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Early outcome of high energy Laser (Excimer) facilitated coronary angioplasty ON hARD and complex calcified and balloOn-resistant coronary lesions: LEONARDO Study

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ABSTRACT

Aim: An innovative xenon–chlorine (excimer) pulsed laser catheter (ELCA X80) has been recently used for the treatment of complex coronary lesions, as calcified stenosis, chronic total occlusions and non-compliant plaques. Such complex lesions are difficult to adequately treat with balloon angioplasty and/or intracoronary stenting. The aim of this study was to examine the acute outcome of this approach on a cohort of patients with coronary lesions.

Methods and Results: Eighty patients with 100 lesions were enrolled through four centers, and excimer laser coronary angioplasty was performed on 96 lesions (96%). Safety and effectiveness data were compared between patients treated with standard laser therapy and those treated with increased laser therapy. Laser success was obtained in 90 lesions (93.7%), procedural success was reached in 88 lesions (91.7%), and clinical success in was obtained in 87 lesions (90.6%). There was no perforation, major side branch occlusion, spasm, no-reflow phenomenon, dissection nor acute vessel closure. Increased laser parameters were used successfully for 49 resistant lesions without complications.

Conclusions: This study suggests that laser-facilitated coronary angioplasty is a simple, safe and effective device for the management of complex coronary lesions. Furthermore, higher laser energy levels delivered by this catheter improved the device performance without increasing complications.

1. Introduction

Despite the increasing use of percutaneous transluminal coronary angioplasty and intracoronary stent placement for the treatment of obstructive coronary artery disease, a large subset of coronary lesions cannot be adequately treated with balloon angioplasty and/or intracoronary stenting alone. Such lesions are often heavily calcified or fibrotic, and undilatable with the present balloon technology. The attempts to treat them with balloon angioplasty or intracoronary stent placement can lead to vessel dissection or incomplete stent deployment with adverse outcomes. Currently, the increase in life expectancy has forced interventional cardiologists to treat patient populations that are getting older with coronary lesions becoming progressively more complex. Among some of these hard lesions, calcified stenosis, chronic total occlusions, and non-compliant plaques remain major technical challenges. Despite advances in technology and technique, these lesions may be resistant or untreatable by percutaneous techniques restricting therapeutic options. Description of recent non-selective cohorts of patients requiring coronary angioplasty included 12% of severely calcified lesions [1], 10% of chronically occluded arteries [2], and 1.5% of non-resilient plaques to balloon angioplasty (non-dilatable or uncrossable) [3].

An innovative xenon–chlorine (excimer) pulsed laser catheter (ELCA X80; Spectranetics, Colorado Springs, CO) capable of delivering higher energy density with lower heat production (smaller area of ablation) has been recently used for treatment of these complex lesions [4]. This instrument is a 6 Fr-compatible catheter that incorporates 65 concentric 50 m fibers with the potential of delivering excimer energy (wavelength 308 nm, pulse length 185 nanoseconds) from 30 to 80 mJ/mm2 (fluences) at pulse repetition rates (frequency) from 25 to

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80 hertz, using a 10-s on and 5-s off lasing cycle. This innovative laser was developed in the style of the existing excimer catheter technology (0.9, 1.4, 1.7, and 2.0 mm catheters) delivering 30–60 mJ/mm^2 at 25–40 hertz using a 5-s on and 10-s off lasing cycle, but it potentially doubles the device's penetration rate while offering the possibility of targeting harder tissue. The reducing of catheter size was done to maximize tissue penetration while keeping photomechanical and photothermal damages within acceptable limits. The catheter functions like high optical fibers, which require increased packing density to maximize the cutting area at the distal tip. Since the early days of coronary laser use, it has been well documented that highly fibrocalcific plaques are laser-resistant and that higher energy could overcome these limitations [5,6].

Therefore, we performed a self-controlled study to examine the acute outcome of laser-facilitated coronary angioplasty on a cohort of patients presenting chronic total occlusion, calcified plaques and/or balloon-resistant lesions. Furthermore, we evaluated if higher energy levels delivered by laser catheter could improve procedural and clinical success without increasing complications.

