South Australian Policy Advisory Committee on Technology (SAPACT)

Health Technology Assessment (HTA) Decision Summary Update

Government of South Australia

SA Health

Shockwave intravascular lithotripsy for the treatment of severe calcified arterial lesions and stent under-expansion

SAPACT MEETING DATES	36th and 28th SAPACT Meetings (21 March 2025 and 27 May 2022)
APPLICATION #	2201
TECHNOLOGY	The Shockwave C2+/C2 Coronary intravascular lithotripsy (IVL) System (AA-Med Pty Ltd) combines sound waves with angioplasty to treat calcified plaque in diseased arteries. The system consists of three components: a single-use standard percutaneous transluminal coronary angioplasty balloon catheter, a reusable generator, and a reusable connector cable. The balloon catheter has integrated lithotripsy emitters designed to enhance angioplasty by disrupting calcium before balloon dilation of the stenosis. The lithotripsy pulse waves also facilitate blood passage and enhance the placement of a stent. C2+ catheter is an upgraded version of C2 that has (a) improved deliverability - the catheter design allows smoother navigation through challenging anatomies and (b) enhanced crossability – better at crossing tight, calcified lesions due to refinements in the catheter profile.
TECHNOLOGY CLASSIFICATION	TGA class III high-risk
PATIENT INDICATION (TGA)	The Applicant has requested to use shockwave IVL for both label and off-label indications: (a) TGA intended purpose: Both the Shockwave C2 and C2+ Coronary IVL Systems are indicated for lithotripsy-enhanced, low-pressure balloon dilatation of severely calcified, stenotic de novo coronary arteries prior to stenting (i.e. IVL then stenting) (b) TGA off-label use: Shockwave IVL applied after stent deployment to address stent under-expansion (i.e. stenting, then IVL)

SAPACT DECISION

☒ TGA labelled indication: Recommended for clinical use with no further need for assessment.

☒ TGA off-labelled indication: Restricted recommendation for clinical use subjected to implementation under audit conditions.

2025 SAPACT Advisory Recommendations

Following a comprehensive review of updated international evidence and local outcomes, SAPACT recommends the adoption of shockwave IVL into routine clinical practice across SA Health for the TGA-approved indication of lithotripsy-enhanced, low-pressure balloon dilatation of severely calcified, stenotic de novo coronary arteries prior to stenting. Use of shockwave IVL should be supported by intravascular imaging to ensure appropriate lesion assessment and safe, effective deployment.

For off-label use in treating stent under-expansion, SA Health clinicians are responsible for obtaining informed consent, disclosing the TGA off-label nature of the procedure, and ensuring clinical justification. Given the current limitations in evidence, SAPACT recommends that off-label use should not be used routinely but with caution, strong clinical judgement and under outcomes review. Future SAPACT reviews may be considered as required.

2025 SAPACT Evidence Review Conclusion

Since the previous SAPACT HTA review, no studies had directly compared shockwave IVL with other techniques or assessed its long-term effectiveness. Conventional methods, such as rotational atherectomy, carried risks like vessel injury, positioning shockwave IVL as a potentially safer, non-ablative alternative. High-quality evidence remained limited, with no published results from ongoing direct comparative trials. Most available evidence for shockwave IVL was observational, with studies in both label and off-label stent under-expansion indications showing high procedural success (96-99%) and clinical success (93%), along with low complication rates and favorable safety outcomes, including major adverse cardiac event (MACE) rates ranging from 2% to 11% and no increased cardiovascular risk. While rare complications, such as coronary dissection and perforation, occurred, they were successfully managed. Ongoing comparative trials like DECALCIFY, EMPOWER CAD, and BASIL are crucial for confirming long-term benefits.

2022 SAPACT Advisory Recommendations

SAPACT recommends for the restricted use of shockwave IVL for the treatment of severe calcified arterial lesions and stent under-expansion to three cases per LHN site (SALHN, CALHN and NALHN) in the first year, with a requirement to monitor and report the clinical outcomes back to SAPACT at the completion of three cases at each site.

2022 SAPACT Evidence Review Conclusions

Based on safety and clinical effectiveness, the limited international literature reported that shockwave IVL appeared to be feasible with high procedural success and low MACE rates in patients with severe calcified arterial lesions who are not amenable to other conventional treatments. However, no direct comparative studies (including randomised controlled trials [RCT]) compare shockwave IVL to other alternate interventions. In addition, the current published literature did not report on important patient-oriented outcomes, including physical functions and quality of life. Two studies, each with small sample size, demonstrated the potential of shockwave IVL as a feasible alternative for managing stent under-expansion due to calcific coronary disease. Current findings need confirmation through high-quality, appropriately powered comparative trials with long-term follow-up and reporting of patient-oriented outcomes.

