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Contemporary treatment options for surmounting the conundrum of calcified coronaries

Opções contemporâneas de tratamento para superar o dilema das lesões coronárias calcificadas

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ABSTRACT – Since the advent of balloon angioplasty in 1977, countless tools and techniques have been introduced and broadened the application of percutaneous coronary intervention in unprecedented anatomic settings. Heavily calcified coronary lesions traditionally continue to pose a challenge for percutaneous coronary intervention, since they are difficult to dilate adequately and/or there is inability to deliver and deploy drug eluting stents appropriately. Poor stent deployment is associated with increased procedural complications and suboptimal long-term outcomes. Thanks to the introduction of dedicated percutaneous coronary intervention tools, like cutting- and scoring balloons, atherectomy devices, and the novel intravascular lithotripsy technology, the treatment of such lesions has become increasingly feasible, safe and predictable. In this focused review, the author provides a summary of the principles, technique and contemporary evidence for various plaque modification strategies, with main objective of optimizing drug eluting stents delivery and deployment, translating into improved patient outcome.

Keywords: Percutaneous coronary intervention; Vascular calcification; Atherectomy; Lithotripsy

RESUMO – Desde o advento da angioplastia com balão, em 1977, surgiram inúmeras ferramentas e técnicas que ampliaram a aplicação da intervenção coronária percutânea em contextos anatômicos complexos. As lesões coronárias muito calcificadas continuam a representar um desafio para a intervenção coronária percutânea, pois dificultam sua dilatação bem como o implante adequado dos stents farmacológicos. A má expansão do stent está associada ao aumento de complicações relacionadas ao procedimento e a desfechos subótimos a longo prazo. Graças ao surgimento de instrumentais dedicados de intervenção coronária percutânea, como balões ateroabrasivos (*cutting balloon* e *scoring balloon*), dispositivos de aterectomia e a nova tecnologia de litotripsia intravascular, o tratamento dessas lesões tornou-se cada vez mais viável, seguro e previsível. Nesta revisão, é abordado um resumo dos princípios, da técnica e das evidências contemporâneas de várias estratégias de modificação de placa, com o objetivo principal de otimizar a navegação e o implante de stents farmacológicos, traduzindo-se em melhor desfecho para o paciente.

Descritores: Intervenção coronária percutânea; Calcificação vascular; Aterectomia; Litotripsia

INTRODUCTION

The extent of coronary artery calcification (CAC), an indicator of advanced coronary artery disease (CAD), strongly correlates with the degree of atherosclerosis and therefore with the rate of future cardiac events.¹⁻³ Despite remarkable progress in the treatment of CAD and improvement in interventional devices and techniques since the advent of percutaneous coronary intervention (PCI), the optimal treatment of lesions with heavy CAC remains a challenge for interventional cardiology professionals.

Advanced age, hyperlipidemia, hypertension, diabetes and chronic kidney disease have all been associated with CAC, and severe CAC affects 6% to 20% of patients treated by PCI.⁴ These conditions inflict endothelial injury and cell dysfunction, escalating an inflammatory response from leukocytes and vascular smooth muscle cells, which leads to calcium deposition in arterial intima and media.⁵ Even if

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routinely encountered, CAC is missed in nearly 50% of cases with coronary angiography alone as demonstrated by intravascular ultrasound (IVUS) studies.⁶

CAC is a surmountable problem in the catheterization lab accounting for inadequate dilatation of vessels, failure to deliver and deploy a stent, impaired drug delivery, and possible polymer damage with drug-eluting stent (DES), stent underexpansion and malapposition. High-pressure balloon inflations lead to perforations along with extensive intimal and medial dissections. Revascularization of lesions with CAC leads to increased procedural complications, long-term adverse events, and high rates of restenosis and stent thrombosis (Table 1).⁴

Table 1. Coronary artery calcification related percutaneous coronary intervention adverse events

Balloon ruptures
Vessel perforation or rupture
Dissection
Unsuccessful PCI due to non-dilatable lesions
Asymmetric, malapposed, and underexpanded stents
Increased MACE
Increased incidence of restenosis and TLR
Increased incidence of stent thrombosis
Higher incidence of periprocedural MI
Reduced drug concentration and uptake into arterial wall from drug-eluting stents

PCI: percutaneous coronary intervention; MACE: major adverse cardiac events; TLR: target lesion revascularization; MI: myocardial infarction.

The objective of this article is to summarize the principles, techniques, and contemporary evidence for currently plaque modification strategies, designed to optimize DES delivery and deployment, and improve subsequent short and long-term outcomes.

DETECTION AND QUANTIFICATION OF CALCIUM

Intravascular ultrasound

The hallmark of CAC on IVUS is echodense (hyperechoic) plaque that is brighter than the reference adventitia with shadowing (Figure 1A); however, dense fibrous tissue is also echodense, and can sometimes cast a shadow. Calcium, but not dense fibrous tissue, produces reverberations. Hyperechoic plaque with shadowing is highly sensitive, whereas reverberations are highly specific.⁷ Quantitatively (the arc of lesion), CAC has been categorized into four classes on IVUS: class I, 0° to 90° calcification; class II, 91° to 180° calcification; class III, 181° to 270° calcification and class IV > 270° calcification.⁸ Semiquantitative grading classifies CAC as absent or subtending 1, 2, 3, or 4 quadrants. Qualitatively CAC is described according to its location:

superficial (leading edge of acoustic shadowing within the most shallow 50% of plaque and media thickness) *versus* deep (leading edge of acoustic shadowing within the deepest 50% of plaque and media thickness).

