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Intravascular lithotripsy for calcific coronary and peripheral artery stenoses

Carlotta Sorini Dini[1,2], MD; Benedetta Tomberli[1], MD, PhD; Alessio Mattesini[1], MD; Francesca Ristalli[1], MD; Serafina Valente[1], MD; Miroslava Stolcova[1], MD; Francesco Meucci[1], MD; Giorgio Baldereschi[1], MD; Fabrizio Fanelli[3], MD, EBIR; Richard Shlofmitz[4], MD; Ziad Ali[5], MD, DPhil; Carlo Di Mario[1]*, MD, PhD, FESC, FACC

1. Structural Interventional Cardiology, Careggi University Hospital, Florence, Italy; 2. Cardiology Division, Spedali Riuniti, Livorno, Italy; 3. Department of Vascular and Interventional Radiology, Careggi University Hospital, Florence, Italy; 4. St Francis Hospital, Roslyn, NY, USA; 5. New York Presbyterian Hospital/Columbia University Presbyterian Hospital and Cardiovascular Research Foundation, New York, NY, USA

C. Sorini Dini and B. Tomberli contributed equally to this work as first authors. Z. Ali and C. Di Mario contributed equally to this work as senior authors.

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KEYWORDS

- atherectomy
- calcified stenosis
- intravascular ultrasound
- optical coherence tomography
- rotablator

Abstract

Heavily calcified lesions may be difficult to dilate adequately with conventional balloons and stents, which causes frequent periprocedural complications and higher rates of target lesion revascularisation (TLR). High-pressure non-compliant balloon angioplasty may be of insufficient force to modify calcium and, even when successful, may be limited in its ability to modify the entire calcified lesion. Scoring and cutting balloons hold theoretical value but data to support their efficacy are lacking and, because of their high lesion crossing profile, they often fail to reach the target lesion. Rotational and orbital atherectomy target superficial calcium; however, deep calcium, which may still impact on vessel expansion and luminal gain, is not affected. Intravascular lithotripsy (IVL), based on lithotripsy for renal calculi, is a new technology which uses sonic pressure waves to disrupt calcium with minimal impact to soft tissue. Energy is delivered via a balloon catheter, analogous to contemporary balloon catheters, with transmission through diluted ionic contrast in a semi-compliant balloon inflated at low pressure with sufficient diameter to achieve contact with the vessel wall. With coronary and peripheral balloons approved in Europe, peripheral balloons approved in the USA and multiple new trials beginning, we review the indications for these recently introduced devices, summarise the clinical outcomes of the available trials and describe the design of ongoing studies.

**Corresponding author: Structural Interventional Cardiology Division, Careggi University Hospital, 50134 Florence, Italy. E-mail: carlo.dimario@unifi.it*

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Abbreviations

CT computed tomography
CTO chronic total occlusion
DES drug-eluting stent(s)
IDE investigational device exemption
IVL intravascular lithotripsy
IVUS intravascular ultrasound
MACE major adverse cardiac events
MI myocardial infarction
NC non-compliant balloon(s)
OCT optical coherence tomography
PCI percutaneous coronary intervention
TLR target lesion revascularisation
TVR target vessel revascularisation

Introduction

As the population ages and the prevalence of diabetes and renal disease continues to rise, the prevalence of cardiovascular calcium has also risen[1,2]. Severely calcified lesions remain a challenge for interventional cardiologists. Coronary artery calcification (CAC) impacts on interventional outcomes by impairing stent crossing[3], delaminating the drug-eluting polymer from the stent[4], affecting drug delivery and elution kinetics, and reducing stent expansion and apposition[5]. Similarly, calcified peripheral arterial disease (PAD) adds to lesion complexity and is present in 20% of revascularisation procedures[6]. Transfemoral access for large-bore procedures such as transcatheter aortic valve implantation (TAVI) has become well established as the access of choice[7-9]. Calcified iliofemoral disease is the predominant reason why alternative access sites are utilised[10].

Current techniques to treat calcified lesions including balloon angioplasty, specialty balloons (e.g., cutting, scoring, ultra-high-pressure) and atherectomy have limitations. Balloon dilation, including by specialty balloons, may be of insufficient force to lead to calcium fracture and vessel expansion. Rotational and orbital atherectomy may be biased by the guidewire towards non-calcified segments of the artery[11], resulting in ineffective ablation. Even when effective in facilitating stent delivery, atherectomy may have a limited effect on deep calcium, which restricts complete stent expansion and vessel wall apposition[5,12]. In addition, periprocedural PCI complications including slow flow and periprocedural myocardial infarction (MI) are still significantly higher with atherectomy than traditional balloon-based therapies **(Table 1)**[13-15]. Calcification also increases the risk of vascular complications following treatments for PAD including dissection, perforation, distal embolisation and restenosis after percutaneous transluminal angioplasty (PTA) or stenting[16-18].