2. Material and methods

Eighty patients referred to four centers experienced in excimer laser angioplasty from January to November 2012 were screened for enrollment in this multicenter study. Each patient had diagnostic coronary angiography, before interventional procedure. Safety and effectiveness data were compared between two groups: 41 patients treated with standard laser therapy (SLT) defined by laser energy at 60 fluence and 40 hertz and 39 patients treated with increased laser therapy (ILT) defined by laser energy at 60 fluence and 80 hertz or 80 fluence and 80 hertz (Fig. 1). The treatment scheme mandated use of the X80 catheter at standard laser parameters on all patients and increase of these parameters to higher levels in stepwise increments if deemed necessary to cross the target lesion. Proceeding as described, all patients treated with increased laser parameters had to present lesions refractory to treatment with standard laser parameters.

The primary endpoint was the ability of the X80 catheter to cross the lesion. The secondary endpoints included A) procedural success defined as reduction of the target lesion to < 50% residual diameter stenosis after adjunctive therapy, as measured by quantitative coronary analysis, and B) clinical success, defined as reduction of the target lesion to <50% residual diameter stenosis after adjunctive therapy as measured by quantitative coronary analysis with absence of major adverse cardiac events at hospital discharge.

All eligible patients for coronary revascularization > 18 years old presenting at least a primary or restenotic lesion in a native coronary artery or a saphenous vein bypass graft were screened. To be included in the study, the target lesion had to be severely stenotic (≥80% diameter stenosis as assessed by visual estimation) with angiographic evidence of calcification or a chronic total occlusion with absence of acute coronary syndrome 3 months prior to index procedure. Vessels with reference diameter smaller than 2.0 mm were also excluded, such angulated lesions and extreme tortuosity were allowed to be included. Patients with acute ischemic events, shock (cardiogenic or not cardiogenic), left ventricular ejection fraction ≤ 25%, previous coronary angioplasty within 6 months, and contraindication to aspirin or heparin were excluded from the study (Fig. 2). During a single hospitalization only one lesion was allowed to be treated. In patients presenting more than one stenosis suitable for inclusion/exclusion criteria of the study, the lesion more severe at angiographic examination was treated during first hospitalization, while other lesions were treated after at least three months. All participants gave written informed consent before enrollment in the study that was approved by the institutional ethics committees of all the involved centers.

2.1. Study protocol

Patients were pretreated with ≥ 80 mg of aspirin daily for > 24 h, and intravenous heparin was administered during the index procedure to maintain an activated clotting time > 250 s. All anti IIb/IIIa agents use were left to the operator's discretion with proper heparin dosage adjustments. Intracoronary nitroglycerine (>100 μg) was given before intervention and at the end of index procedure prior to final angiogram. Patients falling within inclusion criteria were treated with the X80 laser catheter starting at 60 fluence and 40 hertz laser parameters (SLT). After the successful laser passage, adjunctive balloon angioplasty and stenting were performed to complete treatment according to the standard procedure. When the laser catheter failed to cross target lesion completely, laser parameters were increased to 60 fluence and 80 hertz and then to 80 fluence and 80 hertz (ILT) in an attempt to traverse the lesion. If still unsuccessful, the laser catheter was withdrawn, recalibrated, and reinserted, and three more laser sequences were attempted. Three successive laser sequences without catheter tip progression had to be experienced before increasing laser parameters. At