Figure 1. Intravascular ultrasound and optical coherence tomography images depicting coronary artery calcium. (A) Intravascular ultrasound revealing the bright leading edge of superficial calcium closer to the lumen than adventitia (red arrow) with deeper shadowing (red star). Coronary artery calcium thickness and area cannot be assessed. (B) Optical coherence tomography showing the signal-poor and heterogeneous region with sharply delineated leading, trailing and lateral borders. Measurement of coronary artery calcium thickness and area is possible.

Optical coherence tomography

Optical coherence tomography (OCT) identifies CAC as signal-poor or heterogeneous region, with sharp delineated borders (Figure 1B). Its evaluation by IVUS is limited, because high intensity reflection with acoustic shadowing precludes assessment of thickness (Table 2). Since the penetration of calcium by OCT is greater than for other tissues, OCT, unlike IVUS, can measure CAC thickness, area and volume.⁹ Lesions with CAC score of 4 (2 points for maximum angle >180°, 1 point for maximum thickness >0.5mm, and 1 point for length >5mm) in OCT carry increased risk of stent underexpansion.¹⁰

Table 2. Various imaging modalities for coronary artery calcification

CAC	CAG	CT	IVUS (superficial calcium detection)	RF-IVUS (IVUS-VH; color-coded tissue composition)	OCT (sharp delineation of calcium area)
Detection	+	+++	+++	+++	++++
Localization	+	+++	+++	+++	++++
Quantification	+	+++	++	+++	++++

CAC: coronary artery calcification; CAG: coronary angiography; CT: computed tomography; IVUS: intravascular ultrasound; RF-IVUS: radiofrequency intravascular ultrasound; IVUS-VH: intravascular ultrasound virtual histology; OCT: optical coherence tomography.

Coronary angiography

CAC in coronary angiography is classified as none or mild, moderate, or severe. Moderate CAC is defined as radiopacities noted only during the cardiac cycle before contrast injection, whereas severe CAC is defined as radiopacities seen without cardiac motion, usually affecting both sides of the arterial lumen.

Computed tomography

A CAC score is calculated using a weighted value assigned to the highest density of calcification in each coronary segment, which is multiplied by the area and finally summed up for all arteries, to give a total coronary calcium score correlated with the patient outcomes.¹¹ Compared with individuals with a CAC of zero, those with a CAC >400 had a 1.8 to 3.2-fold increased risk of all-cause death, and a 3.1 to 5.1-fold increased risk of cardiovascular disease death.¹² The presence of spotty calcifications have been correlated with similar virtual histology and grayscale IVUS findings, which are indicative of unstable plaques.¹³

PLAQUE MODIFICATION STRATEGIES

Achieving adequate stent delivery and full stent expansion and apposition are critical to avoid many adverse outcomes associated with PCI in lesions with heavy CAC. A variety of plaque modification strategies have been developed to accomplish these goals (Table 3).

Non-compliant balloons

A non-compliant (NC) balloon may be the first step to enhance uniform expansion of the balloon. The risk of eccentric balloon expansion is not fully mitigated even with this due to the increased hoop stress conferred by severe calcification. The focal points of resistance within a lesion result in nonuniform balloon expansion and “dog boning”, with hyperexpansion in the more compliant segments without fracturing the calcium. The NC balloons exert more dilating force against a lesion than compliant balloons. A compliant balloon at high pressure in calcified lesions might cause dissection. The lesion may become resistant to high pressure dilatation to NC balloon when the arc of calcium extends to a large segment of the circumference of the vessel mandating the use of other adjunctive tools.^{14,15}

Super high-pressure balloon

In addition to standard NC balloons, super high pressure NC balloons, such as OPN (SISMedical AG, Winterthur, Switzerland), have been developed to deliver high post-dilatation pressure of ≥ 35 atm.^{16,17} It utilizes a twin-layer balloon technology permitting the use of very high-pressure inflations and ensures uniform expansion over a wide range of pressures, eliminating dog-boning. The balloon is highly NC, rapid exchange with a nominal pressure of 10atm and rated burst pressure (RBP) 35atm. Each balloon is factory tested to 45atm. The balloon diameters range from 1.5mm to 4.5mm, with available lengths of 10, 15 and 20mm.¹⁷ Diaz et al.¹⁸ used this super high-pressure balloon in patients of calcified, non-dilatable lesions, and achieved

Table 3. Lesion modification methods

Device	Mechanism
Non-compliant balloon	Little change in volume even at high pressure, concentrating dilating force at calcification site. The focal points of resistance within a lesion result in dog boning
Super high-pressure balloon	Use of ≥ 35 atm pressure inflation ensuring uniform expansion over a wide range of pressures, eliminating dog-boning
Constrained semi-compliant balloon	OTW balloon catheter with a mounted-nitinol-constraining structure, specifically designed for uniform, controlled inflation, and a rapid deflation facilitating an atraumatic dilation
Intentional balloon-assisted micro-dissection	Controlled vessel dissection facilitating delivery of secondary equipment beyond calcific lesion
Cutting balloon	Creation of 3 or 4 endovascular radial incisions through calcific tissue allowing further expansion with conventional balloons. The blades also anchor into the intima, therefore preventing balloon slippage and causing more uniform balloon expansion
Scoring balloon	Large and predictable luminal expansion by rectangular nitinol scoring edges
Lacrosse® non-slip element catheter	Leopard-crawl technique followed by scoring effect
Rotational atherectomy	Differential cutting
Orbital atherectomy	Differential sanding
Excimer laser coronary atherectomy	Photothermal ablation
Shockwave coronary lithotripsy	Transient acoustic circumferential pressure pulses

OTW: over-the-wire.

75% success rate without any adverse sequelae, thus providing a new way of yielding lesions when other NC balloons have failed. There is a significant increase of minimal lumen diameter (MLD) and acute luminal gain after OPN NC over a wide range of pressure, reducing risk of balloon rupture, vessel damage and coronary perforation.¹⁷ The main limitation of this balloon is its relatively high profile, which, together with the stiffness of the twin-layer technology, in most cases undermines any attempt to recross when inflated. Guide extension catheters may have to be used for successful delivery of these balloons in the lesion.

