items 35306 and 35309 are not specific to this population, i.e., symptomatic PAD patients with moderate to severe calcification. Moreover, MBS items 35306 and 35309 are not confined to the peripheral arteries. The commentary considered that the estimate of the effects was overestimated and therefore, this relative risk should have been applied to the baseline probability of stenting (18.3%) reported in the DISRUPT PAD III study.

The ADAR did not provide data about the rate of stenting with IVL use in practice to allow a comparison between the two interventions. Of note, the DISRUPT PAD III OS study reported that 31.8% of lesions were treated with stents along with IVL procedures. Hence, the stent insertion rate accompanying IVL procedures taken from the DISRUPT PAD III RCT is likely to be lower than what would be observed in Australian clinical practice.

- **Transition probabilities-**

Probability of loss of patency - The probability of patency loss was calculated separately for cycle 1 to capture patency loss due to SBA failure and from cycle 2 onwards to capture patency loss due to TLR/restenosis. The probability for cycle 1 was calculated based on the stent rate in MBS utilisation data for the SBA arm, and the relative risk (RR) of 0.25 was applied for the IVL arm.

The ADAR did not use the baseline rate for stenting from the DISRUPT PAD III trial but rather used MBS data that is not specific to the PICO population and applied the relative risk from the trial, overestimating the percentage of stenting avoided with the use of IVL.

The probability of loss of patency from cycle 2 onwards was calculated based on DISRUPT PAD III RCT data. Then, the model assumed that the rate of transitioning from the first 2 years is constant and was extrapolated for the rest of the time horizon. The commentary considers that this may not be clinically plausible as patency will be lost at a higher rate in subsequent years.

Probability of progression from patency/loss of patency to chronic limb ischaemia (CLI) - The data was sourced from a systematic review.¹⁰ The commentary considers that this data is related to the IC patients progressing to CLI, not the progression from loss of patency to CLI. Furthermore, the systematic review cited in the ADAR is based on studies conducted among PAD patients in different settings (e.g., hospital, community, and population-based) and included patient groups other than the intended patient population (PAD patients with moderate to severe calcification).

The ADAR assumes an RR of 0.9 to the probability of progressing from loss of patency to CLI based on the additional literature search provided in the ADAR. The commentary considers that this additional systematic review did not provide any association between loss of primary patency and the Rutherford category.

Probability of progression from CLI to amputation - The data was sourced from IN.PACT Global study¹¹ which evaluated the safety and efficacy of DCB for treating femoropopliteal lesions. Hence, this is not relevant.

Mortality - The ADAR incorporated baseline age-specific mortality from Australian lifetables (Australian Bureau of Statistics, 2019-2021), and an RR of 2.11 was applied to general

¹⁰ Sigvant, B., Lundin, F., & Wahlberg, E. (2016). The Risk of Disease Progression in Peripheral Arterial Disease is Higher than Expected: A Meta-Analysis of Mortality and Disease Progression in Peripheral Arterial Disease. *Eur J Vasc Endovasc Surg*, 51(3), 395-403.

¹¹ Reijnen, M. M. P. J., van Wijck, I., Zeller, T., Micari, A., Veroux, P., Keirse, K., Holewijn, S. (2019). Outcomes After Drug-Coated Balloon Treatment of Femoropopliteal Lesions in Patients With Critical Limb Ischemia: A Post Hoc Analysis From the IN.PACT Global Study. *Journal of Endovascular Therapy*, 26(3), 305-315.

population mortality estimates based on deaths reported in DISRUPT PAD III RCT. A constant RR of mortality of 2.11 is applied regardless of health states.

The commentary noted that assuming the same mortality rates for all health states is not appropriate. The mortality rate is not similar in the IVL and SBA arm of the DISRUPT PAD III RCT (10 deaths in the IVL arm compared with 7 deaths in the SBA arm reported over two years). Furthermore, patients with more severe disease have a higher mortality rate. Epidemiological studies reported a 4%-6% annual mortality rate associated with the PAD, which is increasing with the disease progression to severe health states.¹²

- **Utility weights**

The utility value for the patent health state was derived from a study to derive population norms for the EQ-5D-3L using an adult sample in Queensland, Australia.¹³ The mean utility values based on Australian, UK and USA value sets for those aged 65-74 were 0.82, 0.80 and 0.85, respectively. However, the commentary noted that the utility value included in the model (0.85) was based on the USA value set. The value based on the Australian value set would be more applicable to the Australian setting.

The ADAR included baseline utilities from DISRUPT PAD III RCT to inform the loss of patency health state. ESC considered that it is not appropriate to assume that loss of patency is equivalent to baseline utility value of symptomatic patients.

The trial-based QoL data was not used in the economic model except for using baseline EQ-5D data for the trial population as the utility for loss of patent health state.

The utility values for CLI and amputation health states were based on a time trade-off study conducted in 1996.¹⁴ This study reported a utility of 0.35 for CLI, 0.61 for below-the-knee and 0.20 for above-the-knee amputation. The commentary considers the CLI utility value reported in this study is comparatively low. Hence, this value was not used in other economic evaluations. Some studies used a utility value of 0.6 for the CLI state.³ The amputation health state of the ADAR did not specify below the knee or above the knee but used the utility value for below-the-knee amputation. Of note, the value of 0.61 used in the ADAR for amputation health state is in line with the other cost-effectiveness analyses.³

- **Healthcare resource use and cost**

The ADAR included MBS utilisation data for stent rate in the SBA arm to calculate procedure cost. As noted earlier, this assumption is not valid. Moreover, the ADAR used 45% in the SBA arm and 0.25 RR in the IVL arm to calculate device costs related to the stent. The commentary noted that this approach overestimates the cost in the SBA arm (stent costs \$232.09 in the IVL arm and \$928.35 in the SBA arm).