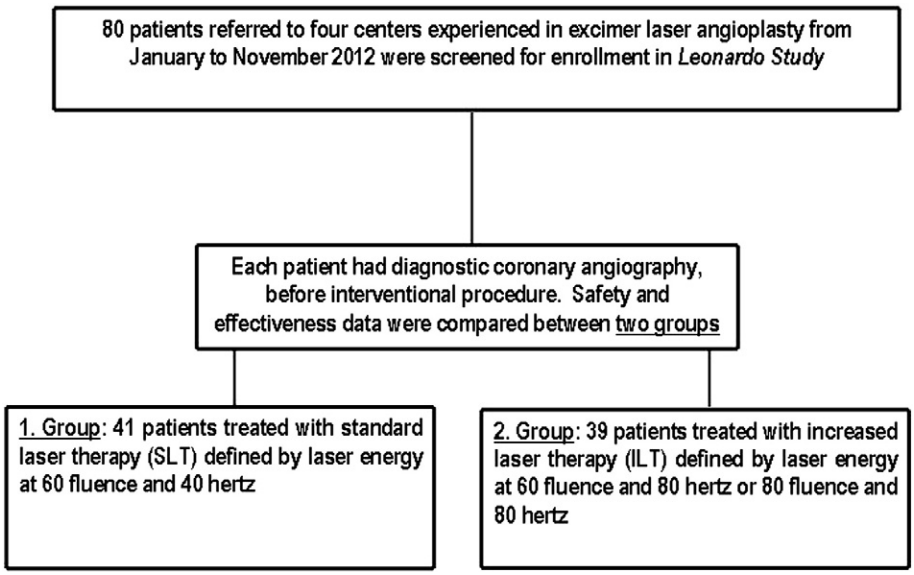

Fig. 1. Flow chat: patients enrolled in the study, divided in two groups.

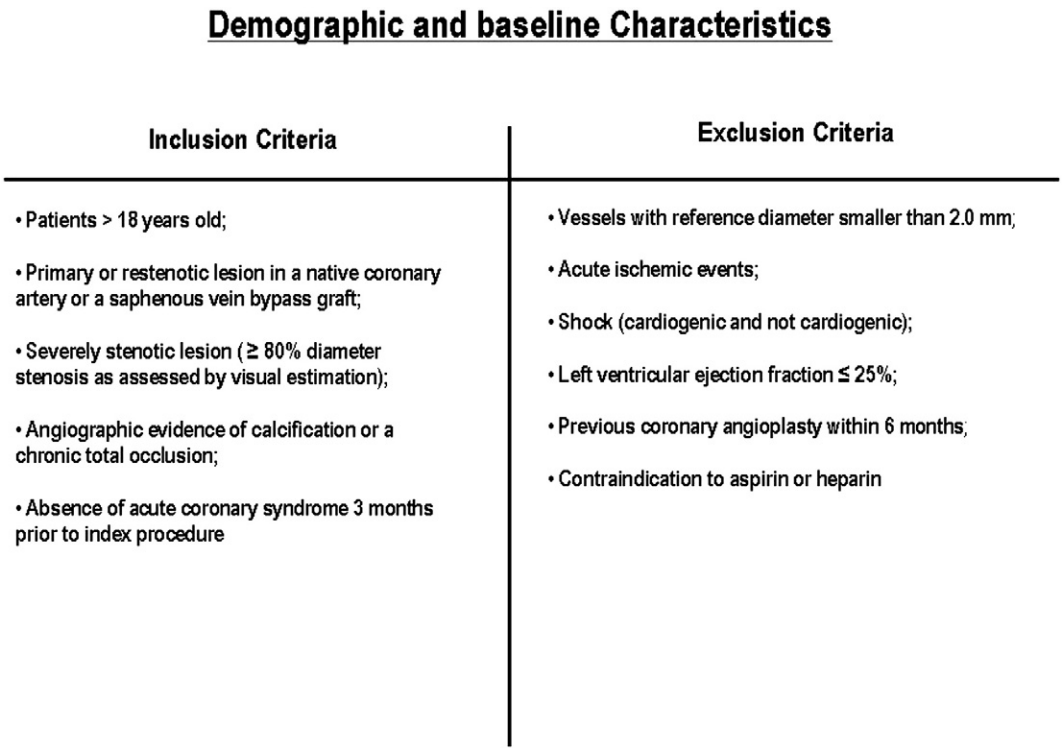

Fig. 2. Characteristics of patients enrolled in the study.

least 12 laser trains were attempted before failure was declared (3 × 60 fluence/40 hertz, 3 × 60/80, 3 × 80/80, and 3 × 80/80 postrecalibration). After the procedure, sheaths were removed immediately (radial approach) or 6 h later. Creatinine kinase measurements and electrocardiogram were obtained on all patients prior to and 24 h after index procedure. No clinical follow-up was recorded after hospital discharge.