Intentional balloon assisted microdissection

A small (usually 1.20mm to 1.5mm) Threader (Boston Scientific, Natick, MA, USA) or Glider balloon (Boston Scientific, Natick, MA, USA) is negotiated as far as possible into the lesion and inflated at high pressure until it ruptures. This intentional balloon assisted microdissection causes intentional and controlled vessel dissection while maintaining wire position in true lumen, thus facilitating delivery of secondary equipment beyond calcific lesion. Intentional balloon assisted microdissection should be used as a last resort measure whether other strategies have failed or not available.¹⁹

Cutting balloon

The first atherectomy device to be developed is the cutting balloon (Flextome™, Cutting Balloon, Boston Scientific, Natick, MA, USA) available in monorail or over-the-wire (OTW) in a 6, 10 or 15mm long balloon catheter with three or four microtomes (microsurgical blades). These blades mounted longitudinally on the surface of a NC balloon are five times sharper than conventional surgical blades.²⁰ The cutting balloon should be inflated sequentially first 2atm, then 4atm and finally 6atm. During deflation, this device creates three or four endovascular radial incisions through calcified tissue, allowing further expansion with conventional balloons. Additionally, the blades anchor into the intima, thereby preventing balloon slippage within eccentric lesions, and cause more uniform balloon expansion. Its diameter and inherent rigidity can create difficulty in crossing the lesion. Furthermore, the pressure of the cutting balloon should not exceed 12atm in order to avoid embedding the device into the arterial wall.^{21,22} Above 16atm the risk of rupture is quite high, and a ruptured cutting balloon might become difficult to reinsert onto the guiding catheter. Use of this device prior to DES has been demonstrated to improve stent delivery, and lower target lesion revascularization (TLR).²⁰ The Wolverine™ cutting balloon (Boston Scientific, Natick, MA, USA) has a reduced crossing profile with precise and controlled cutting.

Scoring balloon

The most successful iteration of scoring balloon technology has been the AngioSculpt® (AngioScore, Inc., Fremont,

CA, USA) system, which consists of a dual lumen catheter with a semi-compliant, nylon balloon surrounded by an external nitinol-based helical scoring edge. The expansion properties of three rectangular spiral struts are influenced by a fixed distal end and a semiconstrained proximal end in relation to the balloon. This particular design enables a controlled and uniform expansion of the balloon and nitinol cage, preventing significant device slippage while scoring the plaque and maximizing lumen expansion. The AngioSculpt® is more flexible and deliverable compared to cutting balloon. However, it maintains the merits of cutting balloon including decreased incidence of balloon slippage, more uniform balloon expansion, reduced elastic recoil and an optimal MLD. The AngioSculpt® enhanced stent expansion, compared with direct stenting and plain balloon angioplasty with semi-compliant balloons, in an observational study comprising 299 patients undergoing IVUS-guided DES implantation.²³ Unfortunately no randomized controlled comparison exists between cutting and scoring balloons, and any consideration on the comparative performance of these devices is speculative. It is advisable to undersize the scoring balloon, inflating it at close to RBP. Both cutting and scoring balloons are used in lesions with mild to moderate CAC.²⁴

Constrained semi-compliant balloon (Chocolate®balloon)

The Chocolate®balloon (TriReme Medical, Pleasanton, CA, USA) is an OTW balloon catheter, with a mounted nitinol constraining structure specifically designed for uniform, controlled inflation, and a rapid deflation, facilitating an atraumatic dilatation without the need for cutting or scoring. The nitinol constraining structure generates balloon segments or “pillows” that make contact with the vessel, and functions to minimize local forces. The “grooves” promotes modification of the plaque. The distinctive pillow and grooves facilitate in minimizing vessel trauma, reducing the rate of dissection, leading to a decreased need for bailout stenting.²⁵

Lacrosse®non-slip element catheter and “leopard-crawl” technique

The design of the scoring catheter is subject to a potential “slacking” phenomenon and is also unable to create multiple scoring effects. The cutting balloon lacks flexibility, with an increased risk for causing vessel perforation. The “leopard-crawl” technique overcomes these obstacles, using a low inflation pressure to create a wedge into the calcification and, subsequently, advancing the catheter during balloon deflation to facilitate catheter delivery across the lesion across tortuous vessel. This technique is well suited for the Lacrosse® non-slip element (NSE) due to the unique catheter design. The Lacrosse® NSE catheter (Goodman Co, Ltd, Japan) is available in 2.0-4.0-mm balloon sizes,

contains three triangular nylon elements (width, 0.014" x height, 0.015") that are free floating on the outside of the balloon surface, and attached proximal and distal to a 13-mm balloon length. Dilation using a Lacrosse® NSE creates a scoring effect into calcified tissue through a focused transmission of force through the very distal portion of these elements. The Lacrosse® NSE elements are attached distal to the balloon location, and for instances whereby the catheter is unable to cross lesion location, a "leopard-crawl" technique can assist in facilitating smooth device delivery. This is considered an effective technique given the preconditions of: a low profile of the distal catheter that allows the tip to be advanced to the lesion location; and a good re-wrap functionality of the balloon.²⁶ Following Lacrosse® NSE deflation, the connection of elements located distal to the balloon folds is similar to folding mechanism of an umbrella, with the distal profile derived from the size of the folded element. The elements refold parallel to the body of the catheter, ensuring that the Lacrosse® NSE distal portion maintains a low profile. In comparison, other scoring balloons have either: fewer elements, making multiple scoring effects difficult; or a blade contained within the balloon segment affecting the rewrap functionality. A larger balloon profile post inflation affects the ability to perform the leopard-crawl technique.²⁶

