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ORIGINAL ARTICLE

ELLIS Study: Comparative Analysis of Excimer Laser Coronary Angioplasty and Intravascular Lithotripsy on Drug-Eluting Stent as Assessed by Scanning Electron Microscopy

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BACKGROUND: Stent underexpansion is a significant challenge in percutaneous coronary intervention, critically impacting patient outcomes. While excimer laser coronary angioplasty (ELCA) and intravascular lithotripsy (IVL) are increasingly used to address this issue, their full impact on the integrity of drug-eluting stents remains unclear, raising concerns about their safety and efficacy.

METHODS: This in vitro study assessed the effects of ELCA and IVL on the structural integrity of drug-eluting stents using scanning electron microscopy. Nine stents, 5 Onyx Frontier (with durable circumferential polymer coating) and 4 Cre8 (polymer-free), were implanted in a 3-dimensional coronary artery simulator following standardized protocols. After implantation, treatments with saline-ELCA, contrast-ELCA, IVL, and high-pressure balloon dilatation were applied. A comprehensive evaluation of the stent surface was performed at 60-fold magnification.

RESULTS: Scanning electron microscopy analysis revealed significant differences in polymer damage between the techniques. High-pressure balloon dilatation and contrast-ELCA exhibited substantial polymer fragmentation and detachment compared with IVL, saline-ELCA, and conventional dilatation. High-pressure balloon dilatation demonstrated the highest incidence of polymer shaving and overcoating. No significant alterations were observed in polymer-free stents, regardless of the technique used.

CONCLUSIONS: IVL and saline-ELCA applied immediately after stent implantation produce minimal polymer damage, whereas high-pressure balloon dilatation and contrast-ELCA cause significant damage to the polymer coating. The integrity of polymer-free drug-eluting stent appears stable regardless of the technique used. Further research is needed to validate these findings and explore their clinical implications.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: coronary artery disease ■ drug-eluting stents ■ lithotripsy ■ microscopy, electron, scanning ■ percutaneous coronary intervention

Stent underexpansion (SU) remains an unresolved challenge despite advances in new coronary techniques and intracoronary imaging. SU is observed in up to 12% of percutaneous coronary interventions and serves as the strongest predictor of adverse clinical outcomes, particularly in-stent restenosis and stent thrombosis.[1–5]

Although appropriate plaque modification before stent implantation is essential to prevent SU, sometimes, this phenomenon cannot be avoided despite

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WHAT IS KNOWN

- Stent underexpansion is a frequent complication in coronary interventions, often leading to adverse clinical outcomes.
- Excimer laser coronary angioplasty and intravascular lithotripsy are commonly used, but their effects on the structural integrity of drug-eluting stents are not fully established.

WHAT THE STUDY ADDS

- The ELLIS study (Comparative Analysis of Excimer Laser Coronary Angioplasty and Intravascular Lithotripsy on Drug-Eluting Stent as Assessed by Scanning Electron Microscopy) demonstrates that intravascular lithotripsy and saline-excimer laser coronary angioplasty cause minimal damage to the polymer coatings of drug-eluting stent, while high-pressure balloon dilatation and contrast-excimer laser coronary angioplasty result in significant polymer fragmentation.
- Polymer-free stents exhibit no significant structural damage from any of these techniques, suggesting their potential advantage in complex coronary interventions.

Nonstandard Abbreviations and Acronyms

DES	drug-eluting stent
ELCA	excimer laser coronary angioplasty
HP	high-pressure balloon dilatation
IVL	intravascular lithotripsy
SEM	scanning electron microscopy
SU	stent underexpansion

meticulous efforts.[6,7] Current treatment options for underexpanded stents are limited to super high-pressure balloons or prolonged dilatations with non-compliant balloons at high pressures (high-pressure balloon dilatation [HP]). Rotational atherectomy and orbital atherectomy are off-label options with variable results.[8–10] However, these techniques are unsuitable for the treatment of acute SU due to stent structure damage.