2.2. Laser procedure

The excimer laser is a pulsed xenon–chlorine-based mid ultraviolet wave length (308 nm) laser relying on absorption in the nonaqueous components of the atherosclerotic plaque, such as proteins and nucleic acids, for debulking [7]. The new X80 catheter measures 0.9 mm in diameter with concentric fibers. It was built to deliver energy up to 80 mJ/mm^2 at 80 hertz with a lasing cycle characterized by 10 s of active firing and 5 s of silence. The laser system requires a 5-min warm-up period to turn on. The catheter is prepared by flushing the central guidewire lumen and connecting the proximal end to the laser console. Calibration of the catheter is then performed, and the desired energy level is set up. The catheter is then passed over the guidewire just proximal to the lesion. The flush-and-bathe technique [8] for blood and dye clearance from the entire system by saline infusion is mandatory prior to each lasing train. Lasing is performed by applying gentle forward pressure to the catheter in order to cross the lesion under fluoroscopy while energy is emitted from the catheter distal tip with foot pedal activation. The procedure is then finalized by laser catheter removal and the additional balloon and stent use according to the standard practice. Repeat arteriography after intracoronary nitroglycerine was recorded after laser use, before any adjunctive therapy and at the end of the procedure.

2.3. Definitions

Laser technical success was defined as the laser catheter crossing the entire length of the stenotic lesion determined by angiographic evidence of the catheter tip in the artery distal to the stenosis. Procedural success was defined as < 50% residual stenosis after laser and adjunctive therapy. Clinical success requested procedural success with absence of major adverse cardiac events at hospital discharge. Major adverse cardiac events included death of all causes, non-Q-wave and Q-wave myocardial infarction, need for target lesion revascularization, tamponade, and life-threatening arrhythmias. Q-wave myocardial infarction was defined as elevation of creatinine kinase levels > 3 times above laboratory normal values with any abnormal MB fraction and the development of new pathology Q-waves on the electrocardiogram. A non-Q-wave myocardial infarction was defined as the development of similar creatinine kinase elevation without Q-waves.

Anterograde flow was assessed by the thrombolysis in myocardial infarction (TIMI) scale [9]. Lesion morphology was characterized by the modified American College of Cardiology/American Heart Association (ACC/AHA) score [10]. Laser complications included dissection type C or worse according to the National Heart, Lung and Blood Institute classification [11], coronary spasm, thrombus formation, no reflow, embolization, perforation, loss of major side branch (>2 mm in diameter), and acute closure. Spasm was defined as transient reduction in blood flow with vessel caliber narrowing relieved either spontaneously or by nitroglycerine. Thrombus formation was defined as the new appearance of an intraluminal filling defect, lucency, or haziness refractory to intracoronary nitroglycerine. No reflow was determined by reduction of ≥ 1 TIMI flow grade without angiographic demonstration of embolization, whereas embolization was characterized by new appearance of a distal intraluminal filling defect or loss of a distal branch. Perforation requested demonstration of a persistent extravascular collection of contrast medium beyond the vessel wall. Finally, acute closure was defined as sustained TIMI 0 to 1 flow grade caused by obstruction of the target lesion.

2.4. Data collection and analysis

Detailed in-hospital case report forms were prospectively completed for each patient. A study monitor traveled to each site for independent verification of case report form accuracy. Angiograms were evaluated

by individual operators using local online quantitative coronary analysis software and visual assessment. However, all the angiograms were evaluated at the independent QCA Core Laboratory. No significant discrepancies between the online and offline analyses were seen.

Data were entered into a SAS database (software version 7.2, SAS Institute). Statistical calculations used Wilcoxon scores (rank sums) and McNemar analysis for frequency tables. A P value < 0.05 was required for statistical significance.