Careful consideration of both sizing of the catheter and the inflation pressure applied is important. Generally, the Lacrosse® NSE can be safely and effectively used for calcified lesions through selection of a catheter size that limits expansion to a smaller size than the adventitia or media. Confirmation of vessel diameter and luminal size of the calcified lesion using IVUS imaging prior to PCI is preferable. The size selection based on 25% to 50% less than the vessel diameter at calcified location, determined by coronary angiography, is considered a safe alternative when IVUS evaluation is unavailable. Balloon inflation pressure should commence from a low inflation and increase slowly (4atm, to 6atm, to 8atm). After successfully delivering the Lacrosse® NSE to the distal site, dilatation using higher pressure (close to RBP which is 14atm) can be performed to treat the target lesion.²⁷

ATHERECTOMY

A strategy of debulking calcified lesions, as a part of bail-out technique to address balloon undilatable stenoses, has evolved into a primary lesion preparation approach called "primary atherectomy". Compared to bail-out atherectomy, the primary atherectomy is associated with decreased procedural and fluoroscopy times, contrast volume, and the number of predilatation balloon catheters used.²⁸ This alters plaque morphology, inducing fractures in CAC and changing lesion compliance, to increase the likelihood of maximal MLD and complete stent expansion. Atherectomy is currently achieved with either rotational (RA), orbital (OA) or laser atherectomy (Figure 2).

Figure 2. Schematic illustrations of atherectomy devices used for modifications of coronary artery calcium. (A) Stenotic artery. (B) Rotational atherectomy. (C) Orbital atherectomy. (D) Excimer laser atherectomy.

Rotational atherectomy

The RA acts on the principle of "differential cutting" and "orthogonal displacement of friction". The commercially available Rotablator® (Boston Scientific, Natick, MA, USA), invented by Auth and described by Ritchie et al.,²⁸ selectively ablates inelastic fibrocalcific plaques while sparing adjacent elastic tissue. These microchips coated on the burr grind calcified plaque into microscopic particles (5 to 10µm in diameter), smaller than red blood cells, which are washed downstream and are removed from the circulation by the reticuloendothelial system. This selective ablation of fibrocalcific plaque renders a polished smooth luminal surface compared to multiple intimal tears/dissection with balloon angioplasty.²⁹ It minimizes vessel wall stretch and elastic recoil, eliminates vessel barotrauma, and modifies plaque to facilitate stent delivery and expansion. With ablation of plaque burden, less pressure is required for further balloon expansion.

The Rotablator® system

The Rotablator® system (Boston Scientific, Natick, MA, USA) is composed mainly of advancer, console and burr. The advancer has a burr knob control on the upper part and, on the side, it has a saline infusion port, a fiber optic tachometer cable connection, and an advancer hose with the compressed gas connector. The nickel-plated burr has an elliptical shape and is encrusted with 2,000 to 3,000 diamond microchips. The burr is attached to a nickel-plated driveshaft, covered by a Teflon sheath that allows the saline solution to cool and lubricate the rotating components, while preventing possible driveshaft-induced injury to the vessel.

A new generation of RA system (ROTAPRO™, Boston Scientific) has been being launched with major modifications mainly directed to simplifying its use. The foot pedal has been replaced with a button positioned on the top of the burr control knob of the advancer. The Dynaglide™ pedal has also been replaced by a button on the side of advancer. The Dynaglide™ mode enables the burr to rotate at a

fixed speed between 60,000 and 90,000rpm to facilitate burr exchange. The assembly is smaller, easier, streamlined, with a new digital display with deceleration indicators on the control console.

Contemporary rotational atherectomy technique

Contemporary RA has been refined,³⁰ from the strategy (primary *versus* bailout),³¹ the procedural set-up to the tools and techniques applied. The arterial access that was traditionally a large 8-F femoral sheath, is now a contemporary 6-F radial or femoral sheath. The wiring technique has been facilitated by the use of a regular workhorse wire or hydrophilic wire subsequently exchanged over microcatheters or OTW balloons with the rotawire. Fundamental elements of optimal technique include use of a single burr (1.5mm) with burr-to-artery ratio of 0.6, rotational speed of about 140,000 to 180,000rpm, gradual burr advancement using a pecking motion, short ablation runs of 15 to 20 seconds, and avoidance of decelerations >5,000rpm. However, in lesions not crossable with a 1.5-mm burr (Figure 3) or in

very long tortuous segments, a 1.25-mm burr with step-wise escalation may be necessary (Table 4). The need for a temporary pacemaker has been reconsidered due to significantly lower incidence of transient heart block with smaller burrs and lower speeds, easily manageable with the use of either atropine or aminophylline.

Advancer knob should be locked 2cm to 3cm forward before advancing the burr into a guide catheter. When burr is proximal to lesion, any forward tension on drive shaft is relieved by unlocking advancer knob and pulling it back. The rotation is commenced with loosening the advancer knob, depressing the hand pedal and gently moving the burr forward into the lesion. One must ensure that the initial burr speed is similar to that set outside the patient. The rotational speed significantly below that level would indicate the friction within the guide, and will reduce burr performance. The operators must avoid over-tightening Y-adapter, dottering, stopping burr in and distal to lesion, adjusting rpm during ablation, advancing rotating burr to point of contact with the guidewire spring tip, and avoid burring in the guide catheter.³² After each

Figure 3. Use of rotational atherectomy in non-dilatable calcified lesion. (A) Coronary angiogram depicting diffuse calcific lesion (black arrow) of proximal and mid left anterior descending artery. (B) Evidence of dog boning (black arrow) despite high-pressure dilatation with non-compliant balloon. (C) Plaque modification by rotational atherectomy using 1.5mm burr (black arrow). (D) Final angiographic result after dilatation with non-compliant balloon and deployment of two overlapping drug eluting stents.

