National Institute for Health and Care Excellence

IP1758 Intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention

IPAC 16/01/20 & 09/04/2020

1	Consultee 1 NHS professionals on behalf of British Cardiovascular Society and the British Cardiovascular Intervention Society	**General**	The British Cardiovascular Society (BCS) and the British Cardiovascular Intervention Society (BCIS) agree that there are limited data regarding the safety and efficacy of this technology. The data which are available [redacted] do not raise a safety concern with the device. Early experience of its use amongst UK interventional cardiologists also suggests that the device is safe and easy to use. It would appear to be effective in facilitating dilatation of severely calcific coronary artery lesions. Efficacy however is more difficult to demonstrate. Use of rotational atherectomy (rotablation) is the current standard of care for non-dilatable coronary artery lesions. A randomized controlled trial comparing intracoronary lithotripsy with rotablation for lesion preparation in heavily calcified vessels would be desirable. There would, however, be formidable logistic difficulties in performing such a trial because patients with sufficiently severe calcification to require such additional lesion preparation are relatively rare and it is often only possible to determine this need as a case proceeds, making prior informed consent impossible. Choosing appropriate endpoints for such a trial would also be very difficult as intracoronary lithotripsy or rotablation would only ever be a small part of a complex intervention, often in older patients with multimorbidity. Surrogate endpoints such as residual stenosis or post-procedural cardiac biomarker elevation might be feasible, but these might not be very accurate predictors of more meaningful longer-term clinical outcomes. Target lesion	Thank you for your comments. Section 1.1 of the draft guidance has been amended in the light of additional evidence and consultation comments.

			failure during follow-up would probably be the best marker of success or failure of the different approaches. It seems unlikely that such a trial will be performed. We would support the development of a registry which records the details of all cases involving intracoronary lithotripsy. This would help to establish the utility of the device in a UK population. This would need to be funded, potentially by the manufacturer, and may well be costly if applied nationally. In the absence of such a registry however, we would be very concerned if this device became unavailable for NHS use in selected patients. This is because the device has rapidly established itself as a useful tool to overcome particular problems encountered during percutaneous coronary intervention. Specifically, non-dilatable coronary lesions or unexpandable coronary stents. These scenarios cannot be accurately predicted prior to the start of the procedure and must be addressed as and when they arise during the procedure. There are often no other readily available ways to treat such lesions and without intracoronary lithotripsy, patients would potentially be left with suboptimally treated coronary arteries, exposing them to the risk of ongoing ischaemic symptoms, stent thrombosis, myocardial infarction, and restenosis. In conclusion, we recommend that the availability of intracoronary lithotripsy is retained for use in highly selected patients who have specified coronary artery lesion criteria which justify its use in order to facilitate the safe completion of complex procedures thereby reducing the risk of adverse clinical outcomes. This includes calcified, undilatable lesions or stents which are associated with an arc of calcium ≥270 degrees on intravascular imaging. All cases should be included in a UK registry.	

2	Consultee 2 NHS Professional	**1**	I have used IVL in 3 cases to date for calcified vessels especially in native vessels with occluded grafts after CABG. All cases have included heavily calcified native vessels where grafts supplied have occluded. The device is easy to use and has proven safe. There is a need to pre-dilate as much as possible and to use the largest size balloon to deliver the most energy. Once this has been done, dilating with non-compliant balloons has been made much easier to further prepare the vessel prior to stenting. It has revolutionised the treatment of heavily calcified vessels safely and quickly. Imaging is recommended to define calcification, vessel size and result of IVL to optimise results. I recommend continuing to builds experience with this technology, collating data and expanding its use.	Thank you for your comments. IPAC considered the comments regarding your clinical experience of this procedure.
3	Consultee 3 NHS Professional	**General**	My Hospital is a large University Hospital which does not have Cardiac Surgery. It has the Regional:- Trauma Unit, Vascular Unit, Renal Transplant Unit, Burns &Plastics and Neurosurgical Unit. The Cardiology Dept. is medium sized doing 250 PCI a year - too small a number to use Rotablator safely. The patients that come to the Cath Lab often have severe calcification associated with Age, Diabetes and Renal disease and this only becomes apparent once the procedure is underway. We have used IVL on a small number of patients and on each occasion successfully with no complications. It is a safe and effective tool which when used infrequently is uncomplicated and straightforward to use. It is an ideal tool for low volume PCI centres where occasionally unexpected heavily calcified coronary artery disease can be tackled effectively without having to transfer the patient to another centre. This transfer is expensive in time and resources and the patient is vulnerable during it. Had we not had IVL available, the procedure would have been abandoned the patient transferred possibly as an emergency and would have been at risk of sudden deterioration.	Thank you for your comments. IPAC considered the comments regarding your clinical experience of this procedure.