Intravascular lithotripsy (IVL) is a new technology that delivers pulsatile sonic pressure waves converted to mechanical energy to modify vascular calcium. It leverages similar principles to urologic lithotripsy, which has been used as a safe and effective treatment for kidney stones for several decades[19,20]. Both therapies use electrohydraulically generated sonic pressure waves that pass through soft tissue, but interact strongly with high-density calcium, producing significant shear stresses that can fracture calcium. In contrast to focal, high-energy urological lithotripsy, the acoustic energy produced by IVL is tuned specifically for vascular applications. IVL safely selects and effectively modifies both intimal and medial calcium[21] without negatively impacting on soft tissue across a wide range of vascular applications to increase vessel compliance, and thereby enables the optimal treatment option for the patient and simplifies complex calcified vascular procedures.

With additional peripheral IVL catheters and modifications to the above-the-knee catheters recently cleared for use in Europe and the USA, next-generation coronary IVL catheter approval in

Table 1. Comparison of rotational atherectomy, orbital atherectomy and intravascular lithotripsy in severe coronary calcification.

	Rotablator	Orbital atherectomy	IVL
Guidewire	0.09" proprietary wire	0.014" proprietary wire	0.014" wire of choice
Lesion crossing	+++ 1st line for balloon uncrossable lesions		– Higher crossing profile than contemporary balloons
Wire bias	+++ Calcium modification wire-bias dependent		– Balloon inflation eliminates wire bias, providing circumferential calcium modification
Side branch protection	– Side branch wire must be removed during atherectomy		+++ No interaction with side branch wire
Distal embolisation	++ Atherectomy actively liberates atherosclerotic debris		– Theoretically same risk as contemporary angioplasty balloon
Perforation	++ Accepted risk of atherectomy, higher in tortuous anatomy		– No recorded perforations
Bradyarrhythmias	+++ Temporary pacemaker standard of care in dominant coronary atherectomy	++ Temporary pacemaker may be considered in dominant coronary atherectomy	– No recorded arrhythmia
Plaque ablation	++ Dependent on selected burr size	+++ Increased atherectomy with increased minimal lumen area	– No plaque ablation
Effect of deep calcium	– Atherectomy impacts on superficial calcium only		+ Theoretically modifies deep calcium

Europe, along with multiple clinical trials underway, we provide a timely review on IVL in both coronary and peripheral applications.

Calcific coronary stenoses

DEFINITION AND PROGNOSTIC IMPLICATIONS

The most commonly accepted definition of angiographically severe coronary calcium is the presence of fixed radiopacities, detected without cardiac motion before contrast injection, compromising both sides of the arterial lumen[22]. While angiography alone underestimates calcium and does not easily allow its quantification[23], multidetector coronary computed tomography (CT), a non-invasive technique able to measure calcium score and assess prognosis, is considered by many to be the technique with the greatest diagnostic utility[24,25]. In the catheterisation laboratory, intravascular imaging techniques can quantify the circumferential and longitudinal distribution of calcium better, and distinguish superficial from deep deposits, thus helping to define thresholds for severity of calcium that would require lesion preparation different from conventional predilatation[26,27]. With intravascular ultrasound (IVUS), calcium is apparent as bright hyperechoic lines with acoustic shadowing. The optical coherence tomography (OCT) features of calcium are low signal attenuation areas surrounded by well delineated external contours, a very different pattern from lipid deposits that cause high attenuation and preclude detection of the outer border[28]. An advantage of OCT over IVUS is its ability to measure calcium thickness and detail protruding calcium masses because of its higher resolution. It has recently been described that a calcium length greater than 5 mm, a thickness of greater than 0.5 mm, and an arc greater than 180 degrees are associated with a higher risk of stent underexpansion[26,29] and are thus more likely to benefit from plaque modification prior to stent implantation[30].

In concert with the progressive ageing of the population, the frequency of severe coronary calcification in patients undergoing PCI, currently estimated to range between 18 and 26%, is likely to grow[31-33]. This is of clinical significance as the presence of severe calcium is a strong predictor of target lesion failure (TLF), late/very late stent thrombosis, major adverse cardiovascular events (MACE) and all-cause mortality in patients undergoing revascularisation[33,34].

CORONARY IVL: RATIONALE, PRINCIPLES AND DEVICE DESCRIPTION

IVL modifies calcific atherosclerotic lesions by inducing calcium fracture before stent deployment with the aim of facilitating drug-eluting stent (DES) expansion and apposition. Coronary IVL follows the same fundamental principles of traditional lithotripsy used for fragmentation of renal calculi, where disruption of calcified tissue using pulsatile mechanical energy is selective to amorphous calcium, minimising soft tissue injury. The second-generation coronary IVL catheter (Shockwave Medical, Santa Clara, CA, USA) is a single-use sterile disposable catheter that contains multiple lithotripsy emitters enclosed in an integrated balloon **(Table 2)**. The emitters create sonic pressure waves in the

Table 2. Technical features of the intravascular lithotripsy system.