Table 4. Tips and tricks for optimal coronary rotational atherectomy³²

Preference for single smaller burr (usually 1.5mm) with burr-to-artery ratio of 0.6
Use of 1.25-mm burr in long tortuous lesions or when lesion not crossable with 1.5-mm burr
Rotational speed of 140,000-180,000rpm
Gradual burr advancement using a pecking motion
Shorter ablation runs of 15-20 seconds
Lesion contact time of 1-3 seconds with longer 3-5 seconds of reperfusion to allow debris clearance
Strict avoidance of decelerations (>5,000rpm for >5 seconds)
Flushing of the system with diluted contrast during the ablation runs
Keeping the guidewire wet at all times to avoid friction
Continuous movement to keep the device from becoming warm especially in angled/tortuous vessels
Final polishing run

ablation, the burr is brought back to the starting position and the patient's clinical status and electrocardiogram are checked. Once the burr has completely crossed the lesion, it can be advanced for longer times and over longer distances for final lesion "polishing". Luo et al.³³ applied the modified strategy comprising: "double flush" with a cocktail from guiding catheter and RA system (increasing the flushing pressure for debris passing through the coronary microvasculature, cools down the Rotablator® turbine, and further reduces slow/no flow occurrence); the "imaging device passage" (1.5mm burr for IVUS crossable, and 1.75mm burr for IVUS uncrossable lesions, based on burr size); and "high" speed (160,000 to 220,000rpm) to cross, followed by "low" speed (140,000-160,000rpm) warrant efficient lesion cross the lesion and sufficient plaque modification.

In a bifurcation lesion requiring RA of side branch, a guide extension is advanced to the ostium of side branch to prevent the main branch guidewire to interact with RA burr. To perform RA of the side branch lesion, the RA burr can subsequently advance through the guide extension catheter.

Contemporary rotational atherectomy evidence

Interventionists began with great enthusiasm for RA, but the initial hope for a lower restenosis rate due to lack of barotrauma and vessel dissection was not supported by the DART (Dilatation vs Ablation Revascularization Trial Targeting Restenosis),³⁴ ERBAC (Excimer Laser, Rotational Atherectomy, and Balloon Angioplasty Comparison),³⁵ STRATAS (Rotablator and Transluminal Angioplasty Strategy)³⁶ or CARAT (Coronary Angioplasty and Rotablator Atherectomy Trial)³⁷ trials. The initial enthusiasm

was struck with marked decrease in the rate of RA. The conundrum of the post-PCI restenosis has been largely eliminated by the advent of DES. It is clear that heavy CAC remains the bugaboo of intervention. DES has 6% failure rate to deliver, and a two-fold higher failure rate of successful deployment in calcified lesions compared to BMS.²⁹ Vigorous manipulations of DES in these lesions can crack the polymer, leading to increase in vascular inflammatory response.^{38,39} Suboptimal deployment of DES could increase stent thrombosis.⁴⁰ DES implantation after RA has been shown to achieve a better prognosis. Theoretically, RA and DES could act synergistically in complex lesions, since RA can avert stent coating damage, and DES can effectively suppress neointimal proliferation. The renaissance of RA in DES era, particularly in very complex CAC, underscores the importance the plaque modifications before DES could be successfully delivered, precisely placed, and deployed to exert the desirable effects. In fact, contemporary observational studies and registries have demonstrated favorable results of DES deployment in heavy CAC after RA.^{41,42} However, the randomized clinical ROTAXUS (Rotational Atherectomy Prior to TaxusStent Treatment for Complex Native Coronary Artery Disease)⁴³ trial failed to demonstrate a superiority of RA versus conventional balloon dilatation before DES in heavy CAC. The patients with heavy CAC can not be treated without RA, and therefore can not be randomized, as shown by the 8% higher crossover rate from plain balloon angioplasty to RA observed in this trial.⁴³ Based on ROTAXUS results, RA could not be routinely recommended for lesion preparation in calcific lesions. Upfront high-speed RA of severely calcified lesions is feasible in nearly all patients, and improves the success of DES deployment compared with modified cutting or scoring balloons, according to results of the contemporary PREPARE-CALC trial (Comparison of Strategies to PREPARE Severely CALCIFIED Coronary Lesions). Although both strategies are equally safe and effective, "the use of RA is no longer associated with excessive late lumen loss in the modern era".⁴⁴

The current PCI guidelines state that RA is reasonable for heavily calcified lesions, which remain balloon uncrossable or undilatable before planned stenting (class IIa, level of evidence C).⁴⁵

Prevention and troubleshooting of rotational atherectomy complications

Procedural complications (Table 5) that occur with RA include dissection, perforation, slow-flow/no-reflow phenomenon, burr entrapment, rotawire entrapment, over heating vasospasm, and transient heart block. Such complications may be reduced by adhering to proper technique; i.e., slower speeds, short runs (<20 seconds) and limited deceleration (<5,000rpm).