REGULATORY APPROVALS		
☒ **Australia ARTG**: • 425113 Shockwave **C2+** Coronary IVL Catheter - 12/10/2023 • 378470 Shockwave **C2** Coronary IVL Catheter - 22/11/2021 • 320483 Shockwave Ultrasonic lithotripsy system consists of the IVL generator and IVL connector cable, excluding the catheter/transducer– 19/7/2019	☒ **US FDA**: PMA approval P200039: 24/10/2024, Shockwave Intravascular System with the C2/C2+ Coronary IVL Catheter PMA document states the product is commercially available in 15 jurisdictions, including the European Union and New Zealand. Shockwave IVL is off-label in the United States for both restenosis and/or stent under-expansion treatment.	☒ **EU CE mark**: May 2017

QUALITY OF EVIDENCE	
Quality of Evidence	Local consultations and inputs with the Chief Applicant also informed the SAPACT Advisory Recommendations. An updated systematic search was performed and SAPACT considered the February 2025 NICE Guidance and HTA review: IVL for calcified coronary arteries during PCI. The NICE report included 14 sources including 8300 people from 2 systematic reviews and meta-analyses (Sagris 2024 and Caminiti 2023), 1 small RCT (Zou 2024), 9 observational studies and 2 case reports. Key studies for this SAPACT review update were Sagris 2024 (38 studies with 2,977 patients), Caminiti 2023 (for under-expanded stents, 14 studies), and Rodriguez-Leor 2024 (REPLICA-EPIC18 single-arm 30-day follow-up study of 426 patients across 26 hospitals in Spain, including those with acute coronary syndrome). Since the previous SAPACT HTA review, high-quality evidence remained limited, with most published studies being observational (with up to 20 months of follow-up). There were no published results available from direct comparative trials, comparing shockwave IVL with other techniques or assessed its long-term effectiveness. Published results from ongoing comparative trials such as DECALCIFY, EMPOWER CAD, and BASIL are essential for confirming long-term benefits. There was limited reporting of patient-related outcomes such as quality of life and shockwave IVL is still being evaluated in the aorta and chronic complete occlusions. The international evidence for its application in off-label cases for stent under-expansion (Caminiti 2023) is limited and had a short follow-up of 2.6 months. <u>2022</u> A comprehensive systematic search for the best available HTA and policy evidence in 6 published and 24 grey literature sources was conducted. Given that HTA reports and a systematic review were identified (ECRI 2021, and NICE Guidance 2020 and Sattar 2021), a SAPACT Evidence Review was not required. The search did not identify any Level II evidence (RCT). Case series, matched registry data and case reports formed the clinical evidence. The studies were at risk of bias from short-term follow-up, lack of controls, lack of patient-oriented outcomes and industry sponsorship. Wiens 2021 (n=50) is a non-industry-sponsored real-world retrospective case-series with 1-year follow-up in Canada. Shockwave Medical sponsored the following pivotal single-arm trials (case-series): • Disrupt CAD IV study; n=64 (Saito 2021; 30-days). Disrupt CAD IV study is for Japanese regulatory approval of shockwave IVL. • Disrupt CAD III study; n=384 (Kereiakes 2022; 1-year outcome article and Hill 2020; 30-days outcome article). The Disrupt CAD III study was designed for US FDA regulatory approval of shockwave IVL and is the most extensive long-term (1-year) analysis of coronary IVL. • Disrupt CAD II study; n=120 (Ali 2019); Europe • Disrupt CAD study; n=60 (Brinton 2019); Australia and Europe The BASIL RCT trial (ACTRN12620000086965) and the DECALCIFY trial (NCT04960319) are two RCTs pending results publication. Completed in late 2021, the BASIL trial is a Shockwave Medical sponsored RCT (n=60) conducted in New Zealand and compares shockwave IVL plus PCI vs balloon angioplasty plus PCI. The DECALCIFY trial is based in Germany and is ongoing, with a completion date of June 2024. Again, this is a Shockwave Medical supported RCT (n=100) comparing shockwave IVL to rotational atherectomy (RA). **Limited studies for the management of stent under-expansion (off-label)** • Yeoh 2021; n=13 is a case series in the UK. • IntravaScular Lithotripsy for the Management of UndILatable Coronary StEnt (SMILE) Registry; n=34 (Ielasi 2020) is a multicentre, retrospective cohort study in Italy.