Furthermore, the ADAR calculated device cost for stent using the cost (\$2,063) for drug-eluting stent (DES) in the Prescribed List of Medical Devices and Human Tissue Products. However, the commentary noted that in the DISRUPT PAD III study, bare-metal stents (BMS) accounted for 91.4% of all stents utilised across PTA and IVL arms (PTA: 89.3% vs IVL: 100%), and all stents used in conjunction with DCB treatment were BMS. The BMS in the Prescribed List of Medical

¹² Dua, A., & Lee, C. J. (2016). Epidemiology of Peripheral Arterial Disease and Critical Limb Ischemia. *Techniques in Vascular and Interventional Radiology*, 19(2), 91-95.

¹³ Clemens, S., Begum, N., Harper, C., Whitty, J. A., & Scuffham, P. A. (2014). A comparison of EQ-5D-3L population norms in Queensland, Australia, estimated using utility value sets from Australia, the UK and USA. *Qual Life Res*, 23(8), 2375-2381.

¹⁴ Sculpher, M., Michaels, J., McKenna, M., & Minor, J. (1996). A Cost-Utility Analysis of Laser-Assisted Angioplasty for Peripheral Arterial Occlusions. *International Journal of Technology Assessment in Health Care*, 12(1), 104-125.

Devices and Human Tissue Products cost \$1,299 (10.01.01 - Bare Metal Stents Peripheral vascular bare metal stents). Therefore, including stent cost based on DES incur a higher cost to both the SBA and IVL arms. Of note, this higher cost affects the SBA arm predominantly as the rate of stent procedures is based on the MBS utilisation data for the SBA arm.

The ADAR did not clearly state that the IVL device cost is for the consumables (IVL catheter) only or in combination with the IVL generator and connector cables (reusable).

The monitoring frequency for each health state was sourced from the study by Venermo et al.¹⁵ However, the commentary noted that this study provided the surveillance recommendation after endovascular treatment for PAD in lower extremities related to IC and CLI. Furthermore, monitoring frequencies included in the model differed from the recommendations provided in the cited paper.

Scenario analysis:

The ADAR presented a scenario analysis for the PICO set 1 (IVL and SBA as stand-alone treatments). The ADAR did not provide the scenario used for the analysis, except the assumption provided in ADAR related to the fact that 55% of patients will use IVL as a vessel preparation strategy.

The transition probabilities for the scenario analysis where IVL is used as a stand-alone treatment were sourced from the DISRUPT PAD II study, a single-arm clinical trial with the longest follow-up duration for this indication. The rate of stenting was based on the rate of flow-limiting dissections requiring stent from the DISRUPT PAD II trial in the IVL arm (1.7%). The rate of stenting in the SBA arm was based on data from Australian clinical practice (45%). This was considered a loss of primary patency in the first cycle. For subsequent cycles, loss of patency was sourced from the DISRUPT PAD II study.

For cost calculations, the ADAR assumed no subsequent treatment with DCB during the index procedure. As such, the cost of the DCB device is not included in the scenario analysis for PICO set 1. However, stent costs are included in the SBA arm per Australian utilisation. In the IVL arm, stent costs are included for the small proportion of people who experience a flow-limiting dissection in the DISRUPT PAD II study (1.7%). As in the base case analysis, the stent procedure rate was applied to calculate procedure and device costs. The cost of subsequent procedures and monitoring by the health state are the same as for the main analysis. Hence, the issues identified in the base case analysis also applied to the scenario analysis.

The commentary noted that the rate of stenting in the SBA arm based on the MBS utilisation data is inappropriate, as discussed earlier. The input of the rate of stent procedures in the SBA arm based on MBS data (45%) and the rate of stent procedures for IVL based on trial data results in a favourable ICER for the IVL arm despite the rate of stent procedures not being relevant for the IVL as a stand-alone procedure (PICO set 1). Hence, this analysis is not appropriate.

¹⁵ Venermo, M., Sprynger, M., Desormais, I., Björck, M., Brodmann, M., Cohnert, T., Aboyans, V. (2019). Follow-up of patients after revascularisation for peripheral arterial diseases: a consensus document from the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases and the European Society for Vascular Surgery. *Eur J Prev Cardiol*, 26(18), 1971-1984.

Results of the trial-based cost consequence analysis

The results of the trial-based CCA are presented in Table 22. The ADAR claimed that the IVL was associated with an incremental cost of \$redacted per patient for the procedure and an incremental cost of \$redacted overall over two years (Table 8).