	Coronary	Peripheral (iliac/femoral)	Peripheral (below the knee)
Guide/sheath compatibility (Fr)	6 guide catheter	6 sheath for 3.5-6.0 mm balloons 7 sheath for 6.5-7.0 mm balloons	5 sheath
Guide extender compatibility	≥5.5 Fr	–	–
Catheter length (cm)	138	110	135
Guidewire compatibility (inch)	0.014”		
Balloon diameter (mm)	2.5-4.0	3.5-7.0	2.5-4.0
Balloon length (mm)	12	60	40
Balloon diameter (mm)/crossing profile (inch)	2.5-2.75 mm: 0.043” 3.0-3.5 mm: 0.044” 3.75-4.0 mm: 0.046”	3.5 mm: 0.054” 4.0 mm: 0.057” 4.5 mm: 0.058” 5.0 mm: 0.062” 5.5 mm: 0.064” 6.0 mm: 0.066”	2.5-3.0 mm: 0.045” 3.5 mm: 0.045” 4.0 mm: 0.050”
Number lithotripsy emitters/ balloons	3	5	5
Pulse frequency	1 pulse/sec		
Maximal duration of energy delivery (sec)	10	30	20
Emitted energy/balloon atm (MPa)	50 atm (5 MPa)		
Maximum pulses/balloon	80 (8 cycles with 10 pulses each)	300 (10 cycles with 30 pulses each)	160 (8 cycles with 20 pulses each)
Minimal balloon pressure during energy delivery (atm)	4		
Nominal pressure (atm)	6		
Rated burst pressure (atm)	10		
CE mark	2015	2017	2018
FDA registration	IDE trial underway	2017	–

shape of a sphere, creating a field effect on vascular calcium circumferentially. These sonic pressure waves selectively disrupt and fracture calcium *in situ*, altering vessel compliance, while minimising injury and maintaining the integrity of the fibro-elastic components of the vessel wall. Compared to contemporary non-compliant balloon crossing profiles (0.033-0.035"), current coronary IVL catheters have a modestly higher profile (0.043-0.046"), similar to contemporary cutting balloons (0.043"). IVL balloon catheters are available in 2.5 to 4.0 mm diameters (in 0.5 mm increments) and 12 mm in length. The IVL catheter is introduced into the target vessel and positioned across the maximally calcified segment of the lesion, using the marker bands as guides, to ensure that the circumferential therapeutic field effect created by the emitters is focused. The IVL catheter is connected via a connector cable to the generator that is pre-programmed to deliver 10 pulses in sequence at a frequency of 1 pulse/second for a maximum of 80 pulses per catheter. The IVL catheter should be sized 1:1 to the reference vessel diameter, inflated to sub-nominal pressures, typically 4 atmospheres (atm), to allow contact with the vessel wall but minimise static barotrauma. If the IVL catheter is unable to pass into the lesion, adjunctive therapies such as predilatation, buddy wire, guide catheter extensions or atherectomy may be performed. Following delivery of a pulse cycle, a brief further dilatation to nominal pressures (6 atm) or higher may be performed if full expansion has not been achieved. IVL treatment is repeated along the target lesion with interval deflation after 10 pulses to allow distal perfusion and overlap of long calcified segments as needed. If the maximum number of pulses per catheter is delivered but lesion preparation is incomplete, further IVL catheters with the same or different diameters may be used **(Table 1)**.

After coronary IVL is performed, intravascular imaging may aid in the detection of the desired calcium fracture within the target lesion **(Figure 1, Figure 2)**. With IVUS, calcium fractures may be subtle, identified as discrete separations across linear luminal echogenicity **(Figure 1)**. Due to its higher resolution, OCT is the technique of choice to identify single or multiple partial or full thickness calcium fractures **(Figure 2)**.