CLINICAL NEED	
Burden of Illness	Calcium build-up in coronary arteries narrows blood vessels, increasing the risk of heart disease. Around 20% of patients undergoing PCI have heavily calcified lesions, which make stent placement less effective and increase the risks associated with the procedure.
Need	Traditional methods to treat calcified plaques, such as high-pressure balloons and rotational atherectomy, often lead to complications like vessel injury or artery perforation. Shockwave IVL is marketed as a technology designed to safely prepare heavily calcified coronary arteries. It uses low-pressure sonic waves to modify calcium without generating heat or causing significant vessel damage, potentially reducing complications and improving outcomes. Shockwave IVL may offer safety advantages over traditional methods like atherectomy or balloon angioplasty, which carry higher risks of vessel injury. Shockwave IVL can treat calcified peripheral arteries, either as a standalone treatment or to optimize stent deployment. However, this SAPACT review will focus solely on coronary applications for the Cardiology Departments.

CLINICAL BENEFITS	
Safety	• **Primary safety endpoint:** Shockwave IVL demonstrated low rates of complications (2 - 11% across studies), with MACE rates comparable to alternative therapies. Notably, there is no evidence suggesting an increased cardiovascular risk associated with IVL, even among high-risk populations.

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- **Rare complications**, such as coronary perforation, rupture, and dissection, have been reported; however, all were managed successfully (NICE 2025; Sagri 2024; Caminiti 2023). At 30 days, the MACE rate, defined as death, myocardial infarction (MI), or target vessel revascularization (TVR), was 3% overall—1% in chronic coronary syndrome (CCS) patients and 5% in acute coronary syndrome (ACS) patients (Rodriguez-Leor 2024). Importantly, no major myocardial infarctions were directly attributed to IVL (Wiens 2021; Rodriguez-Leor 2024).
Studies have consistently shown that IVL does not increase the risk of distal embolization when compared to alternative revascularization techniques. Rare complications, including coronary dissections (1%-2%) and balloon ruptures, were observed but did not result in significant sequelae (Caminiti 2023; Aksoy 2019). Additionally, phenomena such as no-reflow or slow-flow were notably absent in the majority of studies.
- **Off-label use for stent under-expansion:** Rate of intra-procedural complications was 1.6% (Caminiti 2023).
- While various modalities (e.g. noncompliant balloons, cutting/scoring systems, rotablation, and shockwave IVL) are available for managing heavily calcified lesions, they are considered complementary for addressing stent underexpansion. Current data suggest IVL is safe for modifying calcified plaques in coronary arteries, though its efficacy in the aorta, chronic total occlusions, and severely calcified stent under-expansion is still under evaluation (Sagris, 2024).

<u>2022</u>

- **Low 30-day MACE rates following IVL (primary outcome):** 0 - 8.3% (ECRI 2021, Disrupt CAD III and IV studies), compared to 10.4 - 15.0% for atherectomy (Saito 2021, only hypothetical as no direct comparative studies available)
- **Low 1-year MACE:** 13.8% (Disrupt CAD III study, Kereiakes 2022), compared to 16.9 - 24.2% for atherectomy (Saito 2021, only hypothetical as no direct comparative studies available) (cardiac death: 1.1%, MI: 10.5%, ischemia-driven target vessel revascularization: 6.0%) and target lesion failure occurred in 11.9% (ischemia-driven target lesion revascularization (ID-TLR): 4.3%), both driven by non-Q-wave MI (9.2%). Stent thrombosis (definite or probable) occurred in 1.1% of patients (including 1 event [0.3%] beyond 30 days).

*MACE: defined as the composite of cardiac death, MI, or ischemia-driven target vessel revascularisation; target lesion failure defined as cardiac death, MI, or ischemia-driven target lesion revascularisation (ID-TLR).

- **Low rates of periprocedural complications/ adverse events:** 0 - 8%, including in patients with acute coronary syndrome, stent failure, and left main coronary artery lesions (Wiens 2021) and 8.33% (Sattar 2021. Patients developed complications such as vessel dissection)
In ECRI 2021, Hill 2020 reported that 2 of 384 patients experienced severe dissection and abrupt closure or perforation. Aksoy 2019 reported that 6 of 39 patients experienced type b dissections or balloon rupture. Ali 2019 and Brinton 2019 reported that 5% to 6% of patients experienced periprocedural myocardial infarctions. Saito 2021 reported no periprocedural complications.
- **Stent under-expansion (off-label):** There is no procedural, periprocedural, or 30-day major adverse cardiac and cerebrovascular event. (Yeoh 2021) No cardiac death, target lesion revascularisation and stent thrombosis occurred in-hospital and at 30-day follow-up. (SMILE Registry, Ielasi 2020) Non-fatal periprocedural ST-elevation myocardial infarction occurred in one case (2.5%) due to IVL balloon rupture. (SMILE Registry, Lelasi 2020)