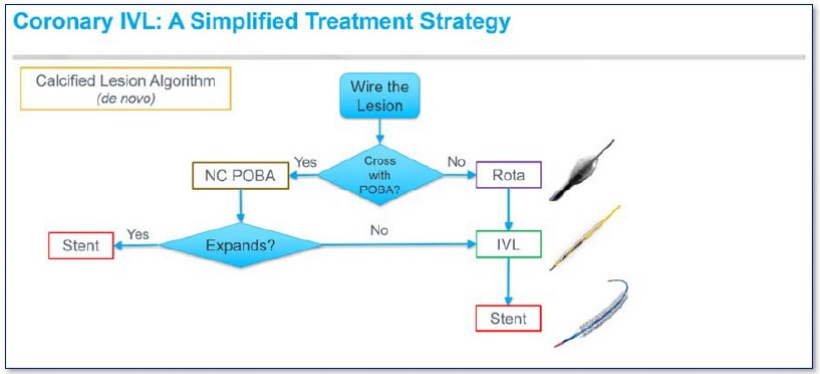
			In general uncomplicated/simple techniques and equipment have a higher success rate and lower complication rate and this seems to be one.	
4	Consultee 4 NHS professionals Interventional Cardiologists at Salisbury District Hospital		Below are the comments of the Interventional Cardiology team (3 Consultants) at [redacted] District Hospital on the draft guidance for coronary intravascular lithotripsy (IVL). We started using this technology in early 2019. Our first case was presented by our Cardiology Registrar at the last TCT meeting in San Francisco, USA. We have now used this technology in 14 patients with severe coronary calcification with no acute complications and no stent failure on follow-up to date. In most of the cases IVL was used because of and subsequent to incomplete NC balloon or scoring balloon expansion. In two cases IVL was used in combination with (after) rotational atherectomy. The majority of these patients had Acute Coronary Syndromes with PCI indicated for prognostic reasons, reducing the risk of subsequent re-myocardial infarction or death. Some of these cases were submitted for presentation at the EuroPCR congress in 2020. With the exception of one patient with eccentric calcification, IVL allowed for full lesion preparation and eventual adequate stent expansion in all patients. We have now treated patients who otherwise wouldn't have been adequately revascularised before IVL was available, given the high risks of incomplete lesion expansion and failed stent delivery. In addition, IVL allowed for better lesion preparation in all but one patient, therefore optimising stent results and reducing the risk procedure failure. Incomplete stent expansion is one of the main risk factors for stent thrombosis / failure. Feedback from patients has been very	Thank you for your comments and sharing your experiences. The focus of this guidance is only Intravascular lithotripsy (IVL) for calcified coronary arteries during percutaneous coronary intervention (PCI). IVL used in combination with (after) rotational atherectomy is out of the remit of this guidance. IPAC considered the comments regarding your clinical experience of this procedure. IPAC considered additional new evidence and consultation comments and amended section 1.1.

			good. Detailed description of cases with life-improving results can be provided under confidentiality. IVL has made PCI safer for patients at [redacted] Hospital, with lower acute risk of failure or complication and higher likelihood of better long term outcomes given the better stent results achieved in a complex subset of patients. It often avoids the use of riskier PCI solutions such as rotational atherectomy or Laser. IVL practice and outcomes are subject to detailed audit at our institution. All cases are done under intracoronary imaging guidance with OFDI or IVUS. This is an outstanding and disruptive technology. It is easy to use and safe. We now estimate we will be treating 20-30 patients per year of an overall PCI volume around 550 patients per year. An overly restrictive guidance on IVL from NICE may have the unintended effect of increasing the procedural risks for these high risk patients and making PCI less safe. It will also inhibit the development of clinical understanding of IVL. The ability to continue using IVL in our Hospital and in the UK and gathering data through the mandatory NICOR registry (intended to capture all use in the UK) is fundamental to realising the promise of this technology for the benefit of our patients.	
5	Consultee 5 Company Boston Scientific	**2.1**	BSC have reviewed the draft guidance and have limited additional commentary. In the context of section 2.1 we agree with the position statement of the committee on the impact of coronary artery calcification which increases the complexity of percutaneous treatment strategies in coronary interventions and would like to highlight that severe calcifications are reported in about 6 to 8% of PCI patients in large contemporary cohorts worldwide (References 1 & 2 below) References	Thank you for your comments. Section 2.1 of the draft guidance is intended to be a short summary of the condition.