Table 8: Results of the cost consequence analysis over two years

Description	IVL	SBA	Incremental
Costs			
IVL (MBS fee)	\$736.25	\$0.00	\$736.25
IVL (catheter)	\$ redacted	\$0.00	\$ redacted
Angioplasty or stent insertion (MBS fee)	\$85.12	\$693.81	-\$608.69
Stent (device)	\$232.09	\$928.35	-\$696.26
DCB (device)	\$798.75	\$495.00	\$303.75
Hospital stay	\$2,111.03	\$2,645.74	-\$534.72
Subsequent treatment (TLR)	\$633.53	\$1,056.18	-\$422.65
Amputation (initial)	\$50.93	\$52.66	-\$1.73
Patent	\$471.53	\$298.15	\$173.38
Off patent	\$450.25	\$1,062.89	-\$612.64
CLI	\$122.72	\$126.86	-\$4.15
Amputation (ongoing)	\$7.13	\$7.38	-\$0.25
Total cost overall over two years	\$ redacted	\$7,367.01	\$ redacted
Outcomes			
Provisional stents at the procedure (trial-based)	4.6%	18.3%	-13.7%
Provisional stents performed (Australian practice based on trial RR)	11.3%	45.0%	-33.8%
Dissections	18.5%	32.3%	-5.4%
Flow-limiting dissections	1.4%	6.8%	-17.0%
Primary patency progression	29.6%	46.6%	-1.7%
MAEs	0.0%	1.7%	-13.7%

Abbreviations: CLI = critical limb ischaemia; DCB = drug-coated balloon; IVL = intravascular lithotripsy; MBS = Medicare Benefits Schedule, RR = relative risk; SBA = standard balloon angioplasty; TLR = target limb revascularisation; MAEs = major adverse events

The commentary noted that the cost calculations for the angioplasty or stent insertion (MBS fee) and the stent (device) cost were based on MBS utilisation data instead of the stenting probabilities reported in the DISRUPT PAD III trial. Hence, CCA presented here is not relevant for the trial-based analysis, and therefore, the results are uncertain.

The commentary noted that there was double counting in the CCA as the incremental cost of IVL vs SBA, inclusive of various procedure costs, were compared against outcomes specified in terms of avoiding those same procedures.

Therefore, the commentary conducted an additional analysis to explore the possibility of providing cost-effectiveness analysis (CEA) and an ICER to provide more clarity. The additional analysis included a stepped economic evaluation based on the following outcomes:

- Provisional stents avoided relevant to the 30-days
- CD-TLR and restenosis avoided at 2 years

The additional CEA was based on DISRUPT PAD III trial data with the probability of provisional stenting being 4.6% in the IVL arm vs 18.3% in the SBA arm.

Stenting cost was not included in the CEA that was based on the provisional stent outcome to avoid double counting. However, the cost of stenting was used in the CEA related to CD-TLR and restenosis avoided at 2 years.

The ADAR included DCB (device) cost based on the percentage of patients who require DCB other than the stent (\$900 DCB device cost*(100-11.3)% and the 11.3% was the rate of stenting based on provisional stents performed (Australian practice based on trial RR). The DISRUPT PAD III RCT evaluated IVL and SBA as a vessel preparation strategy prior to DCB and/or stent. For the 35 patients (28 PTA, 7 IVL) who received stents, the stent placement occurred with 15 stents placed prior to DCB treatment and 20 stents placed after DCB treatment.¹ Therefore, the analysis conducted during evaluation included DCB cost regardless of stent insertion.

MBS costs for IVL and SBA arms were calculated based on the weighted average of relevant MBS items. Table 9 summarises the additional CEA analysis performed during the evaluation.

Table 9: Commentary CEA performed during the evaluation

Provisional stents avoided (30 days)			
Costs	IVL	SBA	Incremental
IVL (MBS) ^a	\$736.25	\$0.00	\$736.25
IVL (device)	\$ redacted	\$0.00	\$ redacted
SBA (MBS) ^b	\$0	\$642.41	-\$642.41
DCB	\$900.00	\$900.00	\$0.00
Total	\$ redacted	\$1,542.41	\$ redacted
Outcomes	IVL	SBA	Incremental
Provisional stents at 30 days	4.6%	18.3%	-13.7%
CD-TLR and restenosis avoided (two years)			
Costs	IVL	SBA	Incremental
IVL (MBS)	\$736.25	\$0.00	\$736.25
IVL (device)	\$ redacted	\$0.00	\$ redacted
SBA and stent insertion (MBS) ^c	\$34.62	\$663.31	-\$628.69
Stent	\$94.39	\$377.54	-\$283.16
DCB	\$900	\$900	\$0.00
Total	\$ redacted	\$1,940.85	\$ redacted
Outcomes	IVL	SBA	Incremental
CD-TLR at 2 years ^d	8.5%	8.8%	-0.3%
Restenosis at 2 years ^e	17.0%	23.7%	-5.7%

Abbreviations: CD-TLR = clinically driven target lesion revascularization; DCB = drug-coated balloon; IVL = intravascular lithotripsy; SBA = standard balloon angioplasty; MAEs = major adverse events, MBS = Medicare Benefits Schedule

Notes: Device costs were modified, and trial-based percentages were used for the rate of stents.

^a IVL MBS item fee included associated balloon dilatation as well.

^b SBA (MBS) cost was based on the weighted average of MBS fee for items 35300 and 35303

^c SBA and stent insertion (MBS) cost was based on the weighted average of the MBS fee for items 35306 and 35309

^d Subjects with provisional stenting at procedure are not included

^e Subjects with provisional stenting at the procedure or CD-TLR are not included.

The additional CEA in the commentary showed that the IVL was associated with an incremental cost of \$redacted and 13.7% provisional stent avoided (\$redacted /stent avoided), and \$redacted (undiscounted) for 0.3% CD-TLR avoided in 2 years (\$redacted /CD-TLR avoided) and 5.7% restenosis avoided in 2 years (\$redacted /restenosis case avoided).

Results of the base-case economic evaluation

The base-case economic evaluation is related to the PICO set 2. The ADAR reported that treatment with IVL compared with SBA resulted in an ICER of \$ redacted /QALY. Table 10 summarises the results of the base case analysis.