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Effectiveness

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- **Primary outcome: Procedural Success**
Shockwave IVL demonstrated high procedural success rates, ranging from 96% to 99%, even in heavily calcified lesions (Sagris, 2024; Rodriguez-Leor, 2024). Notably, 49% of lesions in the Rodriguez-Leor (2024) study were initially deemed undilatable. The primary effectiveness endpoint was achieved in 66% of patients, with comparable rates observed in chronic coronary syndrome (CCS) patients (68%) and acute coronary syndrome (ACS) patients (65%). Angiographic success after IVL was similarly high across both patient groups.
- **Clinical success:** 93% at 30-day (Sagris 2024) **and other clinical outcomes:** Shockwave IVL consistently reduced calcification, significantly improving stent placement and vessel compliance. Post-procedural outcomes showed marked improvements in vessel diameter and a reduction in residual stenosis, decreasing from 69.4% to 14.6% (Caminiti 2023, Sagris 2024 and Aksoy 2019).
- **Managing challenging cases**: IVL demonstrated exceptional efficacy in managing challenging lesions, including those unresponsive to other revascularization techniques. Angiographic success rates exceeded 90% in treating complex calcified lesions (Caminiti 2023 and Cubero-Gallego 2022).
- **Off-label use for stent under-expansion** (Caminiti 2023):
  - Procedural success was seen in 88.7% of patients. There is lower procedural success rate associated with left main lesions, due to increased risk of complications during predilatation and the prolonged inflation period needed for lithotripsy balloons. However, the paper viewed that this should not discourage the use of IVL in such cases.
  - Mean minimal stent area was reported in 6 studies, the pre-IVL value was 3.4mm^2,and the post-IVL value was 6.9mm^2.
  - Mean diameter stenosis was reported in 7 studies, the pre-IVL value was 69.4%, and the post-IVL value was 14.6%.

<u>2022</u>

- **High procedural success (primary outcome, defined as residual stenosis <50% by QCA without in-hospital MACE):** 84 - 95% (ECRI 2021), 92.4% (Disrupt CAD III) and 93.8% (Disrupt CAD IV)
- **High rates of angiographic and clinical success:** 98% (Wiens 2021; n=50)
- Longer-term follow-up is required to determine the **durability of clinical benefit** and the **late impact of optimised stent implantation associated with IVL**. (Disrupt CAD III study)
- **Stent under-expansion (off-label):** The average pre-IVL minimal stent area (MSA) was 2.71 mm^2, which improved to 6.44 mm^2

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	post-IVL treatment, representing an average minimal stent area gain of 238%. (Yeoh 2021). IVL was successful in 34 cases (87.1%), with significant improvement in minimal stent diameter and minimal stent cross-sectional area
SUITABILITY OF PATIENT GROUP	
Suitability of Patient Group	The primary target group for shockwave IVL consists of patients with severe calcified coronary lesions that are unresponsive to other calcium modification techniques. Off-label use is also considered for patients experiencing stent under-expansion after failed high-pressure ballooning. While IVL shows the most benefit in cases unsuitable for conventional methods, optimal patient selection remains challenging. Broader adoption risks overuse in cases where alternative treatments may suffice. <u>2022</u> <u>Number of patients per year:</u> 0 - 10 patients (SALHN); 5 - 10 patients (CALHN) and 10 patients (NALHN). The main clinical indication is severe calcified coronary arteries, confirmed through intravascular ultrasound (IVUS) or optical coherence tomography (OCT), requiring PCI due to significant angina or acute coronary syndrome. These patients are not candidates for conventional techniques like rotational atherectomy, high-pressure balloon dilation, or cutting balloons. Clinicians at SALHN and CALHN have expressed interest in using IVL off-label to address stent under-expansion, as evidenced by IVUS, OCT, or coronary angiograms after PCI. A study by Mousa 2021 suggests that IVL could be a promising option for cracking calcium to improve stent expansion. However, this off-label use is not without risks, including potential damage to the drug-polymer coating of the stent, which may increase the likelihood of thrombosis and restenosis. The manufacturer advises against using IVL within 5 mm of previously placed stents. The clinical impact of IVL on drug-polymer coatings remains uncertain and requires further investigation.
FINANCIAL CONSIDERATIONS	
Device costs	[Confidential to be redacted] <u>2025</u> Applicants have confirmed that [redacted] <u>2022</u> <u>Total costs across SA Health per year (first year)</u>: $[redacted] (per catheter consumable; ex GST) x [redacted] patients = $[redacted] <u>Total costs across SA Health per year (second year)</u>: $[redacted]* (per catheter consumable; ex GST) x [redacted] patients + $[redacted] x [redacted] units (generator (capital); ex GST) = $[redacted] *[redacted] (communication with distributor Diverse Devices, 5 April 2022). [redacted] <u>Comparator cost</u>: $[redacted].
Value for Money	Shockwave IVL devices are considerably more expensive upfront than rotational atherectomy and other calcium-modification techniques. However, they may offer long-term savings by improving procedural success, reducing complications, and lowering re-intervention rates (Caminiti 2023, NICE 2025). No studies specifically address the cost-effectiveness of shockwave IVL. Kassimis (2021) highlights the need for such analysis, suggesting IVL may be cost-effective over time due to fewer complications, less need for additional devices, and better long-term outcomes compared to other techniques. Key factors to consider in a comprehensive cost-effectiveness analysis include: • Device costs • Savings from reduced use of additional devices (e.g., fewer specialty balloons or stents). • Costs of re-interventions for target lesion failure. • Complication-related costs. • Hospitalization costs. • Broader impacts on morbidity and mortality. • Lesion characteristics (e.g., calcium depth, vessel size, or lesion location) and contraindications for specific devices also introduce uncertainties, emphasizing the importance of a thorough economic evaluation.
Australian Funding Approvals	Shockwave IVL has not been evaluated for coronary interventions by PLAC or MSAC, with MSAC's most recent assessment focusing only on peripheral artery disease (PAD), resulting in a deferral. <u>Interstate experiences</u> [Confidential to be redacted] Queensland: SAPACT has contacted Queensland Mackay hospital for their implementation outcomes report for [redacted] patients. This report has provided in confidence. Victoria: In [redacted] Other States: The applicant confirmed that shockwave IVL devices are approved for use in centres across Victoria, New South Wales, Western Australia, the Australian Capital Territory, and Tasmania. Feedback from other jurisdictions has not been reported.