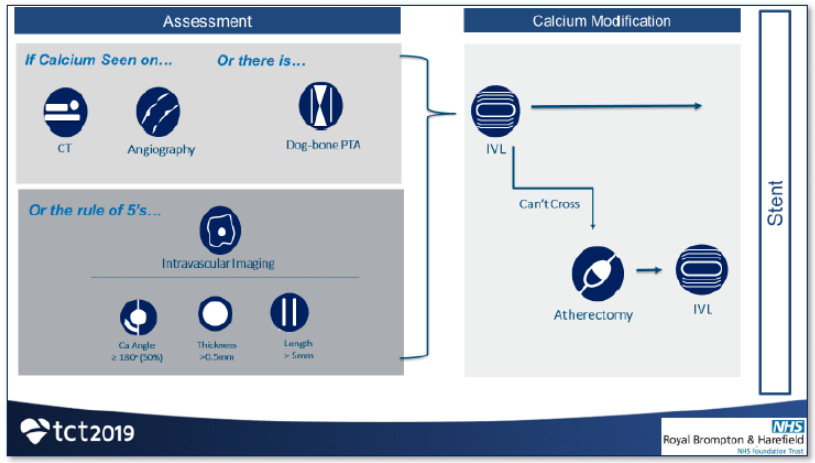
			1. Copeland-Halperin RS, Baber U, Aquino M, et al. Prevalence, correlates, and impact of coronary calcification on adverse events following PCI with newer-generation DES: Findings from a large multiethnic registry. Catheter Cardiovasc Interv. 2017;00:1–8. https://doi.org/10.1002/ccd.27204 2. Généreux P, et. al. Ischemic Outcomes After Coronary Intervention of Calcified Vessels in Acute Coronary Syndromes. J Am Coll Cardiol 2014;63:1845–54.	
6	Consultee 6 Company Shockwave medical		**Executive summary** The prevalence of coronary artery calcification in the UK is increasing due to a combination of advancing age, diabetes and renal insufficiency. Outcomes from Percutaneous Coronary Intervention (PCI) in these patients, using conventional techniques, is sub-optimal, and may be associated with adverse outcomes. Intravascular Lithotripsy (IVL) is a safe and efficacious treatment option for this group of difficult-to-treat patients, particularly those with medial calcification which may prevent optimal intra-coronary stent expansion. There is no other approved technology that can effectively treat this pathology. The intuitive ease of use of IVL, coupled with a well-developed training programme, and accepted treatment algorithms, has led to increasing adoption in the 42 countries in which IVL is available (pages 3-4). IVL is in regular clinical use, in selected patients, in 72/98 (74%) of UK NHS Percutaneous Coronary Intervention (PCI) Centres. Total coronary IVL devices sold in the UK are 2,331 (430 in 2018 and 1,901 in 2019 to December 9). Data from all patients treated with IVL in the UK are collected in the National BCIS/NICOR database and the outcomes are reported annually through the British Cardiovascular Intervention Society. IVL was added as a BCIS/NICOR data field in June 2019.	Thank you for your comments. See responses to comments 7, 8, 9, 10,11. New publications listed by the consultee (below in comment 12) have been checked by the team and responses provided (in comment 12). 3 new studies (Ali 2019, Aksoy 2019, Kwok 2019 and Wilson 2019) have been added to table 2 in the overview. In the light of this new evidence and consultation comments, section 1 has been amended by IPAC.

			Combining the IVL BCIS/NICOR data with the Office for National Statistics (ONS) mortality data will provide continuous analysis of IVL outcomes. We propose augmenting routine BCIS/NICOR coronary IVL data capture by the addition of a 1000 consecutive patient UK coronary IVL registry to explore the outcomes from coronary IVL, specifically in UK patients.  Three UK centres are actively recruiting in the trial. CAD III trial completion is anticipated in Q1 2020 (page 5). Since the last IPAC submission, the Japan Regulatory Approval Trial (CAD IV) has been initiated; scheduled completion Q2 2020 (page 6). Increasing enthusiasm by physicians has led to a growing number of independent Investigator Sponsored Research (ISR) trials in coronary IVL (pages 7-9). Coronary IVL was awarded FDA Breakthrough Device Designation status on August 19, 2020. This category is reserved for technology that has unique features for patient benefit, and may lead to an expedited regulatory approval pathway in the US (page 10). IPAC reviewed very limited peer-reviewed publications at the October 10, 2019 meeting. Since then the number of coronary IVL publications has increased significantly, including multi- and single-centre trials. We have listed both the new publications, and those already reviewed by IPAC in the attached Bibliography (pages 11-14). Proposal	

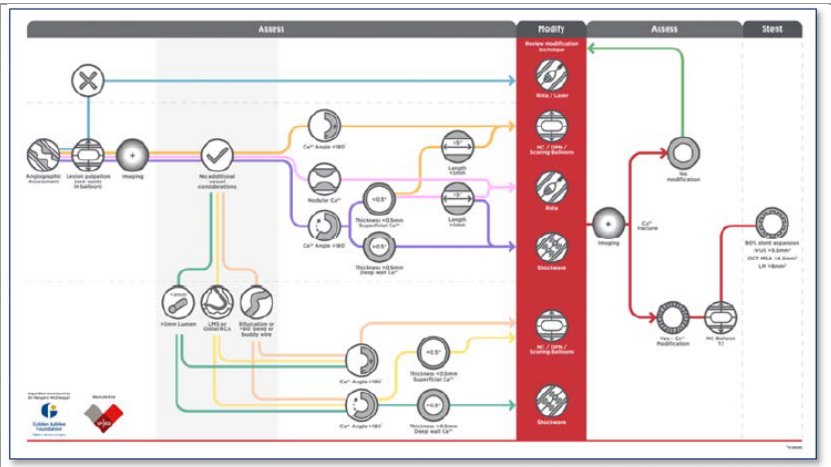
			In view of the increasing evidence listed above, coupled with the widespread use of the device in the UK, Shockwave Medical Inc, the manufacturer of coronary IVL, wishes to propose that IPAC considers reclassifying the Draft Guidance to, 'Use [IVL] with special arrangements for clinical governance, consent and audit', supported by data capture for all patients through the NICOR/BCIS database, coupled with a specific 1000 consecutive patient UK coronary IVL registry to explore the outcomes from coronary IVL in UK patients.	
7	Consultee 6 Company Shockwave medical	**General**	Training All operators, company representatives and distributors are trained on the appropriate use of Coronary IVL, a technology that should only be used in a minority of patients undergoing PCI. Key messages for the safe and effective use of Coronary IVL include: • There must be calcium – if not, use another tool • A Non-Compliant (NC) Balloon is the cheapest and most utilized tool for difficult cases • Before using IVL, use an NC balloon to try to dilate the lesion safely • If the NC balloon can cross and the lesion dilates, then you should NOT use IVL; just stent the lesion • If the IVL balloon cannot cross consider rotational atherectomy • If the NC balloon can cross and the lesion does not dilate, then IVL is a good solution (it will cross and will safely modify the calcium)	Thank you for information about training and different strategies used by clinicians.