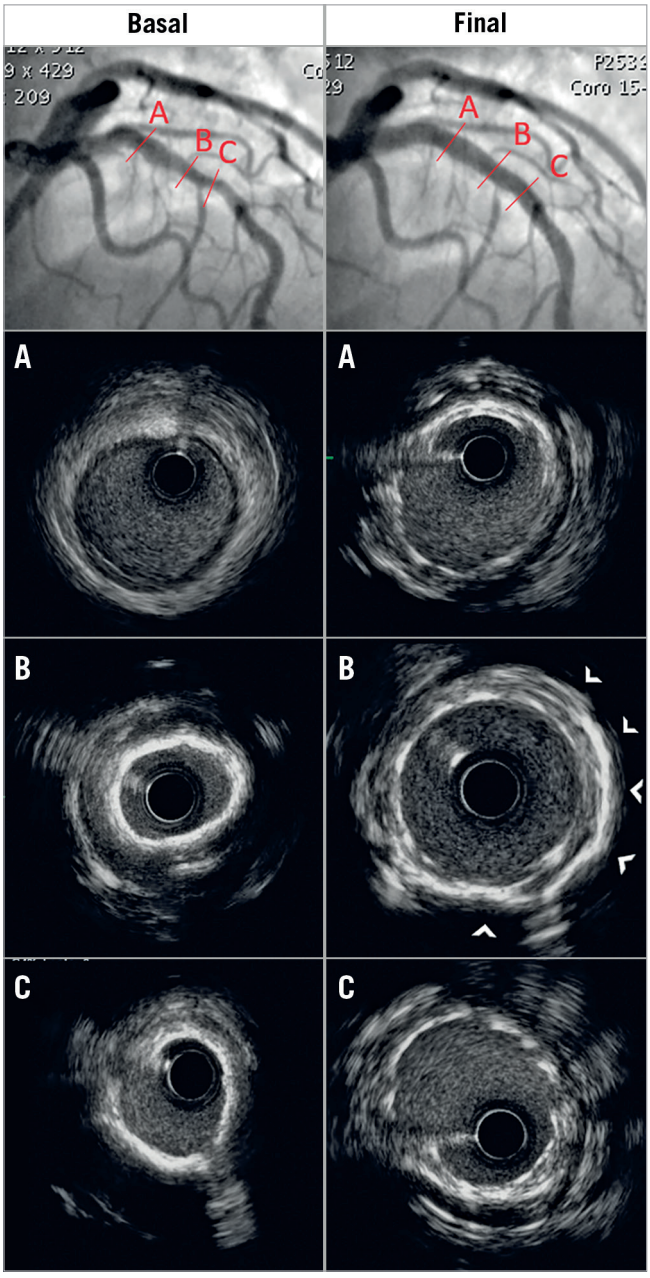

Figure 1. *Concentric calcific coronary lesion. Left panels (A, B & C): coronary angiogram with calcific stenosis of the proximal and mid left anterior descending artery (LAD) (upper panel) was confirmed by IVUS (calcium arc 360°; left panel B & C). Coronary IVL was performed using a 3.5×12 mm Shockwave C2 balloon on the distal lesion and a 3.75×12 mm balloon on the proximal lesion. A 3.5×38 mm DES was implanted at 8 atm followed by post-dilation with a 4.0 mm non-compliant balloon at 14 atm. Right panels (A, B & C): angiography shows minimal residual diameter stenosis, confirmed by IVUS showing large acute gain without malapposition. Arrowheads in panel B denote arc segments with reduced shadowing suggesting calcium modification.*

CLINICAL OUTCOME AND SAFETY OF CORONARY IVL

Disrupt CAD I was the first prospective multicentre, single-arm trial designed to assess the efficacy and safety of coronary IVL in the treatment of calcified coronary lesions **(Table 3)**[34]. Sixty patients with *de novo* moderately or severely calcified coronary stenoses in native vessels were enrolled. Device success was 98.3% and the primary endpoint, residual diameter stenosis <50% after stent implantation without in-hospital MACE (cardiac death/myocardial infarction/target vessel revascularisation [TVR]), was achieved in 95% of patients. IVL was highly effective, achieving acute gains (1.7±0.6 mm) and residual stenosis (13.3±11.6%) similar to those seen in contemporary DES studies comprising largely non-calcified lesions[35]. The OCT substudy of Disrupt CAD I, in 31 patients treated with serial OCT before and after IVL, showed that the mechanism of IVL was intraplaque calcium fracture. Fracture was identified in 43% of lesions and multiple fractures in >25% of lesions, with a greater number of fractures occurring in the most heavily calcified lesions[21].