	<u>Overseas experiences</u> **Updated NICE Guidance (Feb 2025):** NICE recommends using shockwave IVL as an option to treat calcified coronary arteries during PCI with standard arrangements in place for clinical governance, consent and audit. Clinicians should enter details about everyone having the procedure onto the National Institute for Cardiovascular Outcomes Research (NICOR) database and review local clinical outcomes. There is good quality evidence that this procedure is effective and safe. The evidence shows that calcification is reduced and blood vessel diameter is increased after this procedure, meaning a stent can be more easily inserted. People having this procedure already have a high risk of cardiovascular complications, but there is no Previous NICE Guidance (2020): The evidence for shockwave IVL's safety and efficacy in calcified coronary arteries was deemed limited, necessitating special arrangements for governance, consent, and research before widespread adoption.
FEASIBILITY OF ADOPTION	
Organisational Feasibility	<u>Risk assessment</u> The Applicant stated that the risk is considered to be lower than rotational atherectomy. <u>Patient consent</u> The Applicant proposed that PCI consent encompasses all standard techniques; hence, specific consent for this additive technology is not required. <u>Clinical outcomes evaluation and broader retrospective and prospective audit</u> The SALHN Cardiology department will monitor a register of all cases undertaken together with clinical outcomes. In CALHN, the clinicians will evaluate their data as part of the Coronary Angiogram Database of South Australia (CADOSA) registry. In addition, results will be presented regularly at the Cardiology multidisciplinary meetings and as part of the CADOSA data presentation. Also, SAPACT is to be advised of outcomes.
Credentialing and Competency	The CALHN applicant reported that for PCI trained clinicians, no formal credentialing process exists for shockwave IVL. Unlike atherectomy, which requires extensive training and a high operator volume to achieve favorable outcomes, shockwave IVL is simpler to use, as it is delivered similarly to standard catheter-based PCI (balloon angioplasty). After receiving initial training from the device manufacturer, clinicians can independently perform the procedure without ongoing support. The SALHN applicant noted that the only training required focuses on the protocol for delivering the treatment, including the number of shocks per lesion, intervals, and maximum shocks. Minimal training is needed, with just one roll-in patient required before enrolment. Despite its apparent ease of use, shockwave IVL should only be performed by clinicians with specific training and accreditation. Practitioners must be appropriately credentialed and approved by the SA Health Credentialing and Scope of Practice Committee, following the guidelines outlined in paragraph 3.4.3 of the SA Health Credentialing Policy Directive for new clinical procedures, technologies, and treatments.
CONSISTENCY WITH EXPECTED SOCIETAL/ ETHICAL/ LEGAL VALUES	
Values	Consistent with expected societal, ethical and legal values at this time.
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