UK physicians have also developed their own algorithms for teaching the appropriate use of different technologies for treating coronary calcification, two of which are shown here:



Jonathan Hill MD, Royal Brompton Hospital

			 Margaret McEntegart MD, Golden Jubilee Hospital, Glasgow	
8	Consultee 6 Company Shockwave medical	**3**	**CAD III (US Regulatory Approval Study)** Disrupt CAD III is a prospective, multi-centre, single-arm, global IDE study (reference G180146) designed to evaluate the safety and effectiveness of the Shockwave IVL System with the Shockwave C2 IVL Catheter in de novo, calcified, stenotic, coronary arteries prior to stenting. The study population includes subjects with de novo, calcified coronary artery lesions presenting with stable, unstable or silent ischemia that are suitable for percutaneous coronary intervention (PCI). The study is being conducted at 50 centres in four countries (US, UK, Germany and France) and is designed to enroll up to 442 total subjects (392 pivotal subjects plus one roll-in per centre). A minimum of 50% of the total enrollment will come from the United States. On October 17, 2018, FDA granted IDE approval for Disrupt CAD III as a staged study, allowing 25 US sites to enroll 75 US subjects (25 roll-in, 50 pivotal) with the requirement that 30-day outcomes on the first 30 pivotal subjects be submitted prior to expanding to the full study cohort. [redacted]	Thank you for sharing information about the ongoing CAD III study. The NICE IP Methods Guide states that efficacy outcomes from unpublished studies are not normally presented to the Committee. When substantial new evidence is published NICE will review the guidance.

			[redacted] To date (December 13, 2019) a total of 335 patients have been enrolled in CADIII; Pivotal 294 (75%), Roll-in 41 (82%), OCT sub-study 99 (99%). The anticipated trial completion date is Q1 2020. ClinicalTrials.gov Identifier: NCT03595176.	
9	Consultee 6 Company Shockwave medical	**3**	**CAD IV (Japanese Regulatory Approval Trial)** Study Objective: Assess safety and effectiveness of the Shockwave C2 IVL Catheter to treat de novo, calcified, stenotic, coronary lesions prior to stenting. Study Device: Shockwave Coronary C2 IVL System. Subject population: Subjects with de novo, calcified coronary artery lesions presenting with stable, unstable or silent ischemia that are suitable for percutaneous coronary intervention (PCI). Study Design & Performance Goal: Based on CAD III (US & OUS);	Thank you for sharing information about the ongoing CAD IV study. This information has been added to page 16 in the overview.

			confirmatory study in the Japanese population; prospective, multi centre, single arm study. Sites/Subjects: 8 sites, 64 subjects (plus 1 roll-in per site) in Japan. Total enrolled = 72. Follow-up: Discharge, 30 days, 6, 12 and 24 months. First Enrollment = 6 Nov, 2019 (Shonan Kamakura, Dr. Saito).Total enrolled = 15 (as of 13 Dec, 2019). Last planned patient enrollment June 2020. ClinicalTrials.gov Identifier: NCT04151628.	
10	Consultee 6 Company Shockwave medical	**3**	**Investigator Sponsored Research** Shockwave Medical Inc. encourages physicians to undertake independent arm's length Investigator Sponsored Research (ISR) to investigate strategically important and scientifically robust applications coronary IVL in a variety of patient sub-sets. Funding for the following studies has been approved (December 13, 2019):	Thank you for sharing information about 4 ongoing studies. This information has been added to page 16 in the overview.

			<table><tr><td>**Principal Investigator**</td><td>James Spratt, MD</td></tr><tr><td>**Institutions**</td><td>St George's University Hospital, London, UK</td></tr><tr><td>**Study Title**</td><td>The IVL-Left Main Study</td></tr><tr><td>**Study Objective**</td><td>To investigate the mechanical and procedural outcomes of PCI with coronary IVL in patients with obstructive calcific distal LM disease and a clinical indication for revascularization.</td></tr><tr><td>**Study Design**</td><td>This is a prospective, multi-centre, non-randomised, open-label pilot study. Patients with obstructive calcific distal LM disease (> 270° calcium in at least one stenotic segment) and a clinical indication for revascularization will undergo PCI with adjunctive coronary IVL.</td></tr><tr><td>**Subject Population**</td><td>Fifty (50) patients with obstructive calcific distal LM disease (> 270° calcium in at least one stenotic segment) and a clinical indication for revascularization.</td></tr><tr><td>**Study Duration**</td><td>Approximately 24 months. Subjects will be followed through 12 months.</td></tr><tr><td>**Primary Endpoint**</td><td>The co-primary effectiveness endpoints are the minimum stent area (MSA) and residual area stenosis (<50%) index immediately post procedure. The primary safety endpoint is a composite of major adverse cardiac events (all-cause mortality, non-fatal MI, or target lesion revascularization) at 30 days.</td></tr><tr><td>**Secondary Endpoints**</td><td>MACE, target lesion failure and target vessel failure at 30-days and 12 months Angiographic and procedural success</td></tr></table>	