3. Results

A total of 80 patients with 100 lesions were enrolled in the study at four centers: Montevergine Clinic (Mercogliano; 64 lesions), S. Maria della Misericordia University Hospital (Udine; 20 lesions), Spedali Civili University Hospital (Brescia; 6 lesions), and Ospedali Riuniti University Hospital (Ancona; 10 lesions). Forty-five patients (56.3%) were enrolled under the calcification primary indication, 25 patients (31.2%) were enrolled under the balloon failure primary indication, and 10 patients (12.5%) under the chronic total occlusion primary indication. Table 1 depicts the characteristics of the lesions selected for the study. Mean patient age was 69 ± 13 years old; 70% of which were male with 55% presenting unstable angina. The left anterior descending artery was the target vessel in 48% of cases, the right coronary artery in 35%, the circumflex in 10%, and the left main artery in 4%. Three saphenous vein grafts were also enrolled.

During enrollment, inclusion criteria violation occurred in 12 lesions that consequently were excluded. In seven cases we found a second lesion distal to the treated one, and for some of these patients, due to economic considerations, we decided to treat multiple lesions during a single interventional procedure. Treatment of calcified lesions with less than 80% stenosis occurred in three cases, while treatment of non-calcified 99% stenosis occurred in two cases.

3.1. Procedural outcome

In four lesions (two calcified plaques and two chronic total occlusion), we recorded failure of the delivered treatment per protocol. In all cases, the guidewire did not cross, the procedure was aborted, and patients were ultimately treated medically. Subsequently, 96 lesions were treated with excimer laser coronary angioplasty. Overall, laser success, the primary endpoint of the study, was obtained in 90 lesions (93.7%). Furthermore, dividing the study's population according to the indication at laser angioplasty, the endpoint was reached in 96.4% of the cases with calcified lesions (53/55), 93.7% of the cases with balloon failure (30/32) and in 77.8% of the cases with chronic total occlusion (7/9). After a successful laser passage in all patients, adjunctive balloon angioplasty and stenting were performed. In 88 of the lesions we used drug-eluting stent. We decided to use bare metal stent in only two cases because it was unfeasible to perform double antiplatelet therapy for at least six months. The results of the quantitative coronary analysis are shown in Table 2. Among the six lesions that could not be crossed by the X80 catheter, even with the use of increased laser energy, four were treated successfully with adjunctive balloon angioplasty, while two had, after laser failure, an unsuccessful rotational atherectomy (RA) because RotaWire was also unable to cross the lesion, and were discharged on medical treatment.

Regarding the secondary aims of the study, procedural success was reached in 88 lesions (91.7%). In two lesions belonging to two different patients, after X80 catheter crossed the lesion, we could not obtain a satisfying final angiographic result. These patients were discharged with medical treatment.

Finally, we recorded only one major adverse cardiac laser-related event. Consequently, clinical success, the other secondary aim of the study, was obtained in 87 lesions (90.6%). In this patient, we experienced ventricular fibrillation requiring cardio-pulmonary resuscitation during laser treatment. This resulted in a non-Q-wave myocardial infarction despite the absence of flow disturbances.

Importantly, no perforation, dissection, major side branch occlusion, spasm, no-reflow phenomenon, nor acute vessel closure was seen with laser treatment even when increased energy was used.

3.2. Increased laser parameters

Of the 90 laser-treated lesions, 41 (45.5%) were successfully crossed with standard laser parameters, namely, 60 mJ/mm^{2}at 40 hertz. Increased laser parameters were used for 49 resistant lesions. Among these, the X80 catheter successfully crossed 42 lesions, and seven were eventually treated by balloons and stents even though the laser catheter tip had not entirely cross the target lesion.