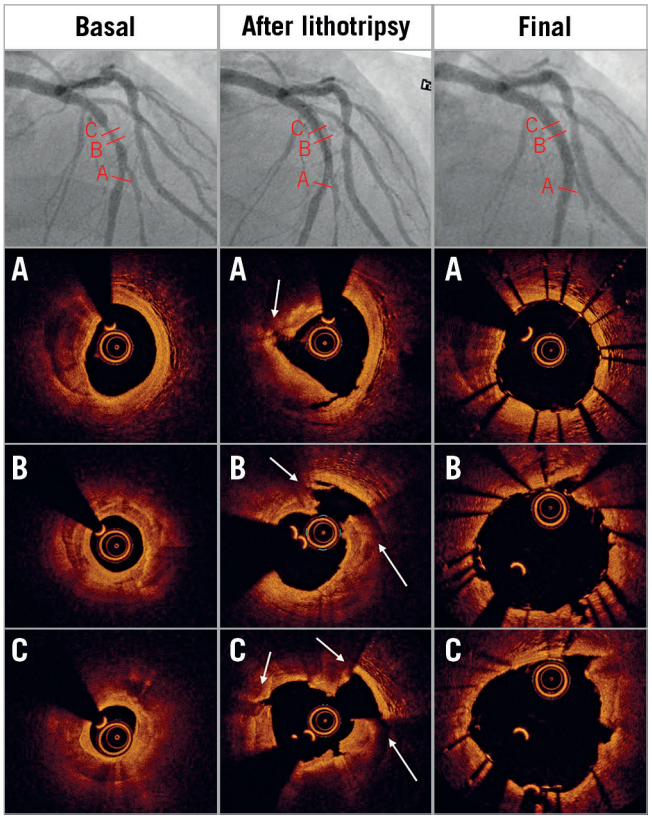

Figure 2. *Multiple fractures of a thick calcific coronary plaque. Left panels: coronary angiography identified a long calcific stenosis of the mid left anterior descending artery (LAD). Pre-PCI OCT examination confirmed a severely calcified lesion (MLA 1.1 mm², max calcium thickness 1 mm), with multiple calcium morphologies (A-C). Central panels: 3.5×12 mm and 3.75×12 mm IVL balloons delivered therapy at 4/6 atm. OCT showed multiple fractures (arrows). Right panels: final angiographic and OCT results confirming large luminal gain and minimal malapposition (3.5×18 mm DES deployed at 10 atm).*

Data derived from clinical trials and from real-world experience of selected centres have consistently shown coronary IVL to be safe. No intraprocedural complications including perforation, abrupt closure, thrombosis or slow flow/no-reflow were described in the trial[34]. The rate of MACE was 5% and 8% at one and six months, respectively, comprising three non-Q-wave MI and two cardiac deaths deemed unlikely to be related to the index procedure. The absence of vessel perforation, the most fearsome and life-threatening complication of calcific lesions, appears to be a potential major advantage of IVL, but the absence of comparative large trials limits this evidence to anecdotal.

Two IVL studies are currently underway. Disrupt CAD II (NCT03328949), a post-marketing registry, evaluating the safety and performance of coronary IVL in 120 real-world patients is currently enrolling in 15 centres in Europe. Disrupt CAD III (NCT03595176) is a prospective, multicentre, single-arm, global investigational device exemption (IDE) study of 392 patients at 50 centres evaluating IVL for treatment and device-related adverse events (cardiac death/MI/TVF). Similar to Disrupt CAD I, this study will also have an OCT substudy focused on understanding the IVL mechanism of action further.

In addition to these clinical studies, a growing body of anecdotal clinical evidence is emerging. Several case reports discussing the use of IVL in underexpanded stents, where the reason for the underexpansion is calcium, secondary to inadequate vessel preparation, have been reported[36-39].

Calcific peripheral stenoses

Peripheral IVL may be used for the treatment of moderate-severe calcific lesions in different sites with a variety of indications. The rationale, indications and clinical outcome of IVL in peripheral stenosis are discussed in the online supplementary data **(Supplementary Appendix 1, Supplementary Figure 1, Supplementary Figure 2)**.

Table 3. Completed intravascular lithotripsy trials.

	Disrupt CAD I[34]	Disrupt PAD I/II[49,50]	Disrupt BTK[51]
	Multicentre – Single-arm		
No. of patients, no. of sites	60 patients, 7 sites	PAD I: 35 patients, 3 sites PAD II: 60 patients, 8 sites	20 patients, 3 sites
Inclusion criteria	– *de novo* moderate/severe calcific coronary lesions – stenosis ≥50% – RVD 2.5-4.0 mm – lesion length <32 mm	– intermittent claudication (Rutherford Class 2–4) – ABI ≤0.9 – moderate/severe calcification – SFA/popliteal lesions >70% stenosis – RVD 3.5-7.0 mm – lesion length ≤150 mm	– intermittent claudication (Rutherford Class 3–5) – moderate/severe infrapopliteal disease – infrapopliteal lesions ≥50% stenosis – RVD 2.5–3.5 mm – lesion length ≤150 mm
Procedural success	98.3%	100%	95%
Clinical success	95%	98.9%	95%
Acute gain	1.7 mm	2.9 mm	1.5 mm
30-day MACE/MAE	5.0%	1.1%	0.0%
6-month MACE/MAE	8.3%	1.1%	–

ABI: ankle-brachial index; MACE: major adverse cardiovascular events; MAE: major adverse events; MI: myocardial infarction; RVD: reference vessel diameter; SFA: superficial femoral artery

Conclusion

Both in coronary and peripheral arteries, IVL delivered at low atmospheric pressures can circumferentially fracture calcium, augmenting expansion in severely calcified lesions. IVL is an appealing alternative to more invasive surgical approaches to insert large catheters for TAVI, thoracic endovascular aortic repair (TEVAR) or mechanical circulatory support. Data from large real-world applications and controlled comparisons with the other available treatments are necessary to understand the anatomic characteristics of the calcified lesions with the optimal response. Future iterations of IVL which fine-tune energy delivery to increase efficacy in particularly thick calcium plates while maintaining safety are awaited.