Excimer laser coronary angioplasty (ELCA) has been utilized in this scenario with positive clinical outcomes,[11,12] and intravascular lithotripsy (IVL) has emerged as an increasingly used alternative in this context.[13,14] However, to date, their use in this setting is limited to small studies with short clinical follow-up.[15] In addition, it has been postulated that these techniques may damage the polymer of the stents.[16,17] Nevertheless, the evidence supporting this hypothesis is currently limited, and to date, there are no studies comparing the structural alterations that occur in stents when using these techniques.

The aim of this study is to compare the in vitro effects of HP, ELCA, and IVL on drug-eluting stent (DES) structure as assessed by scanning electron microscopy (SEM).

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

DES Samples Examined

Nine different stents were examined in the study: 5 DES Onyx Frontier (Medtronic, Santa Rosa, CA) with a durable polymer coating and 4 DES Cre8 (CID S.p.A, Saluggia, Italy) with a polymer-free structure. The Onyx Frontier stent consists of a cobalt-chromium platform with a strut thickness of 81 µm and a 12-µm-thin coating of a BioLinx circumferential polymer and zotarolimus. The Cre8 is a polymer-free stent with an 80-µm-thin cobalt-chromium structure characterized by the presence of amphilimus, a sirolimus formulated with a nonpolymeric amphiphilic carrier in the abluminal stent surface.

CT-Derived 3-Dimensional Printing for Coronary Artery Simulator

The coronary artery simulator model was generated from multislice synchronized cardiac computed tomography images acquired at 70% of the R-peak-to-R-peak interval (Toshiba Aquilion 64; 120 kV, 400 m, 0.96 s, with 1-mm spatial resolution). The acquired DICOM data were segmented and converted to STL format using Synopsys' Simpleware ScanIP software. Subsequently, AutoDesk's Meshmixer 3D modeling software was used to optimize the print model, while FormLabs PreForm software defined printing parameters and generated the g-code for the 3-dimensional printer. Finally, the model was prepared for printing using the CURA software of Ultimaker, Inc, and fabricated with Flexible Resin 80A (Figures S1 and S2).

In Vitro Stent Implantation and Stent Expansion Techniques

Stent dimensions were selected in a 1:1 ratio in relation to the size of the targeted coronary artery segment for implantation. An experienced interventional cardiologist (A.J.-R.) assisted by an interventional cardiologist fellow (B.R.-S.) and a nurse specialist in interventional procedures expanded all stents to the nominal pressure recommended by the device manufacturer under sterile conditions in air under fluoroscopic guidance. Subsequently, techniques of IVL, ELCA, and HP were applied. As controls, an Onyx Frontier stent and a Cre8 stent were dilated to nominal pressure without further application of additional techniques.

Intravascular Lithotripsy

The IVL System (Shockwave Medical, Inc, Santa Clara, CA) includes a rapid exchange semicompliant balloon catheter equipped with integrated lithotripsy electrodes. An accompanying electrical pulse generator is utilized to generate unfocused circumferential mechanical energy. The procedure was performed according to standard techniques. A lithotripsy balloon

was used in a 1:1 ratio to the reference coronary diameter. Once positioned over the stent, the Shockwave balloon was initially inflated to a pressure of 4 atm, and 4 runs of 10 pulses were applied. Subsequent balloon inflation at 6 atm was performed after every run (Video S1).

Excimer Laser Coronary Angioplasty

Laser angioplasty includes an ELCA CVX-300 system (Philips, the Netherlands) that emits pulses of UV light to precisely ablate and vaporize atherosclerotic plaque within the coronary arteries. This technique allows targeted and controlled delivery of energy to the affected arterial segments, resulting in plaque removal and vessel dilatation. The procedure was performed according to standard techniques. A 0.9-mm ELCA catheter was used. Before the ELCA application, the catheter was calibrated, and the highest fluency and repetition rates (80 mJ/mm^2 and 80 Hz) were selected. Energy pulses were delivered as the catheter slowly advanced through the stent at a speed of 0.5 to 1.0 mm/s (Video S2). Laser energy was delivered in trains of 10 s, with a total therapy time of 40 s per stent delivering on average 2510±551 pulses. ELCA was performed with simultaneous saline injection in 2 stents and with simultaneous contrast injection in the other 2 stents to achieve maximum laser effect.

High-Pressure Balloon Dilatation

For the HP, a noncompliant balloon (EMERGE, Boston Scientific) at a 1:1 ratio to the reference coronary diameter was used at a pressure of 28 atm for a duration of 30 s.