Table 5. Prevention and troubleshooting of rotational atherectomy complications

Complications	Prevention and troubleshooting
Bradycardia and atrioventricular block	Limiting ablation times (<15-20 seconds)
	Pretreatment with atropine
	Deactivation of burr if heart rate decreases
	Temporary pacemaker for right coronary artery and left circumflex lesions
Slow flow/no-reflow	Use of smaller burr
	Intermittent ablation
	Avoidance of significant decelerations
	Limiting the ablation time to 15-30 seconds
	Increasing the time between the ablations
	Slower speed (140,000rpm) associated with lower platelet aggregation
	Optimal antiplatelet and antithrombotic regimens
	Optimal blood pressure if low
	Use of intracoronary vasodilators (nitrates/verapamil/adenosine/nitroprusside)
Over-heating	Use of small burr in a pecking-like motion
Burr stalling	Retraction of the burr from the lesion and moving it forward more slowly and less forcefully
	Avoidance of kinking of guide catheter
	A higher burr speed and smaller burr size
Burr entrapment	Deep guide intubation with controlled back and forth traction on the helical shaft
	Setting rotational speed up to 200,000rpm and trying to negotiate the burr into distal true lumen
	Cutting off rotalink shaft distal to the advancer and removal of outer sheath
	Positioning a second guidewire (dual catheter technique) beyond entrapped burr and inflation of balloon proximal to it
	Advancement of snare over the exposed drive shaft as close to the burr as possible and simultaneous retraction on the snare and guide
	Negotiation of child-in-mother catheter
	Subintimal tracking and reentry with balloon dilatation adjacent to the trapped burr
	Emergent cardiovascular surgery
Guidewire fracture	Keeping the guidewire out of small branches
	Repositioning the guidewire frequently during long ablations
	Fastening the wire clip properly
	Avoidance of guidewire tip prolapse
	Retrieval with snares, basket, or forceps
Rotawire entrapment	Advancement of over-the-wire balloon or microcatheter on the Rotablator® wire and tunneling outside the expanded stent to facilitate traction and wire removal

Orbital atherectomy

Similar in operational concept to RA, the OA (Diamondback 360, Cardiovascular System, Inc, St Paul, MN, USA) has been approved for use in the coronary arteries since 2013.⁴⁶ It overcomes some of the limitations of RA. It uses diamond-coated eccentric crown (at the distal end of a drive shaft) that rotates over ViperWire® (Cardiovascular Systems, Inc, St Paul, MN, USA) at 80,000rpm on low speed, and 120,000rpm on high speed. It has a differential sanding mechanism of action to reduce plaque while minimizing damage to the healthy tissue. As with RA, OA utilizes continuous infusion of lubricant solution (Viper-Slide™, Cardiovascular System, Inc, St Paul, MN, USA) for

safe operation; unlike RA, the OA system disables by itself in absence of sufficient flush (Table 6). The OA crown has diamond chips on both front and back, enabling bidirectional atheroablation. The crown entrapment is less likely as compared to burr entrapment⁴⁷ due to retrograde ablation. The OA incorporates centrifugal forces to enlarge the lumen diameter by differential sanding of calcium. The usual recommended duration of treatment is 20 seconds or less per pass. The unique mechanism permits continuous flow of blood and saline during orbit, reducing heat generation (Table 7).⁴⁸ A single 1.25-mm crown delivered through a 6-F guiding catheter can be effective for reference vessels up to 3.5mm in diameter. The 1.25-mm crown size

Table 6. Comparison of rotational and orbital atherectomy

	Rotational atherectomy	Orbital atherectomy
Device	Rotablator®	Diamondback 360®
Manufacturer	Boston Scientific, Natick, MA	Cardiovascular System, Inc., St. Paul, MN
Guidewire	0.009" RotaWire™	0.012" ViperWire®
Lubricant	Rotaglide™	ViperSlide™
Power source	Pneumatic system, requires console, foot pedal and compressed gas supply; nitrogen tank or room air	Electronic system able to be placed on the operating field, connects to a specialized saline pump
Atheroablation	Differential cutting	Differential sanding
Ablative device	Burr	Crown
Diamond chips	Anterior	Anterior and posterior
Axial motion	Rotational, concentric	Centrifugal, eccentric
Longitudinal motion	Pecking, intermittent	Gradual continuous
Device size	Multiple (1.25-2.5mm), interchangeable	Single 1.25mm crown, with larger path carved by higher speed
Guide catheter size	6F (1.25-1.75mm burr) 7F (2mm burr) 8F (2.25-2.5mm burr)	6F
Ablation speed	140,000-180,000rpm	80,000-120,000rpm
Direction of ablation	Antegrade only	Both antegrade and retrograde
Maximum run	20 seconds	25 seconds
Adjustable ablation diameter	No (necessary to change the burr size)	Yes (just control the rotational speed)
Learning curve	Longer	Shorter
Time and complexity of set up	Longer and more complex	Relatively shorter and less complex
Body of experience	Decades	Years
Effect on plaque	Shallower dissections	Deeper dissections
Particle size	5-10µg	2µg
Slow flow/no-reflow	More	Less
Coronary perforation	More	Less

Table 7. Tips and tricks for orbital atherectomy

Positioning of ViperWire® to ascertain minimum of 10-mm distance between OA system and guidewire tip during treatment
Priming of OA system (outside the body), performance of momentary spin, opening of brake, locking control knob, and leaving pump on
Advancement of the OA crown approximately 35mm proximal to lesion and unlocking of control knob
Use of lower speed targeting a traverse rate of 1-3mm/second to maintain the speed within 1-10mm/second range
Avoidance of pecking motion, since this would result in traversing faster than 10mm/second
Use of series of intermittent treatment intervals with rest periods at least equal to treatment duration
Maintenance of 1:1 motion between crown and advancer knob
Use of high speed in non-tortuous large (≥3mm) vessel
Locking of control knob and removal of OA system

OA: orbital atherectomy.

is standard for all coronary arteries (Figure 4) and can treat at larger-sized lumens, by either increasing the speed or by slowing the rate of advancement to allow an increase in

the diameter of the elliptical orbit. By decreasing the traverse speed to 1mm/second at high speed, the burr orbit can exceed 2mm in diameter. Low speed should be used for all initial passes with OA. If an adequate endpoint has not been achieved at low speed, treatment can be escalated to high speed. High speed is not necessary for all cases, and specifically should be avoided in small and excessively tortuous vessels to reduce the risk for perforation.⁴⁸ Whereas the RA burr is moved forward in a slow, pecking motion to allow intermittent ablation to decrease risk of burr stalling or entrapment; the OA crown is advanced with a gradual, continuous motion, even interrupting in a region of interest to permit more time for ablation. The small particulate size and continuous flow during orbit may contribute to the low rates of transient heart block and no-reflow that has been observed in OA as compared to RA (Table 6). The Micro Crown OA system represents the next technological advance aimed at improving the efficiency of orbital atheroablation. This OA iteration has its driveshaft redesigned to aid in crown delivery, the available sanding area increased, and importantly modified to operate at lower rotational speeds (low: 50,000rpm and