Conflict of interest statement

Z. Ali reports equity in Shockwave. He has also received grants and personal fees from Abbott, Medtronic and Cardiovascular Systems Inc., and personal fees from Boston Scientific and Cardinal Health, outside the submitted work. C. Sorini Dini, B. Tomberli, A. Mattesini, F. Ristalli, S. Valente, M. Stolcova, F. Meucci, G. Baldereschi, F. Fanelli and C. Di Mario work in the Careggi Hospital which has been assigned a research grant to conduct the Disrupt CAD II trial, sponsored by Shockwave. C. Di Mario is the worldwide principal investigator of the Disrupt CAD II trial. F. Fanelli has participated in the DISRUPT PAD trial. The other author has no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Calcific peripheral stenoses.

Supplementary Figure 1. IVL-assisted transfemoral TAVI.

Supplementary Figure 2. Subocclusive calcific lesion of a superficial femoral artery in a patient with critical limb ischaemia.

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Supplementary data

Supplementary Appendix 1. Calcific peripheral stenoses

Definition and grading of peripheral calcific lesions

There is no standard definition utilised across trials of severity of calcification in the periphery; however, in a recent SCAI consensus document, moderate-to-severe calcific lesions were defined as calcification >180° involving both sides of the vessel[40]. Among the various scoring systems proposed, the Peripheral Arterial Calcification Scoring System (PACSS score) assesses length (minor or major [more than 5 cm]) and location of calcification (intima, media, mixed, unilateral or bilateral) in the anteroposterior projection by fluoroscopy and digital subtraction angiography[2] and PARC defines severe calcification greater than 180° on both sides of the vessel and greater than one half of the total lesion length[41]. Fanelli et al proposed a different score based on circumferential distribution of calcium as assessed by CT (from 0° to 360°) and length of lesion (smaller or greater than 3 cm) using digital subtraction angiography[42]. As in the coronary circulation, various intravascular imaging techniques may assess the degree and extent of calcium better; however, intravascular imaging in the periphery is infrequently used.

Prognostic impact of calcific peripheral lesions

In patients with peripheral artery diseases, the presence of calcifications is associated with higher critical limb ischaemia, Rutherford class and risk of distal amputation[2]. Percutaneous transluminal angioplasty (PTA) with conventional balloons in severe peripheral artery calcification has low efficacy because of suboptimal vessel expansion, acute recoil and extensive vascular injury, potentially causing long dissections requiring stent implantation, or even vessel perforation[43]. Drug-coated balloons (DCB) have been tested to overcome the limitations of traditional angioplasty and stents, with good acute results in terms of efficacy and safety and durable vessel patency with low

incidence of TLR[44-46]. However, DCB have reduced efficacy in calcified lesions, possibly with calcium acting as a barrier for effective drug penetration into the vessel wall[42].

Combined use of DCB and scoring/cutting balloons or directional atherectomy for better vessel preparation has shown encouraging results[47] but long-term efficacy remains unproven. Although new DES have shown good results in midterm and long-term follow-up, achieving a strong recommendation also in a recent SCAI consensus[40] , very long stents and implantation at bend points result in a high likelihood of mechanical failure (fracture, compression), possibly leading to in-stent restenosis or thrombosis[47].

Five different types of atherectomy device are available to prepare calcific lesions in peripheral arteries better (directional atherectomy, TurboHawk™ [Medtronic, Minneapolis, MN, USA]; rotational atherectomy, ROTABLATOR™ [Boston Scientific, Marlborough, MA, USA] ; aspiration, Jetstream™ [Boston Scientific]; laser atheroablation, Turbo-Elite™ [Spectranetics Corp., Colorado Springs, CO, USA]; orbital atherectomy, Diamondback 360® [Cardiovascular Systems Inc., St. Paul, MN, USA]). They are designed to cut, shave, vaporise or sand intimal calcified plaques, with slightly different indications that depend on specific lesion characteristics. However, none is effective against medial calcification which reduces vessel wall elasticity and compliance, with greater vessel recoil and restenosis[48] . In this regard, IVL in the periphery may offer a significant advantage.