Conventional Dilatation

An Onyx stent and a Cre8 stent were used as controls. For these DES, only dilatation to the nominal pressure recommended by the manufacturer was performed without further application of additional techniques.

DES Processing

After the application of stent expansion techniques, the simulated artery was longitudinally incised, and the stent was then extracted and analyzed by SEM. Stent extraction and saline preservation procedures were performed at the Centro Nacional de Investigaciones Cardiovasculares Carlos III. Finally, drying and microscopic examination of the samples were performed at the Microscopy Service of the University of Leon.

Scanning Electron Microscopic Analysis

SEM imaging was performed with a JEOL JSM-6480LV scanning electron microscope (Tokyo, Japan). All samples were air-dried for 48 hours and mounted on carbon planchettes and sputter-coated with gold (Leica EM ACE200 Vacuum Coater, Vienna, Austria). The accelerating voltage of the electron beam used was 20 kV with an average working distance of 20 to 25 mm. An initial examination was performed at 60-fold magnification from the proximal to distal segments of the stent to detect regions of interest (cracks, overcoating, shaving, fragmentation of polymer, and metal exposure). Relevant areas detected were further examined at 200- to 600-fold magnification to detail and distinguish them from artifacts. Finally, a comprehensive evaluation of the stent surface was performed at 60-fold magnification across 9 stents.

Classification of Polymer Irregularities in SEM Images and Quantitative Analysis

Classification of polymer irregularities in SEM images and quantitative analysis were conducted as follows: the irregularities were categorized into 4 distinct classes using a modified classification system (Table 1; Figure 1) adapted from a previously published study.[18] Minor alterations were defined by the presence of cracks, shavings, or overcoating that did not result in metal exposure, while major alterations included polymer fragmentation or metal exposure. To compare the incidence of irregularities among techniques, a quantitative analysis was performed by comprehensively evaluating the stent surface with SEM at 60-fold magnification.

Statistical Analysis

Variables were presented as mean±SD. ANOVA or the Kruskal-Wallis rank-sum test was used for continuous variables. Two-sided $P<0.05$ was deemed statistically significant. Post hoc testing was performed using the Holm test to compare the different techniques and adjust the level of significance accordingly. All statistical analyses were conducted using R statistical software (v4.2.2; R Core Team, 2022).

Ethical Consideration

The study was approved by the local ethics committee. The experimental procedures are documented and available to any researcher interested in replicating them.

RESULTS

Polymer-Based DES

Qualitative Analysis of Irregularities

A total of 200 SEM images were examined. The incidence of different irregularities is presented in Table 2 and Figure 2.

Minor Alterations

Cracks. The total number of cracks observed was 3.580±2.318 per SEM image at 60-fold magnification. Interestingly, there were no significant differences in

Table 1. Definitions of the Categories of Polymer Irregularities as Assessed by Scanning Electron Microscopy

Categories	Definitions
Crack	Sharp-edged coating irregularity extending from the surface deep into the coating without exposing the metal.
Overcoating	Increased polymer thickness due to outward displacement, forming structures due to excess coating without metal exposure.
Shaving	Reduction in coating thickness without exposing the underlying metal.
Fragments of coating or metal exposure	Pieces of coating, which remain loosely attached (fragment) or are completely detached (total detachment) from the main coating. All metal exposures are also included in this category.