Figure 4. Application of orbital atherectomy in calcified lesion. (A) Coronary angiogram depicting calcified lesion (black arrow) of mid and distal right coronary artery. (B) Navigation of guidewire in distal true lumen (black arrow). (C) Plaque modification of orbital atherectomy with 1.25 crown (black arrow). (D) Final angiographic result after dilatation with non-compliant balloon and deployment of two overlapping drug eluting stents.

high: 70,000rpm). Implementation of this technology is likely to expand the options of atherectomy in increasingly complex patient and angiographic profiles.⁴⁹

The ORBIT 1 trial (Coronary Orbital Atherectomy System for Treating *De Novo*, Severely Calcified Coronary Lesions in Elderly Patients), a prospective, single arm study demonstrated device success of 98% and procedural success of 94% in 50 patients with *de novo* calcified plaque. The major adverse cardiac events (MACE) rate was 18.2% at 3 years, and 21.2% at 5 years.⁴⁶ In the ORBIT II trial employing 443 patients, OA was associated with 97.7% rate of successful stent delivery, and low rates of in-hospital Q-wave myocardial infarction (0.7%), cardiac death (0.2%), and target vessel revascularization (0.7%).⁵⁰ The 3-year follow-up demonstrated the durability of these results, with a 7.8% TLR in patients treated with OA.⁵¹

Kiniet al.,⁵² in a series of 20 patients, assessed the mechanistic differences of impact of RA and OA with OCT. The OA was associated with deeper dissections particularly in more lipid and less calcific plaques. The OA treated patients had a signal toward increased stent expansion and significantly lower incidence of stent strut malapposition

as compared to RA. The COAST (Coronary Orbital Atherectomy System Study) reported the procedural success rate to be 85% (95%CI 76.5-91.4), with 99% successful stent delivery, 99% residual stenosis <50%, and 14% in-hospital MACE.⁵³ The impact of OA on the microcirculation is being evaluated in the prospective ORACLE trial (Comparison of Orbital Versus Rotational Atherectomy Effects On Coronary Microcirculation in PCI; ClinicalTrials.gov IdentifierNCT03021577), which randomized 20 patients with calcified lesions to either OA or RA, and will compare the coronary flow reserve and the volume of myocardial necrosis on serial magnetic resonance imaging scans. The ongoing, randomized ECLIPSE (Evaluation of Treatment Strategies for Severe Calcific Coronary Arteries: Orbital Atherectomy vs Conventional Angioplasty Technique Prior to Implantation of Drug-Eluting Stents: The ECLIPSE Trial; ClinicalTrials.gov IdentifierNCT03108456) is evaluating whether or not routine lesion preparation with OA will result in improved acute luminal gain and 1-year target vessel failure in comparison with balloon angioplasty alone. The integrated applications of RA with intravascular imaging are also being evaluated, and will likely to shed light on our

understanding of how to optimize lesion modification before stenting – ORBID-OA (Feasibility of Orbital Atherectomy System in Calcified Bifurcation Lesion; ClinicalTrials.gov Identifier NCT03058510). In view of simplicity of usage and lesser complications compared to RA (Table 6), OA might gain widespread use in future. However, further controlled studies directly comparing the safety and efficacy of the two modalities are required.

Excimer laser coronary atherectomy

Excimer laser coronary atherectomy (ELCA), by means of a photoacoustic mechanism, has been used to treat resistant coronary stenoses. The ELCA, an alternative treatment approach in CAC, employs photochemical, photothermal and photomechanical mechanisms to ablate plaque. The fragments released are 10µm in diameter, avoiding microvascular obstruction, because they are absorbed by the reticuloendothelial system.^{54,55} The CVX-300 system (Spectranetics, Colorado Springs, CO, USA) emits pulses of ultraviolet light at 308nm wavelength; the generated ultraviolet pulses only penetrate tissue depths of 50µm and, therefore, lead to relatively pure plaque disintegration, without injuring the deeper medial or adventitial layers. Care must be taken to select a guiding catheter that provides adequate back up to remain coaxial during lasing. The size of laser catheters selection is based on the severity of the lesion, the reference vessel diameter, and consistency of the target material. It is recommended to use the 0.9mm rapid exchange ELCA laser X-80 catheter, which can be advanced over any standard 0.014-in guidewire, at a fluence of 80mJ/mm², and a repetition rate of 80Hz with simultaneous saline infusion. To minimize the risk of inadvertent dissections or perforations induced by microbubbles generated from particles within the blood, a continuous normal saline infusion (usually at 1mL/s to 2mL/s) during laser is recommended. The pulses of laser energy are delivered as the catheter is slowly (0.5mm/second) advanced through the lesion, allowing adequate absorption and ablation. The ablation will be sub-optimal if the catheter is advanced too rapidly, so that the tissue does not have time to absorb the light energy.⁵⁵ The ELCA catheter can cross even moderately calcified lesions creating a “pilot hole”, which enables delivery balloons and stents in 93% of all balloon-crossing failures. For heavy CAC, ELCA may provide sufficient plaque modification to allow microcatheter advancement to then switch to an atherectomy wire, which permits the use of atherectomy facilitating optimal balloon expansion and stenting (the RASER technique).^{56,57}