Table 10: Results of the base case economic evaluation

Parameter	IVL	SBA	Increment
Costs	\$ redacted	\$17,064.47	\$ redacted
Life years	NA	NA	NA
QALYs	5.61	5.45	0.16
Incremental cost per life year gained			NA
Incremental cost per QALY gained			\$ redacted

Abbreviations: IVL = intravascular lithotripsy; NA = not applicable; QALY = quality-adjusted life year; SBA = standard balloon angioplasty

The commentary noted that the estimated ICER for PICO set 2 is highly uncertain due to the following issues:

- The model structure presented in the CUA did not accurately represent the PAD disease pathways.
- The ADAR did not use the baseline rate for stenting from the DISRUPT PAD III trial but rather used MBS data that is not specific to the PICO population and applied the RR from the trial, overestimating the percentage of stenting avoided with the use of IVL.
- The 30-year time horizon used in the model is too long for this population given that the starting age in the model is 72 years.
- The ADAR assumed baseline utility values from the DISRUPT PAD III RCT to represent the health state for loss of patency.

Results of the Scenario Analysis

The scenario analysis is relevant for the PICO set 1. The ADAR reported an ICER of \$redacted/QALY with treatment of IVL compared to SBA. Table 11 provides a summary of scenario analysis results.

Table 11: Results of the scenario analysis

Parameter	IVL	SBA	Increment
Costs	\$ redacted	\$17,314.14	\$ redacted
Life years	NA	NA	NA
QALY	5.41	5.34	0.07
Incremental cost per life year gained			NA
Incremental cost per QALY gained			\$ redacted

Abbreviations: IVL = intravascular lithotripsy; NA = not applicable; QALY = quality-adjusted life year; SBA = standard balloon angioplasty

The commentary noted that the estimated ICER for PICO set 1 is highly uncertain due to:

- As discussed under the base case analysis, the model structure presented in the CUA did not accurately represent the PAD disease pathways, and the time horizon is too long for this population.
- The scenario analysis included the rate of stenting (1.7%) in the IVL arm obtained from the DISRUPT PAD II single-arm trial compared with a rate of 45% obtained from MBS utilisation data in the SBA arm that is not specific to this population.

Uncertainty analysis: Model inputs and assumptions

The ADAR performed a sensitivity analysis based on several model input parameters: the rate of stenting in the SBA and IVL arms, the cost of IVL and utility values used in the patency and loss of patency health states. The ADAR stated that the ICER remains cost-effective in all sensitivity analysis scenarios. However, no justifications were provided for the ranges used in the different parameters in sensitivity analysis. Table 12 summarise the key drivers of the model.

Table 12 Key drivers of the model

Description	Method/Value	Impact Base case: \$ redacted /QALY gained
Extrapolation	Treatment effect continued beyond the 24-month trial period for up to 30 years, and the rate of patency loss is constant after 2 years.	High, favours IVL Using a time horizon of 10 years increased the ICER to \$ redacted /QALY gained.
Rate of stenting in the SBA and IVL arms	Rate of stenting based on MBS data for SBA arm and RR of 0.25 IVL arm based on trial data	High, favours IVL The use of a stent rate based on trial data for both arms increased the ICER to \$ redacted /QALY gained.
SBA index procedure cost	SBA index procedure used the rate of stenting based on MBS data to obtain the procedure fee as well as calculate the device cost for the stents	High, favours IVL
Cost of IVL	Cost of IVL based on proposed MBS fee and device cost.	High, favours SBA

Abbreviations: ICER = incremental cost-effectiveness ratio; IVL= Intravascular lithotripsy; QALY = quality-adjusted life year; RR = Relative risk; SBA = Standard balloon angioplasty

As the costs and utilities are a key issue in the economic evaluation, Tables 13 and 14 provided the disaggregated costs and outcomes associated with the base case results, respectively.

Table 13: Disaggregated costs associated with IVL and SBA over the 30-year time horizon

Description	IVL	SBA	Incremental
<i>Costs</i>			
IVL (MBS fee)	\$736.25	\$0.00	\$736.25
IVL (catheter)	\$ redacted	\$0.00	\$ redacted
Angioplasty or stent insertion (MBS fee)	\$85.12	\$693.81	-\$608.69
Stent (device)	\$232.09	\$928.35	-\$696.26
DCB (device)	\$798.75	\$495.00	\$303.75
Hospital stay	\$2,111.03	\$2,645.74	-\$534.72
Subsequent treatment (TLR)	\$1,207.26	\$1,409.24	-\$201.97
Amputation (initial)	\$1,222.71	\$1,246.92	-\$24.20
Patent	\$815.78	\$474.51	\$341.27
Off patent	\$3,600.86	\$5,080.47	-\$1,479.62
CLI	\$2,733.71	\$2,787.72	-\$54.01
Amputation (ongoing)	\$1,274.92	\$1,302.71	-\$27.79
TOTAL	\$ redacted	\$17,064.47	\$ redacted

Abbreviations: CLI = critical limb ischaemia; DCB = drug-coated balloon; IVL = intravascular lithotripsy; MBS = Medicare Benefits Schedule; SBA = standard balloon angioplasty; TLR = target limb revascularisation.

The commentary noted that the differences in the costs between IVL and SBA are due to inaccurate assumptions (Assuming a 45% rate of stent for the SBA arm based on the MBS utilisation data).