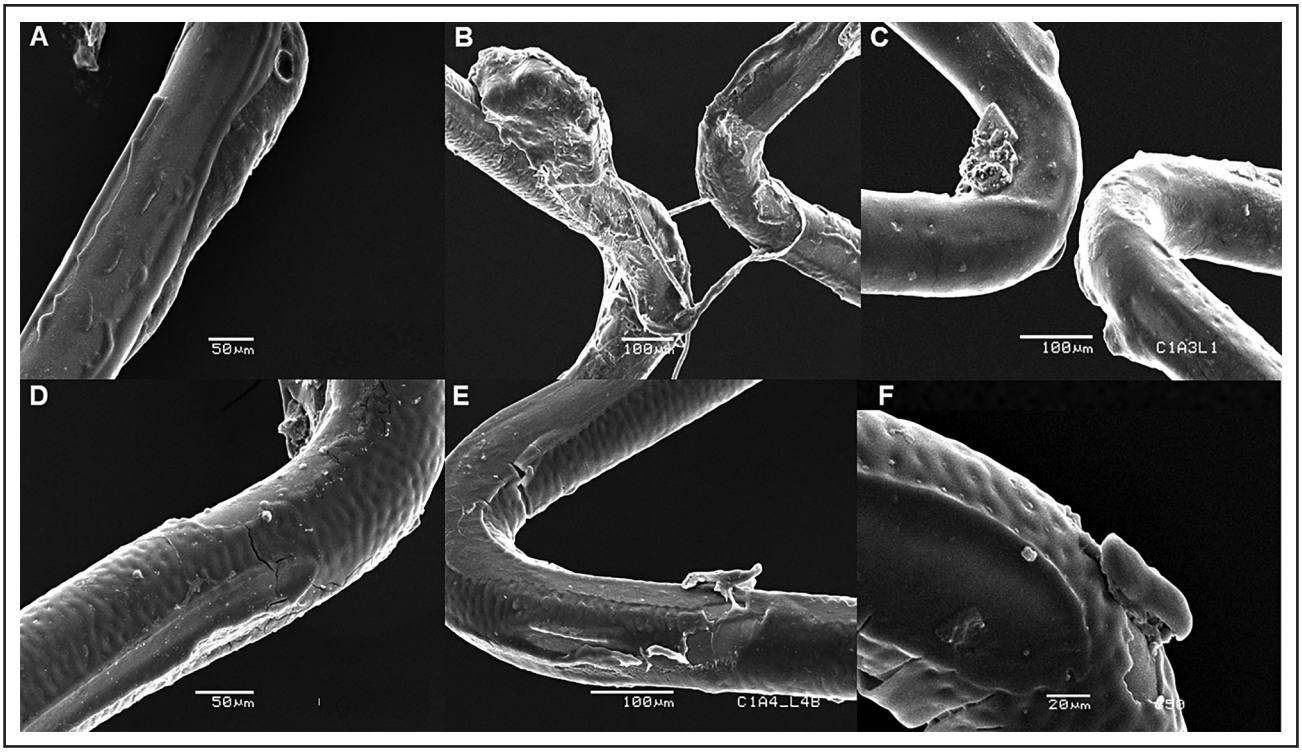

Figure 1. Examples of Onyx Frontier drug-eluting stent polymer coating irregularities observed by scanning electron microscopy.

A, Crater-like irregularity without bare metal exposure on the outer curvature of the strut after intravascular lithotripsy. Polymer coating and bulging on the outside (**B**) and inside (**C**) of the strut after saline-excimer laser coronary angioplasty (ELCA). **D**, Reduction in coating thickness without exposing the underlying metal after intravascular lithotripsy. **E**, Flattened thinning resulting in the shaving of the polymer after high-pressure expansion with a noncompliant balloon. **F**, Fragmentation of the coating, which remains adherent but exposes the underlying strut after ELCA with contrast.

crack incidence between the different techniques used (Table S1).

Overcoating. The overall incidence of overcoating irregularities was 1.35±1.55 per SEM image at 60-fold magnification, with notable differences between the techniques used (P=0.003). Specifically, the use of high-pressure balloons resulted in a significantly higher incidence of overcoating irregularities compared with IVL, ELCA with saline, or ELCA with contrast. However, no significant differences were observed between these other techniques compared with the control (Figure 2; Table S2).

Shaving. The total incidence of shaving irregularities was 0.69±1.21 per SEM image at 60-fold magnification, showing significant differences between the techniques (P<0.001). Particularly, the use of HP balloons was significantly associated with a higher incidence of shaving irregularities compared with other techniques (IVL, ELCA with saline, and ELCA with contrast) although, to a lesser extent, the use of IVL was also associated with a higher incidence of shaving irregularities compared with ELCA with contrast or ELCA with saline (Figure 2; Table S3).