			<table><tr><td>**Principal Investigator**</td><td>Prof. Dr. Franz X. Kleber MD</td></tr><tr><td>**Institution**</td><td>Martin Luther University of Halle-Wittenberg, Wittenberg, Germany</td></tr><tr><td>**Study Title**</td><td>Lithotripsy to aid DCB-only PCI</td></tr><tr><td>**Study Objective**</td><td>To assess the effect of calcified coronary vessel preparation with Intravascular Lithotripsy (IVL) in preparation for DCB-only PCI</td></tr><tr><td>**Study Design**</td><td>Prospective, single arm, single centre study of IVL treatment for DCB-only PCI according to the criteria outlined in the German Consensus Recommendation on DCB for treatment of coronary artery disease.</td></tr><tr><td>**Subject Population**</td><td>Fifty (50) subjects with calcified coronary artery lesions of significant severity to warrant interventional therapy and a clinical need for PCI will be included.</td></tr><tr><td>**Study Duration**</td><td>Approximately 12 months. Subjects will be followed through 4 months.</td></tr><tr><td>**Primary Endpoint**</td><td>Procedural success defined as DCB or stent delivery with a residual stenosis ≤ 30% and without in-hospital MACE</td></tr><tr><td>**Secondary Endpoints**</td><td>Clinical visit at 4 months to include assessment of CCS, NYHA class, target vessel revascularization and myocardial infarction</td></tr></table>	

			<table><tr><td>**Principal Investigator**</td><td>Oriol Rodriguez, MD</td></tr><tr><td>**Institutions**</td><td>Hospital Germans Trias I Pujol de Badalona, Badalona, Spain</td></tr><tr><td>**Study Title**</td><td>The REPLICA Clinical Trial: Spanish real-world registry of coronary intravascular lithotripsy (IVL) for the treatment of calcified coronary arteries</td></tr><tr><td>**Study Objective**</td><td>To evaluate the success of the Shockwave IVL procedure, defined as the performance of IVL without in-hospital complications (cardiac death, myocardial infarction, need for target vessel revascularization) with good angiographic results.</td></tr><tr><td>**Study Design**</td><td>Nationwide, multi-centre, prospective, observational registry</td></tr><tr><td>**Subject Population**</td><td>Four-hundred (400) subjects across 30 sites with calcified coronary artery disease requiring percutaneous revascularization with stent implantation</td></tr><tr><td>**Study Duration**</td><td>Approximately 24 months. Subjects will be followed through 12 months.</td></tr><tr><td>**Primary Endpoint**</td><td>Procedural success, defined as the performance of IVL without in-hospital complications (cardiac death, myocardial infarction, need for target vessel revascularization) with good angiographic results (TIMI grade 3 and residual stenosis < 20%).</td></tr><tr><td>**Secondary Endpoints**</td><td>MACE, target lesion failure and target vessel failure at 30-days and 12 months</td></tr></table>	

			<table><tr><td>**Principal Investigator**</td><td>Seif El-Jack, MD</td></tr><tr><td>**Institutions**</td><td>North Shore Hospital, Auckland, New Zealand</td></tr><tr><td>**Study Title**</td><td>Balloon Angioplasty versus Shockwave Intravascular Lithotripsy (S-IVL) for calcified coronary stenoses (BASIL study)</td></tr><tr><td>**Study Objective**</td><td>The objective of this study is to compare the performance of the Shockwave Coronary Intravascular Lithotripsy (IVL) versus pre-dilatation with conventional balloon angioplasty for the treatment of heavily calcified coronary stenoses prior to stent implantation.</td></tr><tr><td>**Study Design**</td><td>This is a prospective, single centre, randomized (1:1) study</td></tr><tr><td>**Subject Population**</td><td>Sixty (60) subjects with severe coronary calcification as assessed by intravascular ultrasound with presence of ≥ 270° arc of calcification</td></tr><tr><td>**Study Duration**</td><td>Approximately 18 months. Subjects will be followed through 30-days.</td></tr><tr><td>**Primary Endpoint**</td><td>Angiographic success, defined as the ability to pre-dilate the target lesion to facilitate stent delivery without bailout techniques or cross-over; no intra-procedural complications; residual stenosis < 20% after stent deployment. Clinical success, defined as no procedural related major adverse events (MI, stroke, revascularization of the target vessel inclusive of the target lesion after completion of the index procedure), and death prior to discharge.</td></tr><tr><td>**Secondary Endpoints**</td><td>MACE at 30-days</td></tr></table>	
11	Consultee 6 Company Shockwave medical	**General**	**FDA Breakthrough Device Designation** The Shockwave Medical C2 Coronary IVL System received FDA Device Breakthrough Designation on August 19, 2019. The FDA Breakthrough Devices Program is a pathway that supports the FDA mission to protect and promote public health and provides patients and healthcare providers with potential earlier access to medical devices by speeding up the development, assessment and review, while maintaining the requirements for premarket approval. A device receives a Breakthrough Device Designation by meeting the following criteria: 1. The device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; AND 2.The device also meets at least one of the following:	Thank you for your comments and sharing information about FDA approval study. Committee has considered this in their discussions.