Table 14: Disaggregated QALYs associated with IVL and SBA

Health state	IVL	SBA	Increment
Patent	2.626	1.480	1.145
Off patent	2.366	3.338	-0.972
CLI	0.556	0.567	-0.011
Amputation	0.066	0.068	-0.001
TOTAL	5.614	5.453	0.161

Abbreviations: CLI = critical limb ischaemia; IVL = intravascular lithotripsy; QALY = quality-adjusted life year; SBA = standard balloon angioplasty

Table 14 shows that the inaccurate assumption of the transition probability of loss of patency for cycle 1 for the SBA arm based on MBS utilisation data is driving the difference in QALY.

The results of key univariate sensitivity analyses provided in the ADAR are summarised in Table 15 (italics denote the additional sensitivity analysis performed during the evaluation).

Table 15: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$ redacted	0.16	\$ redacted
Discount rate (base case 5%)			
Discount rate 0%	\$ redacted	0.20	\$ redacted
Discount rate 3.5%	\$ redacted	0.17	\$ redacted
Time horizon (base case 30 years)			
Time horizon 20 years	\$ redacted	0.16	\$ redacted
Rate of stenting in SBA arm (base case 45%)			
Rate of stenting in SBA arm +10%	\$ redacted	0.19	\$ redacted
Rate of stenting in SBA arm -10%	\$ redacted	0.13	\$ redacted
RR of stenting in IVL arm (base case 0.25)			
RR of stenting in IVL arm +0.1	\$ redacted	0.14	\$ redacted
RR of stenting in IVL arm -0.1	\$ redacted	0.18	\$ redacted
RR of progression to CLI (base case 0.9)			
RR progression to CLI of 1.0	\$ redacted	0.15	\$ redacted
RR progression to CLI of 0.8	\$ redacted	0.18	\$ redacted
Loss of patency utility (base case 0.74 based on baseline trial data)			
Loss patency utility 0.70	\$ redacted	0.21	\$ redacted
IVL index procedure costs (base case \$8913.23)			
IVL index procedure costs +10%	\$ redacted	0.16	\$ redacted
IVL index procedure costs -10%	\$ redacted	0.16	\$ redacted
SBA index procedure costs (base case \$4762.90)			
SBA index procedure costs +10%	\$ redacted	0.16	\$ redacted
SBA index procedure costs -10%	\$ redacted	0.16	\$ redacted
Sensitivity analysis performed during the commentary			
<i>Assuming a time horizon of 10 years</i>	\$ redacted	0.15	\$ redacted
<i>Patency utility 0.82 based on the Australian value set (base case 0.85 based on the USA value set)</i>	\$ redacted	0.12	\$ redacted
<i>Using the rate of stent insertion from the trial 18.3% in the SBA arm and 4.6% in the IVL arm)</i>	\$ redacted	0.09	\$ redacted
Multivariate analysis			
<i>Assuming a time horizon of 10 years, patency utility of 0.82, and using the rate of stent insertion from the trial</i>	\$ redacted	0.06	\$ redacted

Abbreviations: ICER = incremental cost-effectiveness ratio; IVL = intravascular lithotripsy, QALY = quality-adjusted life year, RR = relative risk, SBA = standard balloon angioplasty.

The rate of stent insertion is one of the major factors driving the economic model and creating a lower ICER. The additional sensitivity analysis performed during the commentary showed that the use of stenting rate from the DISRUPT PAD III RCT (18.3% in the SBA arm and RR of 0.25 for the IVL arm) increased the ICER from \$ redacted (base case) to \$ redacted /QALY gained. The multivariate sensitivity analysis conducted by the commentary showed that using a time horizon of 10 years, patency utility of 0.82, and trial-based stenting rate increased the ICER to \$ redacted /QALY.

14. Financial/budgetary impacts

The ADAR presented a financial impact analysis based on a market share approach to estimate the net costs of the proposed MBS listing of IVL. This is appropriate, considering the IVL is expected to replace or supplement existing MBS items for lower limb PAD endovascular revascularisation.

The financial implications to the MBS resulting from the proposed listing of IVL are summarised in Table 16. The net cost to the MBS is expected to be minimal, with a net cost of \$ **redacted** in Year 1 growing to \$ **redacted** in Year 6. The net cost to all budgets starts at \$ **redacted** in Year 1 and is expected to increase to \$ **redacted** by Year 6.

Table 16: Overall financial impact of IVL listing over 6 years

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
PICO set 1						
Estimated use and cost of the proposed health technology						
Number of people eligible for IVL	redacted	redacted	redacted	redacted	redacted	redacted
Number of people who receive IVL	redacted	redacted	redacted	redacted	redacted	redacted
Cost to the MBS (with appropriate copayments excluded)	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Change in use and cost of other health technologies						
Change in use of SBA and stent insertion	redacted	redacted	redacted	redacted	redacted	redacted
Net change in costs to the MBS (with appropriate copayments excluded)	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Net financial impact to the MBS (PICO set 1)	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
PICO set 2						
Estimated use and cost of the proposed health technology						
Number of people eligible for IVL	redacted	redacted	redacted	redacted	redacted	redacted
Number of people who receive IVL	redacted	redacted	redacted	redacted	redacted	redacted
Cost to the MBS (with appropriate copayments excluded)	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Change in use and cost of other health technologies						
Change in use of angioplasty services	redacted	redacted	redacted	redacted	redacted	redacted
Net change in costs to the MBS (with appropriate copayments excluded)	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Net financial impact to the MBS PICO set 2	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Overall financial impact of IVL listing over 6 years						