Major Alterations

Fragments of Coating or Metal Exposure. The total incidence of fragments of coating or metal exposure was 2.09±1.62 per SEM image at 60-fold magnification, showing significant differences among the techniques applied (P<0.001). Specifically, the use of HP balloons was significantly associated with a higher incidence of

Table 2. Differences in the Frequency of Polymer Irregularities Among Different Techniques

Types of coating irregularities	IVL	Saline-ELCA	Control	Contrast-ELCA	HP	*P* value
Crack	3.0 (2.5)	4.1 (2.2)	2.2 (2.1)	4.4 (2.4)	3.7 (1.6)	0.069
Overcoating	1.6 (1.5)	1.1 (1.4)	0.7 (0.8)	1.1 (1.1)	2.8 (2.2)	0.003
Shaving	1.5 (1.4)	0.1 (0.3)	0.1 (0.3)	0.4 (0.6)	2.1 (1.7)	<0.001
Fragments or ME	1.5 (1.4)	1.4 (1.1)	1.2 (1.4)	3.2 (0.8)	3.9 (1.9)	<0.001

Values are expressed as mean and SD. ELCA indicates excimer laser coronary angioplasty; HP, high-pressure balloon dilatation; IVL, intravascular lithotripsy; and ME, metal exposure.

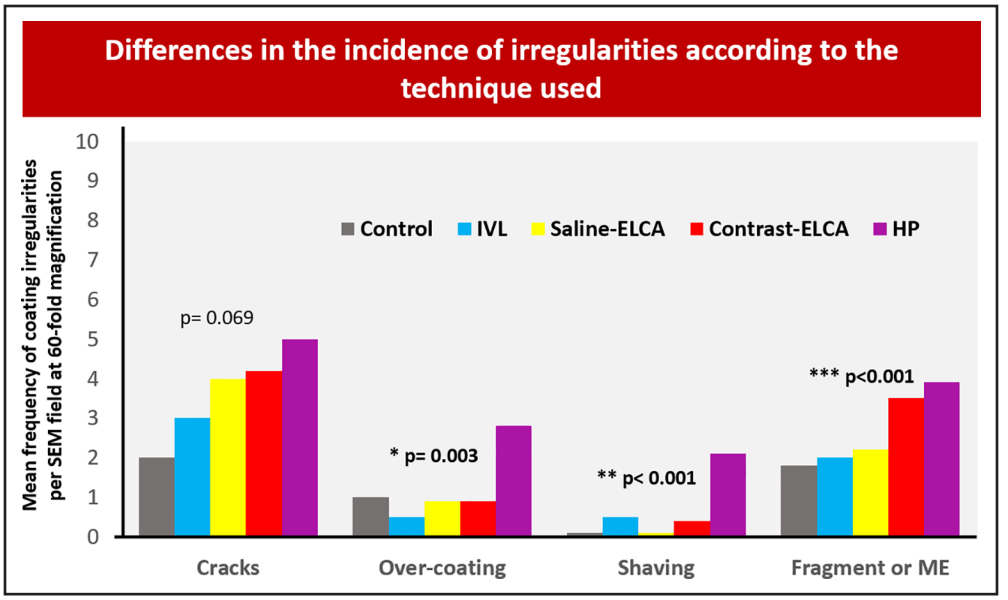

Figure 2. The mean frequency of coating irregularities per scanning electron microscopy (SEM) field at 60-fold magnification for different stent expansion techniques.
Control (gray), intravascular lithotripsy (IVL; blue), saline-excimer laser coronary angioplasty (ELCA; yellow), contrast-ELCA (red), and high-pressure balloon dilatation (HP; purple) were compared. Significant differences were observed in overcoating, shaving, and fragment/metal exposure (ME) categories. IVL and saline-ELCA demonstrated minimal polymer damage, while HP and contrast-ELCA resulted in significant polymer fragmentation and detachment. *P* values in bold indicate statistically significant. **P*<0.03, ***P*<0.01, and ****P*<0.001.

irregularities compared with IVL or ELCA with saline. Similarly, the use of ELCA with contrast was associated with a higher incidence of coating fragments or metal exposure compared with IVL, ELCA with saline, or the control. However, there was no significant difference in the number of irregularities between HP balloons and ELCA with contrast (Figure 2; Table S4).