Energy of 60 mJ/mm^2 at 80 hertz was required in 21 lesions (23.3% of the laser-treated lesions), while 28 lesions (31.1% of the laser-treated lesions) required laser levels that reached up to 80 mJ/mm^2 at 80 hertz. Increasing laser energy delivery resulted in an increase in the success rate from 42.7% to 93.7% (P < 0.01) and, consequently, improved the technique procedural and clinical success rates from 42.7% to 91.7% (P < 0.001) and from 42.7% to 90.6% (P < 0.001), respectively.

Fourteen of the 49 increased parameter used were on lesions which failed prior to balloon angioplasty, and in 11 cases the catheter successfully crossed the lesion. Laser-induced complications did not seem to be related to these increased laser parameters.

4. Discussion

The excimer laser coronary angioplasty was approved by the U.S. Food and Drug Administration in 1992. Original indications included angioplasty on a very specific subset of lesions, such as saphenous vein graft, total occlusions, calcified lesions, ostial lesions, lesions greater than 20 mm in length, and balloon dilatation failures [5,6,12]. These indications have been substantiated by numerous registries. Unfortunately, prospective randomized studies failed to demonstrate the superiority of this technique over balloon angioplasty in some of these predefined

Table 1
Lesion characteristics (n = 100).

	n	%
Calcification	57	57
Percutaneous transluminal coronary angioplasty failure	32	32
Chronic total occlusion	11	11
Target vessel distribution		
Left anterior descending coronary artery	48	48
Right coronary artery	35	35
Left circumflex coronary artery	10	10
Left main artery	4	4
Saphenous vein graft	3	3
ACC/AHA classification		
A	0	0
B1	5	5
B2	67	67
C	28	28

ACC/AHA = American College of Cardiology/American Heart Association.

Table 2
Quantitative coronary analysis (n = 90).

	Mean	Standard deviation	Range
Reference diameter (mm)	2.8	0.6	1.1–4.1
MLD (mm) pre-laser	0.4	0.4	0–1.7
Stenosis percentage pre-laser	84.1	14.6	46.0–100.0
MLD (mm) post-laser	1.0	0.5	0–2.50
Stenosis percentage post-laser	62.7	16.2	5.0–100.0
MLD (mm) final	2.6	0.7	0.0–3.8
Stenosis percentage final	13.3	18.7	0.0–100.0
Lesion length (mm)	14.6	6.9	4.0–39.0

MLD = minimum luminal diameter.

complex lesions. The Amsterdam–Rotterdam (AMRO) trial investigated the comparison of excimer laser coronary angioplasty and conventional balloon angioplasty in lesions greater than 10 mm on 308 patients. Procedural success and 6-month cumulative rates of major complications were identical in both groups [13]. Despite these deceiving results, partially attributed to first generation devices used on relatively non-complex disease, excimer laser technology kept some applications and enthusiastic promoters [14]. The Excimer Laser Rotational Atherectomy Balloon Angioplasty Comparison (ERBAC) trial randomly assigned 685 patients to excimer laser angioplasty, conventional balloon angioplasty, or RA. Procedural success rate was 80% for balloon angioplasty, 77% for excimer laser angioplasty, and 89% for RA, with 6-month clinical events rate of 32%, 46%, and 42%, respectively [15]. By 1995, the need for intracoronary saline infusion during excimer laser angioplasty to prevent vapor bubble formation and its corresponding acoustomechanical trauma to the vessel wall was well documented. This modification in laser technique resulted in operators minimizing their procedural complications, which was most commonly occurred during dissections [8]. Despite the improvements seen with saline infusion, coronary laser uses have been restricted to applications that include the treatment of in-stent restenosis [16] and debulking of undilatable or uncrossable lesions [3].