			a. Represents Breakthrough Technology b. No Approved or Cleared Alternatives Exist c. Offers Significant Advantages over Existing Approved or Cleared Alternatives d. Device Availability is in the Best Interest of Patients Shockwave Medical demonstrated that the device meets criterion 1 and criteria 2a, 2c, and 2d; these criteria are consistent with the NICE mission and goals in that both FDA and NICE strive to identify technology that allows for the best way to treat disease with interventions that streamline patient care and cost. The Shockwave Medical C2 IVL System supports these missions and goals as follows: •IVL Treats Calcium Circumferentially and at Lower Pressures: Lithotripsy is distributed uniformly across the emitters in ultrashort pulses at a lower pressure. In contrast, high pressure modification can increase mechanical vascular trauma. This clinical effect is supported by no unresolved flow-limiting dissections or perforations in the CAD I and CAD II data. • IVL Minimizes the Need for Secondary Interventions: The favorable clinical success with low procedural complications in CAD I and CAD II – as well as the data sets from “real-world” studies – demonstrate that IVL is a viable treatment option that minimizes the need for secondary intervention compared to well-established rates of target lesion revascularization of other calcium modification tools in other studies. Specifically, the balloon-based technology may lower the risk of atheromatous embolization compared to free debulking devices. This low risk is supported by the CAD I and CAD II data where no patients experienced slow-flow or re-flow events, and there was a low rate of in-hospital MI. • IVL Increases Patient Geographic Access to Care: Unlike atherectomy, IVL requires no specific training; the well-understood PTCA design platform of IVL provides a benefit in the physician learning curve, subsequent adaptability and	

			accordingly, broad availability to a wide range of physicians in high and low percutaneous coronary intervention (PCI) volume hospitals, many of which do not currently have access to advance calcium modification tools. By putting this technology in the hands of more physicians, there is an opportunity to increase access to care for patients with calcified cardiovascular disease in rural areas that rely on community hospitals. • IVL Streamlines Procedures: Ease-of-use of the IVL technology also translates to a streamlined preparation and procedure, which may be more beneficial to physicians, patients and treatment centres.	
12	Consultee 6 Company Shockwave medical	**3**	**Coronary Intravascular Bibliography (as of December 12, 2019)** **Coronary IVL Publications not previously considered by IPAC:** **Multi-centre Studies** 1.Ali, Z, Nef, H, Escaned, J, Werner, N, Banning, A, et al. Safety and Effectiveness of Coronary Intravascular Lithotripsy for Treatment of Severely Calcified Coronary Stenoses. Disrupt CAD II Study. Circ: CardiovascInterv. 2019; 12:e008434. Data from the post-market Disrupt CAD II Study, which was designed to evaluate the safety of IVL in more patients and in more centres. The clinical outcomes for the 120 patients enrolled and the findings of the 47 patients enrolled in the OCT sub-study are presented, confirming the early experience seen in Disrupt CAD I; demonstrating low residual stenosis, favorable stent expansion and low rates of complications. 2. Aksoy, A, Salazar, C, Becher, U, et al. Intravascular lithotripsy in calcified coronary lesions: A prospecitve, observational, multi-centre registry. Circulation: Circ Interv. 2019; 12:e008154. DOI: 10.1161/CIRCINTERVENTIONS.119.008154.	Thank you for your comments. Publications References 1, 2, 3 (Ali 2019, Aksoy 2019, Wilson 2019) were found in our update search and added to table 2 in the overview. Reference 4 (Costoya 2018) has already been added to appendix as it is a small case series of 3 patients.

			A prospective, multi-centre registry that evaluated the success of IVL in three different groups. A total of 78 patients were treated and separated into IVL as primary, secondary or tertiary strategy. The primary endpoint was strategy success and safety outcomes. The primary and secondary groups had higher rates of success than the tertiary, with a low rate of MACE events in all 3 groups. **Single-centre Studies** 3. Wilson, S, Spratt, J, Hill J, Spence, M, Cosgrove, C, et al. Coronary Intravascular Lithotripsy is Associated with a High Incidence of "shocktopics" and Asynchronous Cardiac Pacing. EuroIntervention. 2019: DOI: 10.4244/EIJ-D-19-00484. A single centre experience of 54 consecutive patients treated with IVL. Specifically describing how the mechanical acoustic waves may induce a stretch activated response that may lead to ventricular pacing during the 10 seconds of lithotripsy. The authors found this phenomenon was largely dependent on baseline heart rate and was not associated with any clinical sequalae. 4. Costoya, I, et al. Coronary Lithoplasty: Initial Experience in Coronary Calcified Lesions. Rev Esp Cardiol. 2018. **https://doi.org/10.1016/j.rec.2018.11.017** Initial single centre experience using IVL in calcified coronary lesions. IVL treatment in three patients is described along with case images. The authors conclude that IVL is safe and efficacious in cases not suitable for rotational atherectomy, simple to learn and provides an option to protect lateral branches. **Case Reports** 5. De Silva, K, et al. A Calcific, Undilatable Stenosis. Lithoplasty, a New Tool in the Box? JACC: CI. 2017: 10(3); 304-306. 6. Morabito, G, Tripolino, C, Tassone, EJ, Grillo, P and Missiroli, B. A case of stent under-expansion due to calcified	Case reports 5 case reports (references 5, 8, 12, 15, 17 [de Silva 2017, Forero 2018, Tassone 2018, Vainer 2019, Sgueglia 2019]) are already included in the appendix in the overview.