INTRAVASCULAR LITHOTRIPSY

Intravascular lithotripsy (IVL, Shockwave Medical, Fremont, CA, USA) is a novel device that delivers localized pulsatile sonic pressure waves, modifying preferentially calcific

plaque without affecting the endovascular soft tissue, and subsequently facilitating stent delivery and optimization. The mechanism is leveraging electrohydraulic-generated lithotripsy to create high-speed sonic pressure waves, which pass through soft tissues to selectively disrupt calcium.⁵⁸ IVL for the treatment of coronary calcification was first performed in 2016.⁵⁸ The balloon catheter containing multiple lithotripsy emitters is advanced to the target lesion over a standard coronary guidewire. The balloon is attached to the external pulse generator. After the balloon is inflated at low pressure (4atm), a burst of ten pulses of high energy is delivered over 10 seconds, followed by further balloon inflation at 6atm, for 15 to 20 seconds before deflation (Figure 5). This process can be repeated at a target lesion to a total of eight cycles per balloon (80 pulses). The balloon sizing is based on the desired stent size for that target lesion (i.e., 1:1 for the reference vessel diameter), and is often guided by the IVUS or OCT.⁵⁹ The IVL coronary balloons are all 12 mm in length and range from 2.5mm to 4.0mm diameter in 0.5-mm increments. Guide catheter extenders and buddy-wire support may be used to facilitate deliverability and positioning of this large profile balloon.

The IVL therapy creates calcium fractures as assessed with IVUS or OCT, and achieves optimal stent expansion in non-dilatable lesions, resistant to specialty balloons and RA.⁶⁰⁻⁶² In contrast, some lesions might not be amenable to IVL therapy, or may remain resistant after application of all 80 pulses. IVL balloon catheter deliverability and positioning could be affected by severe tortuosity or angulation, critical lumen reduction, plaque indentation into the lumen, and small vessels and multiple stent layers. Up to 46% of the lesions might also require dedicated lesion pre-dilation and/or post-dilation with NC balloons, or could benefit from adjuvant lesion preparation with conventional devices such as cutting or scoring balloons, or atherectomy, to either facilitate balloon delivery or increase calcium compliance after IVL therapy.^{61,63} IVL works without concerns of guidewire bias, for the inflated balloon attacks CAC circumferentially. Reduced learning curve, apparent lack of embolization and perforation are all very attractive attributes of IVL as compared to atherectomy. Furthermore, IVL is possible after stenting, in contrast to atherectomy.

The IVL can cause vessel complications although balloon rupture is uncommon. The sudden balloon burst has been described with arterial dissection during lithotripsy therapy. It should be used with caution in critical stenosis or tortuous artery.^{64,65} Recently there is a case report of perforation following this therapy.⁶⁶ Furthermore, vessels with a diameter >4mm (maximum shockwave balloon size), or important plaque eccentricity, preclude appropriate IVL balloon apposition to the vessel wall, and may reduce the efficacy of the therapy. The Disrupt-CAD (Disrupt Coronary Artery Disease) trial, a prospective multicenter, single-arm study enrolling 60 patients with heavy CAC, treated

Figure 5. Application of intravascular lithotripsy in non-dilatable calcified lesions. (A) Severe mid and right coronary artery stenosis with calcification. (B) Evidence of dog boning (black arrow) despite high-pressure dilatation by non-compliant balloon. (C) Application of intravascular lithotripsy with complete balloon expansion (black arrow). (D) Final angiographic result after stent implantation.

with shockwave IVL, reported 98% device success, 100% stent delivery, low MACE rate, high acute gain and no cases of dissection, perforation, abrupt closure, or no-flow or slow-flow phenomena.⁶⁷ IVL could be safely performed with high procedural success, minimal complications with substantial calcific plaque fracture in most lesions, in a prospective multicenter Disrupt CAD II study.⁶⁸ Disrupt CAD III (ClinicalTrials.gov Identifier: NCT03595176) is a prospective, non-randomized, multicenter study, likely to evaluate the safety and effectiveness of the Shockwave Coronary IVL System in 392 patients of severe CAC, prior to stenting. The study will assess freedom from MACE within 30 days of the index procedure as the primary safety endpoint. The primary effectiveness endpoint is procedural success, defined as stent delivery with a residual stenosis of less than 50 percent and without in-hospital MACE.

CONCLUSIONS

The landscape of PCI has dramatically changed during the last few years. Despite the improvements in the interventional devices and techniques, the subset of CAC

poses significant challenge for PCI. Technical challenges associated with treatment of these lesions can result in worse longer-term outcomes. In current practice, the optimal therapy for significant coronary artery calcification is multi-adjunctive and requires the availability of several strategies in the catheterization lab (Figure 6). PCI of these lesions have demonstrated high procedural success rate and relatively low risk with use of rotational atherectomy, orbital atherectomy, Excimer laser coronary atherectomy or, more recently, of intravascular lithotripsy. The future improvements in balloon catheter flexibility and crossing profile, as well the addition of hydrophilic coatings, will further enhance the negotiability (hence the utilization) of cutting and scoring balloons. The application of an antiproliferative drugs on these balloons would combine the benefit of balloon based atherectomy and antiproliferative properties of drug-eluting balloons. Despite the growing data for various modalities, rigorous head-to-head comparison remains to be performed, and additional randomized trials are needed to further clarify the superiority of one modality over the another.

OCT: optical coherence tomography; NC: non-compliant balloon; ELCA: Excimer laser coronary atherectomy; IVL: intravascular lithotripsy; OA: orbital atherectomy; RA: rotational atherectomy.

Figure 6. Proposed approach for treatment of calcified coronary lesions.

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The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: DD, NA and RM; data collection: DD, NA and RM; data interpretation: DD, NA and RM; text writing: DD, NA and RM; approval of the final version to be published: DD, NA and RM.

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