Rationale and indications for IVL in peripheral stenosis

Peripheral IVL may be used for the treatment of moderate-severe calcific lesions in different sites with a variety of indications **(Supplementary Figure 1, Supplementary Figure 2)**.

a) Calcific stenoses often exist in the iliac and femoral arteries, where large bore access may need to be inserted, such as for transcatheter aortic valve implantation (TAVI), transcatheter endovascular aneurysm repair and/or mechanical circulatory support. The frequent co-existence of severe calcification and tortuosity in patients with these conditions makes them suitable candidates for IVL therapy. IVL will disrupt calcium and modify vessel compliance, allowing the creation of a sufficiently large lumen to negotiate large bore sheaths, facilitating device passage through calcific lesions. Thus, IVL offers a new alternative to traditional high-pressure dilatation or expandable/re-collapsible sheaths.
b) Calcific femoropopliteal lesions in patients with symptomatic claudication or critical limb ischaemia. In this setting, IVL may overcome recoil and balloon underexpansion, achieving sufficient lumen enlargement to reduce the incidence of flow-limiting dissections, and need for provisional stenting[49,50].
c) Calcific small peripheral artery below the knee (BTK) lesions in patients with symptomatic claudication or critical ischaemia. IVL in BTK lesions obtained high procedural success and an excellent safety profile as stand-alone treatment, unlike traditional devices used in BTK arteries that are burdened by a high rate of recoil and restenosis[51].

The IVL system components for use in the peripheral circulation are the same as those described for the coronary artery. Differences in catheter design and procedural application are shown in **Table 2**. Briefly, balloons designed for BTK and above the knee peripheral arteries are longer (40 mm, 60 mm), have a higher crossing profile (0.045”-0.050”, 0.054”-0.066”), have more emitters (five), have a longer duration of energy (20 seconds, 30 seconds) and a greater number of pulses per balloon (160, 300).

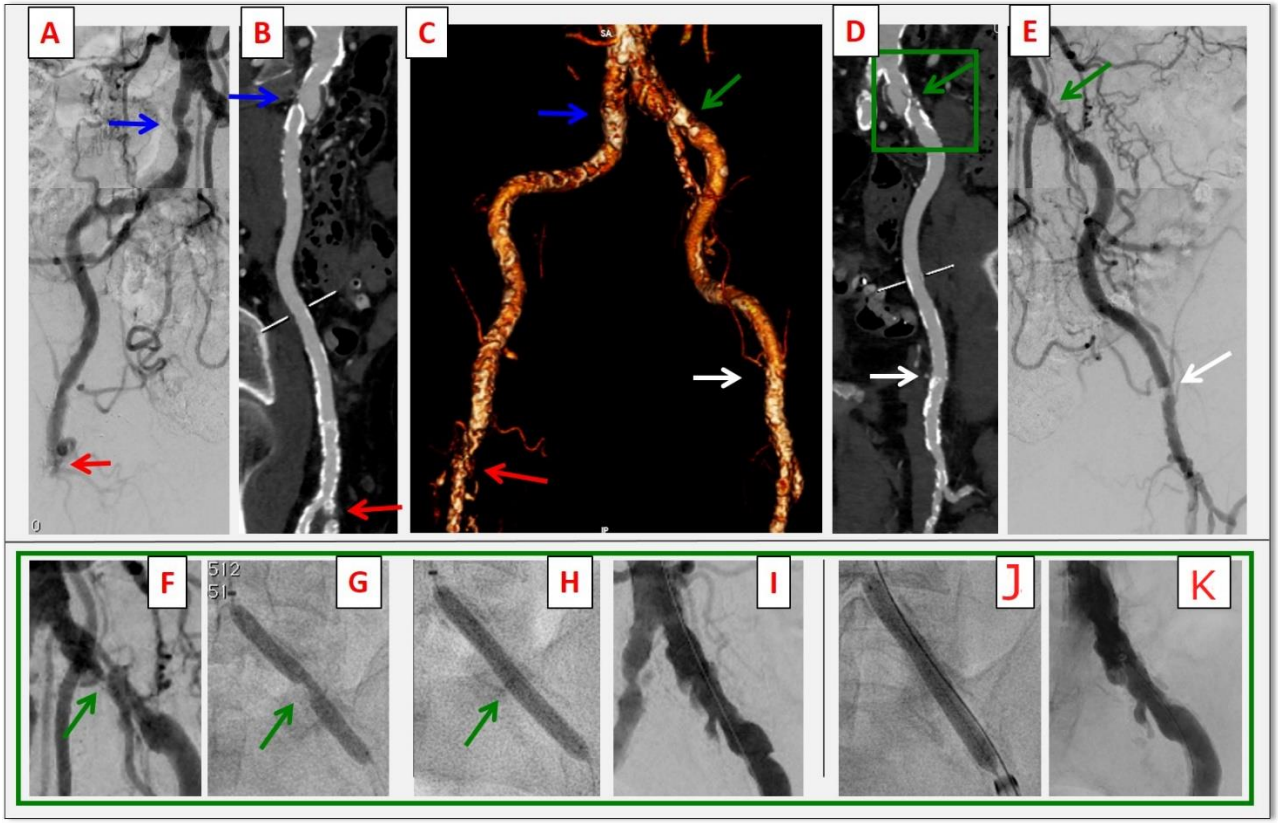
Clinical outcome of peripheral lithotripsy