			plaque treated with shockwave lithoplasty. Cardiology. 2018; 141: 75-77. 7. Watkins, S, Good, R, Hill J, Brinton, TJ, Oldroyd, KG. Intravascular lithotripsy to treat a severely under-expanded coronary stent. EuroIntervention. 2018; Jaa-457 2018, DOI: 10.4244/EIJ-D-18-00780. 8. Forero, MN, Wilshut, J, Van Meighem, N, and Daemen, J. Coronary lithoplasty: a novel treatment for stent underexpansion. European Heart Journal: 2018; DOI:10.1093/eurheartj/ehy593. 9. McQuillan, C, Alkhalil, M, and Johnston, P. A Paced Heart Without a Pacemaker. European Heart Journal. 2019; 40 (10): 819a **https://doi.org/10.1093/eurheartj/ehy749** 10 Ali, Z, McEntegart, M, Hill, J and Spratt,J. Intravascular lithotripsy for the treatment of stent underexpansion secondary to severe coronary calcification. European Heart Journal. 2018:10.1093/euroheartj/ehy747. 11. Warisawa, T, Goto, S, Salazar, C, Akashi, Y, Escaned, J. Safety and feasibility of coronary lithotripsy supported by guide extension catheter for the treatment of calcified lesion in angulated vessel. CRM. 2019; **https://doi.org/10.1016/j.carrev.2019.02.014** 12. Tassone, E. et al. When Calcium Gets tough, the tough cardiologists starts to play…Cardiology. 2018;141:167-171. 13. Lopez-Lluva, M, Jurado-Roman, A, Sanchez-Perez, I, et al. Shockwave Useful but potentially dangerous. JACC: CI. 2019; **https://doi.org/10.1016/j.jcin.2018.12.035** 14. Pineda, A, Puri, A, Jahangri, B. Successful intravascular lithotripsy for severely calcified left anterior descending coronary artery stenosis. NZMJ. 2019; 132(1491): 93-95. 15. Vainer, J, et al Smart solution for hard times: successful lithoplasty of an undilatable lesion. Neth Heart J. 2019. **https://doi.org/10.1007/s12471-019-1261-2**	6 case reports (references 6, 9, 13, 14, 16, 18, 23 [Morabita 2019, McQuillan C 2019, Lopez-Lluva MT 2019, Pineda A 2019, Alfonso F 2019, Azzalini 2019, Kwok 2019]) were found in our update search and added to the appendix in the overview. 6 case reports (references 7, 10, 11, 19, 21, 22) were not found in our searches but added to the appendix in the overview. 2 case reports (references 20, 24 [Jurado-Roman 2019, Chen 2019]) focus on a combined approach using both IVL and rotational atherectomy. These are out of the remit of this guidance and therefore will not be added to the overview.

16. Alfonso, F. et al. Coronary lithoplasty for treatment of undilatable calcified de novo and in-stent restenosis lesions. JACC: CI. 2019; 12(5): 497-499.

17. Sgueglia, G, Gioffre, G, Piccioni, F, and Gaspardone, A. Slender distal radial five French coronary shockwave lithotripsy. Cather Cardiovasc Interv. 2019; 1-4.

DOI:10.1002/ccd.2829.

18. Azzalini, L, Bellini, B, Montorfano, M and Carlino, M. Intravascular Lithotripsy in chronic total occlusion percutaneous coronary intervention. EuroIntervention. 2019;

DOI: 10.4244/EIJ-D-19-00175.

19. Soriano, F, Veas, N. Piccinelli, E, and Oreglia, J. Coronary Dissection due to Intravascular lithoplasty balloon rupture. EuroIntervention. 2019; DOI: 10.4244/EIJ-D

19-00383.

20. Jurado-Roman, A, Gonzalvez, A, Galeote, G, Jimenez-Valero, S and Moreno, R. RotaTripsy: Combination of Rotational Atherectomy and Intravascular Lithotripsy for the Treatment of Severely Calcified Lesions. JACC: Card Int. 2019: **https://doi.org/10.1016/j.jcin.2019.03.036**

21. Cicovic, A, Cicovic, S. Wong, B, Stotrup, N, Ghattas, A and Glenie T. A Quicker Pace: Shockwave Lithotripsy Pacing with Electromechanical Capture. JACC CI. 2019: **https://doi.org/10.1016/j.jcin.2019.04.024**

22. Curtis, E, Khan, A, El-Jack, A and Glenie, T. Precipitation of de novo Atrial Fibrillation during Shockwave Intravascular Lithotripsy After Pacing Capture During the Treatment of Proximal Right Coronary Artery Disease: A Case Report. Euro Heart Journal. 2019; doi:10.1093/ehjcr/ytz147.

23. Kwok, OH and Tse, HF. Ventricular Capture During Shockwave Intravascular Lithotripsy. JACC: Cardio Interv. 2019; DOI: 10.1016/j.jcin.2019.06.046.