Polymer-Free Structure DES

Four Cre8 stents were analyzed. Specifically, IVL, ELCA with saline, and ELCA with contrast were applied. One stent was only dilated to nominal pressure and was used as a control (Figure 2). Concerning cobalt-chromium structure alterations, only minor alterations were found with no differences between the different techniques used. Specifically, the findings identified were indentations with residual material of different morphologies (Figure 3). No major alterations such as fracture or fragmentation of the stent structure were detected.

DISCUSSION

Our study provides, for the first time in the literature, a comparative analysis of the in vitro effects of stent expansion techniques on the structure of DES assessed through SEM. Our findings indicate that HP and contrast-ELCA lead to major polymer alterations, including increased fragmentation and metal exposure compared with IVL, saline-ELCA, or nominal balloon dilatation, which does not produce significant stent alterations. In addition, polymer-free stents are not significantly affected by any of these techniques.

SU is a common phenomenon strongly associated with adverse cardiovascular outcomes. Indeed, SU is implicated as the primary mechanism in 25% of patients with stent thrombosis and up to 55% of those with in-stent restenosis.[7,19–21] Intracoronary imaging–guided percutaneous coronary intervention has been demonstrated to reduce target vessel failure and can predict which patients need more aggressive plaque modification techniques before stent implantation.[22] However, its use is limited to a small percentage of cases,[23,24] and sometimes, even with this guidance, stent expansion could be suboptimal. The options to resolve acute SU are limited to balloon inflation at high atmospheres[25,26] or, supposedly more aggressive techniques, such as ELCA[11] or off-label use of rotational atherectomy or orbital atherectomy with modest results[8–10] and the potential damage to the stent structure. Recently, IVL has presented promising results in this scenario.[13,27] While initial procedural outcomes have been favorable, the lack of long-term outcome data remains a challenge due to the short follow-up periods in existing studies. Furthermore, certain in vitro investigations have identified polymer alterations in DES after IVL.[16,17] Theoretically, these alterations may potentially correlate with increased adverse events during follow-up, including thrombosis or in-stent restenosis. However, some series have shown favorable clinical results of IVL in this setting.[13] Moreover, there has been no direct