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
Net financial impact to the MBS	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Net financial impact to other health budgets						
Net hospitalisation cost of IVL listing	-\$ redacted	-\$ redacted	-\$ redacted	-\$ redacted	-\$ redacted	-\$ redacted
Net device cost of IVL listing	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Net Prescribed List of Medical Devices and Human Tissue Products cost of IVL listing	-\$ redacted	-\$ redacted	-\$ redacted	-\$ redacted	-\$ redacted	-\$ redacted
Net patient cost of IVL listing	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Net financial impact to other health budgets	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted
Overall net financial impact	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted	\$ redacted

Abbreviations: IVL = intravascular lithotripsy, MBS = Medicare Benefits Schedule, SBA = standard balloon angioplasty

Overall, the commentary considers that the financial estimates are subject to several uncertainties (for instance overestimating utilisation and also overestimating the number of stents avoided), based on the following observations:

- MBS utilisation data for MBS item numbers 35300, 35303, 35306, and 35309 were used to calculate PAD procedure market growth and project utilisation over 6 years. These MBS items are not confined to the peripheral arteries.
- The ADAR calculated the annual growth rate based on total procedures for MBS items 35300, 35303, 35306, 35306 and then used data from The DISRUPT PAD III OS study to allocate proportion for PICO sets 1 and 2. However, only MBS items 35300 and 35303 are relevant for the PICO set 1 (stand-alone procedure).
- The expected uptake estimated by the applicant is uncertain. The ADAR assumed a 15%-50% uptake over six years to calculate PAD procedure market growth and project utilisation. The assumed 15%-50% uptake rates were based on experience in overseas markets and similar technologies, but data were not provided in the ADAR to support these estimates. Sensitivity analysis suggests the financial results are sensitive to plausible variations in key assumptions, particularly the uptake rate of IVL.
- The ADAR included a risk ratio of 25% based on the DISRUPT PAD III RCT to estimate the number of stent procedures prevented due to IVL listing from 1st month, which may not reflect the difference in stenting rates in the longer term and could have overestimated stents avoided. Therefore, the ADRA overestimated the cost saving due to stents avoided.
- The ADAR added the number of avoided stent procedures to the number of DCB procedures to calculate the total number of stent and angioplasty procedures after listing IVL. This was based on the assumption that the patients with avoided stent procedures after IVL listing will instead receive treatment with IVL followed by DCB. This assumption was not adequately supported by the literature, with the exception of the DISRUPT PAD III RCT which found that the patients who did not receive stents were treated with DCB. This RCT was designed to evaluate IVL as a vessel preparation strategy. Hence, the assumption is not valid in Australian clinical practice.
- The ADAR incorporated the price of DES in the Prescribed List of Medical Devices and Human Tissue Products to calculate the device cost. This is more expensive compared to the BMS. The DISRUPT PAD III RCT reported that the BMS accounted for around 91% of stents used in the SBA and IVL arms.
- Sensitivity analyses by the ADAR suggest that the financial results are sensitive to plausible variations in key assumptions, particularly the uptake rate of IVL.

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- Very low numbers of adverse events were seen in studies supporting both PICO set 1 (intravascular lithotripsy (IVL) used as a stand-alone treatment) and PICO set 2 (IVL used as a vessel preparation strategy). There was no comparative safety evidence available to support IVL as a stand-alone treatment (PICO set 1). Comparative evidence suggests that IVL is associated with non-inferior safety compared to standard balloon angioplasty (SBA), when used as a vessel preparation strategy (PICO Set 2).
- ESC accepted the evidence based on one randomised controlled trial and one single arm study that IVL is associated with superior efficacy when compared to SBA when used as a vessel preparation strategy (PICO set 2). IVL appears to be non-inferior to SBA when used as a stand-alone treatment (PICO set 1), but the evidence is weak and based on non-comparative data only.

Economic issues:

- The economic model structure presented in the cost-utility analysis which adapts the the Simpson et al. (2014) model¹⁶ did not accurately represent peripheral artery disease (PAD) clinical pathways as it replaces the state of asymptomatic disease with patency and intermittent claudication with loss of patency. The health states in the model should be updated to reflect clinical practice and the Simpson model; and to distinguish between the PICO set 1 and PICO set 2 populations given that the available evidence differs for each and PICO set 2 only reflects 5% of the target population.
- The ADAR did not use the baseline rate for stenting from the DISRUPT PAD III trial, but instead used MBS data that are not specific to the PICO population and applied the relative risk from the trial. This potentially overestimates the percentage of stenting avoided with the use of IVL compared to SBA.

Financial issues:

- The financial estimates are uncertain, as the uptake rate of 15–50% over 6 years was based on assumptions and not on evidence presented.
- The annual utilisation growth for both PICO set 1 and PICO set 2 was calculated using MBS data that are broader than what is applicable to PICO set 1.

Other relevant information:

- Providers include trained vascular surgeons and interventional radiologists. No additional specialised training is required, although providers may still require IVL device-specific training.
- MSAC may wish to consider whether there should be one MBS item that can be claimed once per limb per occasion of service, rather than an MBS item for multiple limbs or multiple MBS

¹⁶ Simpson, E., Kearns, B., Stevenson, M., Cantrell, A., Littlewood, C., & Michaels, J. (2014). Enhancements to angioplasty for peripheral arterial occlusive disease: systematic review, cost-effectiveness assessment and expected value of information analysis. *Health Technology Assessment*, 18(10).

items to reflect the number of arteries. At the same time the application of the Multiple Operation Rule in such a scenario may create perverse incentives.

- Frequency restrictions in the item descriptor would be inappropriate because PAD is a multivessel disease and so a patient may require more than one IVL procedure in the same year,
- It may be appropriate to include the fluoroscopy service, which was not currently included in the proposed MBS item, in the IVL service rather than having it co-claimed as a separate service.

