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Super high-pressure balloon versus scoring balloon to prepare severely calcified coronary lesions: the ISAR-CALC randomised trial

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KEYWORDS

- calcified stenosis
- cutting balloon
- drug-eluting stent
- optical coherence tomography

Abstract

Background: The comparative efficacy of balloon-based techniques to prepare severely calcified coronary lesions before stenting remains poorly studied.

Aims: We sought to compare stent expansion following preparation of severely calcified coronary lesions with either a super high-pressure balloon or a scoring balloon.

Methods: In this randomised, open-label trial, patients with severely calcified coronary lesions were enrolled at five centres in Germany and Switzerland. After unsuccessful lesion preparation with a standard non-compliant balloon (<30% reduction of baseline diameter stenosis), participants were randomised to predilation with either a super high-pressure balloon or a scoring balloon before drug-eluting stent (DES) implantation. The primary endpoint of the study was stent expansion index as assessed by optical coherence tomography (OCT). The key secondary endpoints included angiographic, strategy and procedural success.

Results: OCT data after DES implantation were available for 70 out of 74 patients (94.6%) enrolled. Lesion preparation with a super high-pressure balloon versus a scoring balloon led to a comparable stent expansion index (0.72±0.12 vs 0.68±0.13; p=0.22). Compared with the scoring balloon, the super high-pressure balloon increased the minimum lumen diameter (2.83±0.34 mm vs 2.65±0.36 mm; p=0.03) and reduced the diameter stenosis (11.6±4.8% vs 14.4±5.6%; p=0.02) without difference in terms of angiographic success (100% vs 97.3%; p>0.99). Strategy success (91.9% vs 83.8%; p=0.48) and procedural success (100% vs 89.2%; p=0.12) were numerically more frequent with the super high-pressure balloon versus the scoring balloon.

Conclusions: In patients with severely calcified coronary artery lesions, preparation with a super high-pressure balloon versus a scoring balloon was associated with comparable stent expansion on intravascular imaging and a trend towards improved angiographic performance.

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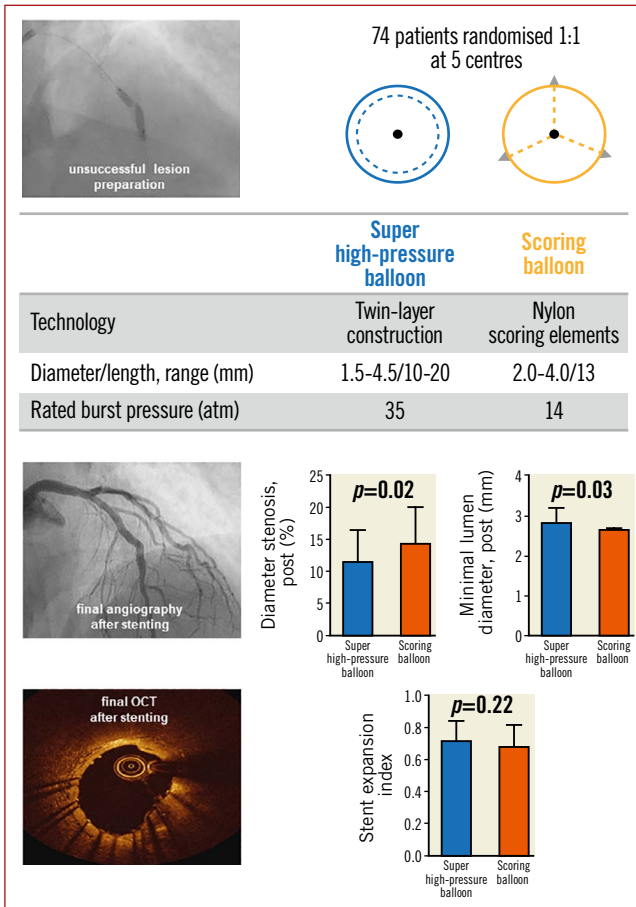

Visual summary. *A ComparIson of Strategies to PrepAre SeveRely CALCified Coronary Lesions: the ISAR-CALC randomised trial.*

Abbreviations

DES	drug-eluting stent(s)
EES	everolimus-eluting stent(s)
MACE	major adverse cardiac events
MLD	minimal lumen diameter
OCT	optical coherence tomography
PCI	percutaneous coronary intervention

Introduction

Calcified coronary artery lesions are encountered in a considerable proportion of patients treated with percutaneous coronary intervention (PCI)[1]. Given the ageing population, and increasing rates of diabetes mellitus and renal failure, the proportion of patients with calcified lesions is expected to increase further in the years to come.