Disrupt PAD I/II[49,50] are two multicentre single-arm registries, conducted in 95 patients symptomatic for intermittent claudication (Rutherford Class 2-4) and ankle-brachial index (ABI) <0.90, with angiographically calcific femoropopliteal lesions with diameter stenoses ≥70% (average lesion length 61.5 mm) and at least one patent run-off vessel to the foot **(Table 3)**. Severe calcification using the PARC definition was identified in 85.0% of subjects. Procedural success (<50% residual DS) was achieved in all 95 patients, with a mean acute gain of 3.0 mm (from 1.2±0.8 mm to 4.2±0.6 mm), and a reduction of percent diameter stenosis from 76% to 23%[49]. Furthermore, at one- and six-month follow-up there was no TLR with vessel patency rates of 100% and 82%, respectively. In the sixty patients followed up to 12 months, primary patency was 54%, and clinically driven TLR 21%[50]. These angiographic results paralleled a consistent improvement in Rutherford classification (100% in Class 2-3 at index down to 9.5% Class 2 and 0% Class 3 at six months) and ABI (0.7±0.2 to 1.0±0.3). In a Disrupt PAD II subgroup analysis, optimal balloon sizing (1.1:1 balloon to reference vessel diameter) and full coverage of lesion length were associated with 63% patency and a reduction in the rate of clinically driven TLR to 8.6% at 12 months. Peripheral IVL was safe, with major adverse events (one type D dissection requiring stent implantation which was from guidewire re-entry during a CTO recanalisation) occurring in 1.5% of patients without target limb emergency surgical revascularisation, major amputation, thrombus or distal emboli requiring treatment, vessel perforation or abrupt vessel closure. The rate of non-flow-limiting dissection was also low (type B: 8.4%, type C: 6.3%). Disrupt PAD III (NCT 02923193) is a prospective, randomised, multicentre, study comparing IVL with DCB versus PTA with DCB in 400 patients with femoropopliteal lesions followed for 24 months. The study also includes a 1,000-patient all-comer registry to assess real-world, acute performance of IVL in the lower extremities, including iliac, femoral, popliteal and infrapopliteal lesions.

Recent results from the Disrupt BTK study[51] were reported in 20 patients, Rutherford Class 3-5 (16 patients with critical limb ischaemia) with heavily calcific infrapopliteal lesions (angiographic

stenosis 72.6%, mean lesion length 52.2±35.8 mm). Procedural success was achieved in 95% of patients with a residual percent stenosis of 26.2% and an acute lumen gain of 1.5±0.5 mm. Two stents were implanted for residual stenosis but none for flow-limiting arterial dissection (only one grade B dissection reported), without major adverse events.

In addition to the Disrupt PAD and BTK studies, promising results are emerging from case reports and case series of patients with severe calcific lesions in which IVL has been utilised to treat symptomatic disease, including chronic total occlusions and critical limb ischaemia, as well as enabling access for large bore sheaths[52,53]. Similar to the results observed in the Disrupt PAD and BTK studies, the experience in other vessel beds or conditions demonstrates that IVL can successfully disrupt calcium and improve vessel compliance, resulting in a reduction in stenosis, increased acute gain with a low rate of complications. Promising results are also emerging from case series, specifically a consecutive series of more than 40 patients at eight centres in Italy and the USA treated with IVL to enable transfemoral access in patients otherwise precluded from transfemoral access for TAVI[53,54].



Supplementary Figure 1. IVL-assisted transfemoral TAVI.

A, B & C) Right iliac and femoral arteries: CT scan images and angiography showing diffuse calcification with critical stenosis of the proximal common iliac artery (blue arrow) and chronic total occlusion of the common femoral artery (red arrow).

C, D & E) Left iliac and femoral arteries: CT scan images and angiography showed diffuse calcifications, critical stenosis of the proximal common iliac artery (green arrows/box) and severe calcific stenosis of the common femoral artery (white arrows).

F-K) The critical stenosis of the left common iliac artery (primary access for TAVI) was treated with two IVL balloons (6.0 and 7.0x60 mm), with a good angiographic result (K). Note the severe indentation of the balloon (arrow in G) resolved after IVL activation (arrow in H) with no difference in balloon pressure (4 atm).

Supplementary Figure 2. Subocclusive calcific lesion of a superficial femoral artery in a patient with critical limb ischaemia.

A & B) CT scan and angiography showed a subocclusive calcific stenosis of a right distal superficial femoral artery (small box is a cross-section at the level of the stenosis: external contours of calcium are drawn in red, the small white circle represents the intima [corresponding to residual vessel lumen]). C & D) The lesion was dilated with a 5.0x60 mm lithotripsy balloon, with optimal immediate (C) and four-month results (D).