ESC discussion

ESC noted that this application was for Medicare Benefits Schedule (MBS) listing of intravascular lithotripsy (IVL) for the treatment of moderately or severely calcified peripheral artery disease (PAD).

PAD is a manifestation of systemic atherosclerotic disease, which primarily affects the arteries supplying the legs and feet. It is a major contributor to mortality and morbidity in Australia, and accounted for 0.5% of all hospitalisations in 2020–21. Calcification in PAD is associated with a reduction in the effectiveness of endovascular therapies used to treat PAD, such as standard balloon angioplasty (SBA) and drug-coated balloon (DCB) therapy, by increasing risk of complications and reduced long-term patency. Thus, ESC accepted that there was a clinical need for a treatment option that effectively modifies vascular calcium and improves rates of procedural success.

ESC noted that there was no consumer feedback for this application.

ESC noted that there were two populations: PICO set 1 was for patients requiring IVL as a standalone treatment using an IVL catheter and IVL device, and PICO set 2 was for patients requiring IVL as a vessel preparation strategy followed by DCB and/or stent insertion. ESC noted that the available evidence shows that IVL is more commonly used with other adjunctive therapies such as SBA, DCB, stent insertion and atherectomy, rather than being used 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).¹⁷ ESC noted that, although most of the evidence supports PICO set 2, the applicant claimed that in practice about 95% of patients would fall into PICO set 1. ESC also noted that DCB has largely replaced SBA in current clinical practice.

ESC noted the proposed MBS item descriptor. ESC agreed with PASC that there should be one MBS item that can be claimed once per limb per occasion of service, rather than proposing an MBS item for multiple limbs or having multiple items to reflect the number of arteries. This was based on advice from the applicant's clinical expert who acknowledged IVL could be performed on multiple arteries of the same arterial segments of the same limb during a single procedure. However, ESC noted that the Multiple Operation Rule would apply, which could initiate perverse incentives to perform surgeries on each leg at different times.

ESC noted that the applicant's clinical expert indicated that frequency restrictions would be inappropriate as PAD is a multivessel disease. ESC agreed that there is a possibility that a patient

¹⁷Vedani et al. (2023). [Intravascular lithotripsy: a powerful tool to treat peripheral artery calcifications](#). *J Cardiovasc Surg (Torino)* 64(4):406–12.

may require more than one IVL procedure in the same year, so there should be no frequency restrictions.

ESC noted that the proposed MBS item descriptor did not restrict the service to lower limbs only. ESC considered that this is appropriate because the Australian Register of Therapeutic Goods does not specify whether IVL should be restricted to upper or lower limb(s).

ESC noted that the fluoroscopy service was not currently included in the proposed MBS item. However, ESC considered it appropriate to include it in the IVL service, rather than co-claiming it as a separate service. In addition, ESC considered it appropriate to include co-claiming restrictions with angioplasty items (items 35300 and 35303), as the proposed IVL MBS item should replace these services.

ESC noted that the applicant proposed a fee between \$685.05 and \$736.25 for IVL, based on the current fees for peripheral atherectomy (MBS item 35312) and standard balloon angioplasty (MBS item 35300). The applicant considered these procedures to be comparable to the proposed service because of the similar skill level required.

ESC noted that the clinical trials used the Rutherford classification as inclusion criteria, but that this classification is not used clinically. ESC agreed with PASC that defining the population for PAD in terms of “moderately or severely calcified lesions” without reference to a classification system is acceptable, given that there is no specific classification system to decide on the patient's eligibility for IVL treatment in clinical settings.

ESC noted the proposed clinical management algorithm, which proposed IVL as a standalone treatment (PICO set 1) and as an additional treatment in the current clinical pathway (PICO set 2).

ESC noted the trials available (DISRUPT PAD I, DISRUPT PAD II, DISRUPT BTK) to inform PICO set 1 were single arm studies only. PICO set 2 was supported by a prospective, multicentre, single-blind, randomised study of IVL treatment used in combination with DCB versus SBA to treat moderate and severely calcified femoropopliteal arteries and one prospective single arm study (DISRUPT PAD III, DISRUPT PAD III OS).

ESC noted that, for PICO set 1, there was weak evidence for comparative effectiveness of IVL used as a standalone treatment when compared to SBA and weak evidence for non-inferior safety due to the lack of comparative trials. For PICO set 2, ESC accepted the evidence that IVL is associated with:

- superior effectiveness compared to SBA when used as a vessel preparation strategy before DCB or stent insertion (as a result of improved acute procedural success, reducing the requirement for bailout stent insertion)
- non-inferior safety when compared to SBA when used as a vessel preparation strategy before DCB or stent insertion
- non-inferior long-term safety (up to 2 years) compared to SBA, highlighted by the absence of major adverse events, thrombus and distal emboli events in all patients treated with IVL.

ESC noted that the applicant-developed assessment report (ADAR) originally conducted a cost-consequence analysis (CCA) as well as a cost utility analysis (CUA) for the economic evaluation, however ESC agreed with the commentary that the outcomes presented in the CCA are the same outcome measures used in the CUA and that the CUA was the most appropriate in this case to inform MSAC decision-making. The applicant accepted the CUA as the main decision-making model. In addition, the applicant reduced the time horizon to 15 years (from 30 years) and altered the utility estimates to reflect Australian values.