24. Chen, G., Zrenner, B., and Pyxaras, S. Combined rotational atherectomy and intravascular lithotripsy for the

			treatment of severely calcified in-stent neoatherosclerosis: A mini-review. CRM. 2018: https://doi.org/10.1016/j.carrev.2018.10.007 **Review** 25. Yeoh, J and Hill, J. Intracoronary Lithotripsy for the Treatment of Calcified Plaque. Interventional Cardiology Clinic. 2019. 8; 411-424. 26. Shavadia, J, VO, M, Bainey, K. Challenges with severe coronary artery calcification in percutaneous coronary interventions: A narrative review of therapeutic options. Canadian J of Cardio. 2018. 34: 1564-1572. 27. Kassimis, G. Raina, T, Dontogiannis, N, Patri, G, Abrimik, J, et al. How Should we treat heavily calcified coronary artery disease in contemporary practice? From atherectomy to intravascular lithotripsy. CRM. 2019; https://doi.org/10.1016/j.carrev.2019.01.010 28. Dini, CS, Tomberli, B, Mattesini, A, Ristalli, F, Valente, S, et al. Intravascular Lithotripsy for Calcific Coronary and Peripheral Artery Stenoses. EuroIntervention; 2019: DOI: 10.4244/EIJ-D-18-01056. 29. Luigi De Maria, G, Scarsini, R, and Banning, A. Management of Calcific Coronary artery Lesions. Is it time to Change Our Interventional Therapeutic Approach?. JACC: Cardiovascular Interventions. 2019: 12(15); 1465-1478. 30. Khan, S, Li, B, Salata, K, et al. The Current Status of Lithoplasty in Vascular Calcification: A systematic review. Surgical Innovation. 2019; 26(5): 588-598. **Editorial** 31. Serruys, P. et al, Shaking and Breaking Calcified Plaque. Lithoplasty, a Breakthrough in Interventional Armamentarium? JACC: CI. 2017: 10(3); 907-911.	Review 2 reviews (reference 25, 28 [Yeoh 2019, Dini 2019]) found in our update search have been added to the appendix in the overview. 3 reviews (references 26, 27, 30 [Shavadia 2018, Kassimis 2019, Khan 2019]) have already been added to appendix in the overview. One review (reference 29 [Luigi De Maria 2019]) was not found in our update search but added to the appendix in the overview. Editorial Reference 31 is an editorial and therefore not included in the overview. Publications previously considered by IPAC 3 studies (references 32, 33, 34 [Brinton 2019, Ali 2017, Wong 2019]) have already been included

			Coronary IVL Publications previously considered by IPAC: **Multi-centre studies** 32.Brinton, T.J., Ali, Z., Hill, J., Meredith, I., Maehara, A., Feasibility of Shockwave Coronary Intravascular Lithotripsy for the Treatment of Calcified Coronary Stenoses: First Description. Circulation, 2019. 139:834-836. An overview of the Disrupt CAD I study including safety and effectiveness outcomes. The Disrupt CAD I Study was the premarket study performed in 6 centres in Europe and 1 in Australia. The outcomes of the 60 patients that were enrolled and followed out to 6 months demonstrated decrease in residual stenosis, an increase in acute gain and low rate of angiographic and clinical complications. 33.Ali ZA, Brinton TJ, Hill JM, Maehara A, Matsumura M, et al. Optical Coherence Tomography Characterization of Coronary Lithoplasty for Treatment of Calcified Lesions: First Description. JACC Cardiovasc Imaging. 2017; 10:897-906. Outcomes of the Disrupt CAD I OCT sub-study, including mechanistic imaging reviewed by the core lab in the 31 patients enrolled in the sub-study. This study concluded that calcium modification with fracture was a major mechanism of action of IVL in vivo and demonstrated significant improvement in acute gain and favorable stent expansion. **Single-centre studies** 34. Wong, B. et al. Shockwave Intravascular Lithotripsy for Calcified coronary lesions: First real-world experience. J Invasive Cardiol. 2019; 31(3): 46-48. Initial experience with coronary IVL in New Zealand. This ‘real-world’ patient population was more complex that those included in other clinical studies. The authors report similar outcomes in this group that included left main, STEMI patients etc., as was reported in the Disrupt CAD I study.	in table 2 in the overview and considered by IPAC.

13	Consultee 7 Royal College of Physicians	**General**	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the BCS and BCIS response.	Thank you for your comments and agreeing with the main recommendation.
14	Consultee 1 NHS Professional British Cardiovascular Society (joint response with British Cardiovascular Intervention Society)	**Section 1 & Lay description**	Both BCS and BCIS are supportive of the revised guidelines for this technology. We have some specific suggestions for the initial lay summary that we hope make the role of the technology more clear: “Coronary arteries (the main blood vessels supplying blood to the heart) can become narrowed or blocked with fatty deposits. At times, the fatty deposits contain calcium and the arteries become stiff (calcified). Sometimes, as well as tablets, doctors may offer treatment to stretch open these narrowed arteries. To do this, a thin wire is passed down the affected artery (percutaneously, that is, via an artery in the groin or arm), and a small balloon is inflated to widen the narrowed artery, squashing the fatty deposits against the arterial wall so that blood can flow freely. Sometimes a small wire mesh tube (stent) is also placed in the artery, expanded to fit the size of the artery and left in place to keep the artery open. In a lithotripsy procedure, the balloon used to stretch the artery contains a device that delivers ultrasound shock waves. These break up the hard deposits (lithotripsy) to make it easier to insert the stent and to avoid damaging the artery. This can be especially helpful when the hard deposits have made it impossible to fully expand a stent to its right size. Leaving a stent that is not fully expanded is an occasional cause of serious heart problems, including heart attack or persisting angina. Lithotripsy allows doctors to fully expand stents that might not be fully expanded otherwise. This may reduce the chances of later heart problems.”	Thank you for your comments and agreeing with the main recommendation. Lay description in the overview has been amended.