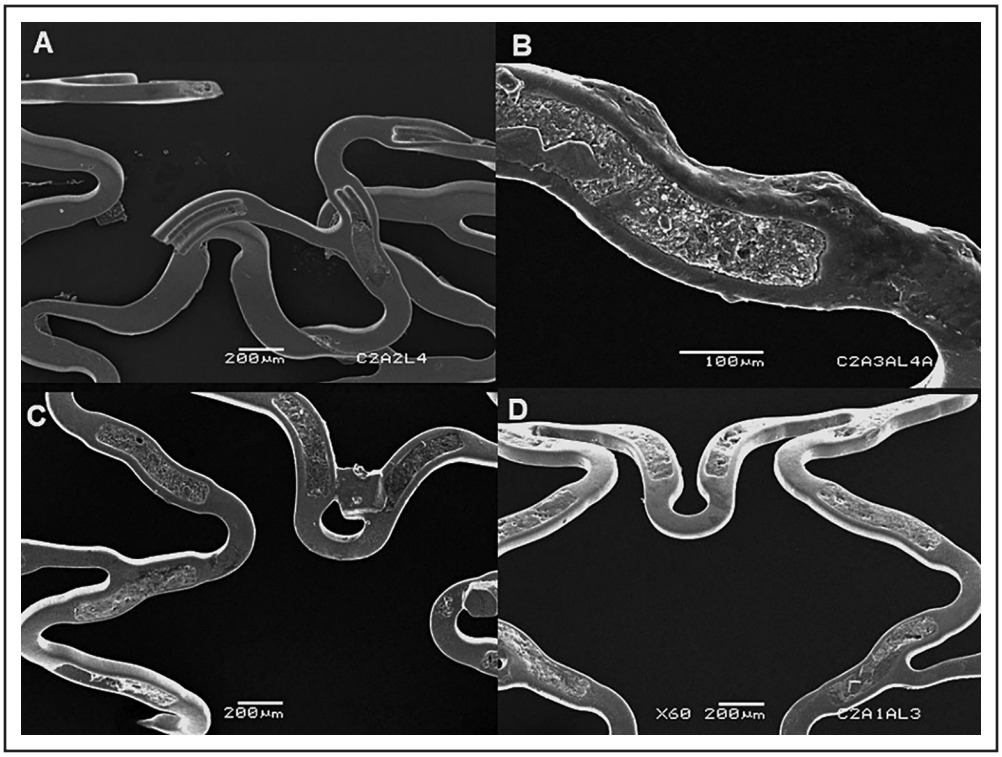

Figure 3. Examples of Cre8 drug-eluting stent chromium structure alterations observed by scanning electron microscopy. Large indentations filled with the material inside after application of saline-excimer laser coronary angioplasty (ELCA; **A**) and contrast-ELCA (**B**). Granular material–filled clefts in control stent (**C**) and after intravascular lithotripsy application (**D**). Cubic or prismatic material was found on the stent surface in all samples.

comparison of the impact of different techniques such as ELCA or IVL on the polymeric coating.

In our study, a comparative analysis was conducted between ELCA and IVL when applied immediately after stent implantation with the objective of elucidating the potential effects of these techniques on acute SU assessed by SEM. In addition, a comparative analysis was also conducted of these techniques with HP, which is currently the main approach for treatment in this setting. Interestingly, the use of HP, initially perceived as relatively harmless, resulted in a higher incidence of major alterations compared with the use of saline-ELCA or IVL. Moreover, it exhibited comparable polymer damage to that observed with contrast- ELCA. These findings may be aligned with recent research suggesting that polymer damage in other devices such as angioplasty guidewires may be greater with aggressive dilatations, even more so than with the use of saline-ELCA.[28]

In regard to polymer-free stents, they have been extensively investigated as a potentially more biocompatible alternative to polymer-based DES.[29,30] Furthermore, another potential advantage of these stents could be their use in scenarios where aggressive techniques that may affect the polymer are anticipated. However, robust data supporting these claims are scarce, as there have been no studies evaluating alterations in polymer-free stents after the application of stent expansion techniques. Because of this, the analysis of polymer-free stents was included in the ELLIS study (Comparative Analysis of Excimer Laser Coronary Angioplasty and Intravascular Lithotripsy on Drug-Eluting Stent as Assessed by Scanning Electron Microscopy) to assess the possible impact on stent structure when applying ELCA or IVL. A novel finding from the ELLIS study is that polymer-free stents remained unaltered despite the use of IVL or ELCA, suggesting their resistance to aggressive techniques. This may suggest their potential preference in complex percutaneous coronary intervention scenarios where aggressive stent dilatation or acute use of techniques such as ELCA or IVL is anticipated.

Limitations

The present study has several limitations. First, the in vitro analysis does not fully replicate the in vivo environment. Despite designing a specific coronary model for this study that considers the real size and curvature of arteries, factors such as vascular calcification, which could potentially cause damage to the metal platform or polymer, were not analyzed. Second, while careful handling and processing were conducted in an experienced laboratory, it cannot be ruled out that some irregularities in the platform or polymer may be attributed to the handling process itself rather than the technique used. Third, these in vitro findings may not be directly applicable to other types of stents with diverse platforms or polymer

compositions different from those used in this study. In addition, the clinical scenario studied, the use of ELCA and IVL for newly implanted stents, is less common and typically occurs as a bailout strategy. Most cases treated with these techniques occur sometime after implantation. Therefore, it is not clear whether these in vitro findings would translate into different clinical outcomes. These limitations, combined with the modest size of our study, restrict the generalizability of the results to all coronary stent platforms and different anatomic scenarios that can lead to SU, such as intrastent or extrastent calcification, multiple stent layers, and the presence of neointimal proliferation, which may potentially hinder the extrapolation of these findings to real-life clinical practice.

Conclusions

This study provides valuable insights into the comparative in vitro effects of various stent expansion techniques on the structure of DESs. IVL and saline-ELCA only produce minor modifications of the polymer when applied immediately after stent implantation. In contrast, HP or contrast-ELCA is associated with major alterations in polymer integrity. Further research is needed to validate these findings in clinical settings and explore how these techniques can be optimized to improve long-term outcomes.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S2
Videos S1–S2

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