However despite these changes ESC noted that there were some remaining features of the economic evaluation which limit its usefulness for MSAC decision-making, The ADAR's model adapts the Simpson et al. (2014) model¹⁸, but replaces the state of asymptomatic disease with patency and intermittent claudication with loss of patency. ESC noted that the commentary queried whether this approach may misrepresent clinical pathways. The applicant stated in the pre-ESC response that while there is no established correlation between patency and clinical symptoms, it is clinically plausible that symptomatic PAD is associated with patency. However, ESC agreed with the commentary that the original Simpson model was more clinically accurate.

ESC considered that the use of baseline utility values (of 0.74) from the DISRUPT PAD III RCT to reflect quality of life in the 'loss of patency' health state was not appropriate as it assumes that the baseline utility of symptomatic patients was equivalent to that for the 'loss of patency' health state. ESC noted the pre-ESC response stated that the literature identified a similar, alternative utility value for intermittent claudication of 0.7 and the use of this alternative value would reduce the ICER. However, ESC queried the clinical validity of this value, given that as discussed above, the model uses the state of 'loss of patency' and it is unclear whether this can be equated to a state of intermittent claudication.

ESC noted the model did not use the baseline rate for stenting from the DISRUPT PAD III trial; rather, it used MBS data that are not specific to the PICO population and applied the relative risk from the trial. ESC considered that this favours the intervention by overestimating the percentage of stenting avoided with the use of IVL compared to SBA. ESC noted that this was tested in the sensitivity analysis, and the rate of stenting was one of the main drivers of the incremental cost-effectiveness ratio (ICER). ESC also noted that the model used the cost of drug-eluting stents (DES) in the comparator cost rather than bare-metal stents (BMS) used in the trial and the additional cost of the former would tend to favour the intervention.

ESC noted one of the main drivers of the ICER was the rate of stenting, which increased the ICER to \$ **redacted** per QALY when the stenting rate increased to 40.5% for SBA and 23.3% for IVL, compared to the base case ICER of \$ **redacted** (stenting rate of 45% with a relative risk of 0.25 applied). ESC noted that, in one scenario, the ICER increased to \$56,058 when altering the stent insertion rates and using Australian utility values, and ESC considered that this scenario was plausible.

ESC recommended that additional adjustments to the economic modelling would be helpful to MSAC's consideration, specifically:

- Update the health states to reflect clinical practice and the Simpson model.
- Update the model so that the distinction is clear between PICO set 1 and PICO set 2, as the available evidence differs for each of these populations. There is more available evidence for PICO set 2, but according to the applicant this represents only 5% of the target population.

ESC noted that the financial impact was calculated using a market share approach. The net financial impact to the MBS was \$ **redacted** in year 1 to \$ **redacted** in year 6. However, the larger impact is to other health budgets, which increases the overall budget impact to \$ **redacted** in year 1 to \$ **redacted** in year 6. ESC considered there to be a relatively modest impact to the MBS, but noted that there are uncertainties:

- The budget impact relies on assumed uptake of between 15% and 50% over time, which is not based on any evidence presented.

¹⁸ Simpson, E., Kearns, B., Stevenson, M., Cantrell, A., Littlewood, C., & Michaels, J. (2014). Enhancements to angioplasty for peripheral arterial occlusive disease: systematic review, cost-effectiveness assessment and expected value of information analysis. *Health Technology Assessment*, 18(10).

- The ADAR assumed MBS utilisation data for MBS item numbers 35300, 35303, 35306 and 35309 to calculate PAD procedure market growth and project utilisation over 6 years. However, MBS items 35306 and 35309 are not confined to the peripheral arteries. Also, these data are used to estimate PICO set 1 and PICO set 2, although only MBS items 35300 and 35303 are relevant for PICO set 1.
- The estimated stent procedures prevented used a risk ratio of 25% based on the DISRUPT PAD III randomised controlled trial (RCT) from the first month. This may not reflect the difference in stenting rates in the longer term and could overestimate the number of stents avoided.
- The ADAR assumed that the patients who avoid stent procedures after IVL listing will instead receive IVL followed by DCB. This assumption was not adequately supported by the literature, except that, in the DISRUPT PAD III RCT, the patients who did not receive stenting were treated with DCB. Furthermore, as noted previously about the economic model, the ADAR incorporated the price of drug-eluting stents to calculate the stent device cost. This makes the stent device more expensive than the bare metal stent, which favours the intervention.

ESC noted that the sensitivity analysis suggested the key assumptions in the base case favour the intervention, and the financial results are sensitive to plausible variations, particularly the uptake rate of IVL. ESC noted that the main cost driver for IVL is the device itself.

ESC noted that the costs of the IVL generator and consumables were not disaggregated in the application. ESC requested department advise whether patients may potentially incur any out of pocket costs from either the generator or consumables. *[Note: Following ESC, the department confirmed that the cost of the generator is likely to be covered by hospitals as the machine will be used for all patients requiring IVL. However, it is at the discretion of the hospital whether to cover the cost of consumables and therefore patients may potentially incur some out of pocket costs associated with consumables that are not eligible for the Prescribed List of Medical Devices and Human Tissue Products]* ESC noted the applicant claims that significant cost reductions are expected in the hospital budget due to shorter hospital stays resulting from IVL treatment, and in the Prescribed List of Medical Devices and Human Tissue Products due to a decrease in stent insertions.

17. Applicant comments on MSAC's Public Summary Document

Shockwave Medical is encouraged that MSAC recognise the clinical need and effectiveness of IVL over current standard of care. Shockwave Medical will work continue to work with MSAC and the Department so that IVL can be more widely available for patients through the MBS.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)