Some earlier reports suggested an 89% success rate at safely debulking lesions where balloons could not properly expand and dilate or could not simply cross after successful wire placement [14]. However, a clear distinction was made between calcified and noncalcified lesions with respective procedural success rates of 79% and 96% ($P < 0.05$). In addition, the presence of calcifications has been clearly identified, from the beginning of coronary laser use, as an independent predictive factor for the likely failure of the technique [17–19]. It also has been suggested that increased laser energy could improve laser success in calcified lesions. In an attempt at creating a smaller excimer laser coronary angioplasty catheter with lower total energy and lower heat production but higher energy intensity, the laser industry developed a 0.9 mm coronary catheter with 65 concentric 50 m fibers capable of delivering energy level up to 80 mJ/mm^2 at 80 hertz for the treatment of complex calcified plaques. This technology proved its efficacy in vitro on bovine tendon with maximum power of 832 mW and penetration capacity of 0.59 mm/s compared with existing technology, which generates 1,704 mW and 0.26 mm/s penetration rate [20]. The first human study by Fretz et al. [4] described the efficacy of this new catheter technology on seven patients presenting complex calcified lesions. Interestingly, a recent study by Fernandez et al. [21] demonstrated the safety and effectiveness of excimer laser coronary angioplasty in a cohort of 58 patients with balloon failure during percutaneous coronary intervention.

Here we report the data on the safety and effectiveness of 100 complex coronary lesions debulked with this high-energy excimer laser catheter. A procedural success rate of 92% and a clinical success rate of 91% were found with the use of this 0.9 mm X80 excimer laser catheter on this subgroup of patients with extremely complex lesions. Fourteen of the 49 increased parameter uses were performed on lesions that failed prior to balloon angioplasty while in 11 cases the catheter successfully crossed the lesion, suggesting that this therapy would be beneficial in this subgroup presenting limited interventional options. Among the six lesions on which the laser failed to cross, balloons and stents were successfully used in four cases, raising the possibility that even though the laser did not completely cross, however, it had changed the plaque compliance allowing final lesion management. The most common complication after laser treatment was the presence of dissections despite the use of the flush-and-bathe technique with normal saline infusion. Surprisingly, no perforations, spasm, dissection, or no-reflow phenomenon was observed. Overall, potentially laser-related complications were similar to or lower than those observed in comparable studies [3,22]. Consequently, our data highlight the safety and the usefulness of this approach in complex coronary lesions, if compared with other techniques, such as RA. This device, when dealing with calcified lesions, has a favorable effect on both angiographic and clinical outcomes [23]. However, this approach requires advanced PCI training, and requires complicated equipment that delivers a metal burr rotating at high speed into small coronary vessels. Furthermore, life-threatening RA-related complications, such as entrapment of rotablator burr, no reflow/slow flow phenomenon, wire fracture and coronary perforation were rarely found. Moreover, especially in severe calcification, RotaWire was unable to cross the lesion. Conversely, the X80 system is extremely simple to use, is available in over-the-wire or rapid-exchange versions and the catheter is 0.014" wire-compatible and it requires 6 Fr guiding catheter. The X80 excimer laser catheter is a suitable option for many procedures in which RA is considered the best choice, as it is an efficient and user-friendly treatment of calcified lesions. In this regard, a randomized trial aimed at the comparison of these two techniques for the treatment of calcified and undilatable lesions would be extremely valuable.

There are some limitations that need to be acknowledged and addressed regarding the present study. First, we cannot exclude that a part of the lesions considered could be successfully treated without laser use, nevertheless the percentage of procedural and clinical success that we observed in this study using the excimer laser exceeded 90%. This result is rather difficult to obtain using only balloon angioplasty. Furthermore, the sample size is relatively small and limits the reader's ability to draw definitive conclusions, however, self-controlled studies (in which each patient serves as his or her own control) can produce results that are statistically and clinically valid with far fewer patients than would otherwise be required. Finally, because of the multicentric nature of this study, different operators performed the procedures; however, as specified in the methods section, all the angiograms were evaluated at an independent Core Lab where online and offline analyses showed comparable results.

In conclusion, the X80 excimer catheter using higher laser coronary parameters seems to be a safe and effective treatment for management of calcified and nondilatable lesions. Higher laser energy levels delivered by this catheter seem to improve device performance without increasing complications. Its applicability widens the spectrum of coronary excimer laser use, which includes stent restenosis, non-resilient plaques to balloon angioplasty and total chronic occlusions, and also probably in future to debulking in ostial stenosis and complex lesions.

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