Despite iterative improvements in percutaneous coronary devices and stenting techniques, severely calcified lesions remain a procedural and clinical challenge, even with high-performance drug-eluting stents (DES)[2]. Extensive calcification of obstructive coronary lesions may impact adversely on successful dilatation prior to stent implantation, thus increasing the likelihood of DES underexpansion, a known correlate of stent failure[3].

Optimal lesion preparation is a prerequisite for successful stent implantation and expansion in patients with calcific coronary lesions[4]. A number of interventional tools are currently available for the preparation of calcified lesions, including debulking, ablation- and balloon-based techniques. The latter comprise standard non-compliant balloons, super high-pressure balloons, cutting or scoring balloons and intravascular lithotripsy[5]. However, despite the growing interest in this field, the comparative performance of balloon-based techniques to prepare severely calcified coronary lesions before DES implantation remains poorly studied.

Against this background, we conducted a randomised trial in which patients with severely calcified coronary lesions amenable to PCI with DES were allocated to lesion preparation with either a super high-pressure balloon or a scoring balloon before DES implantation after unsuccessful predilation of the target lesion with a standard non-compliant balloon.

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Methods

STUDY POPULATION, RANDOMISATION, DEVICES AND INTERVENTION PROTOCOL

The ComparIson of Strategies to PrepAre SeveRely CALCified Coronary Lesions (ISAR-CALC) trial was an investigator-initiated, prospective, randomised, multicentre, assessor-blind, open-label trial (ClinicalTrials.gov Identifier: NCT03487432). Patients were enrolled at five participating centres in Germany and Switzerland between July 2018 and September 2019. A complete list of all inclusion and exclusion criteria is provided in **Supplementary Table 1**.

Patients who met all inclusion criteria and none of the exclusion criteria were assigned to either a super high-pressure balloon or a scoring balloon in a 1:1 randomisation fashion. The super high-pressure balloon (OPN NC®; SIS Medical AG, Frauenfeld, Switzerland) consists of a rapid-exchange, non-compliant balloon with twin-layer technology developed to deliver inflation pressures ≥35 bar and up to 55 bar[6]. The scoring balloon (NSE Alpha; B. Braun, Melsungen, Germany) consists of a rapid-exchange, semi-compliant balloon with three triangle-shaped, non-slip, nylon scoring elements attached proximally and distally on the outer surface of the balloon.

The two treatment groups were studied concurrently. Once enrolled in the study, patients received lesion preparation according to randomisation. If satisfactory dilation of the target lesion was not achieved with the allocated study device, additional lesion preparation techniques, such as rotational atherectomy, could be implemented at the discretion of the operator. Crossover to the non-assigned device was not permitted. Following lesion preparation, stenting was performed in the same setting using a latest-generation, thin-strut, biodegradable polymer, everolimus-eluting stent (SYNERGY™; Boston Scientific, Marlborough, MA, USA). Optical coherence tomography (OCT) imaging for primary endpoint assessment was performed once an optimal angiographic result was achieved after DES implantation, as per the operators' visual assessment. Stent optimisation after OCT imaging could be performed at the operator's discretion.

CLINICAL AND IMAGING DATA MANAGEMENT

Relevant data were collected and entered into a dedicated computer database (edc2go; Genae, Antwerp, Belgium). All events were adjudicated and classified by an independent events adjudication committee blinded to the treatment groups. All serious adverse events as well as the primary and secondary endpoints in this trial were monitored on-site. In addition, 25% of all patients with 100% source data verification were monitored in all centres.

Coronary angiograms were digitally recorded and assessed offline in the quantitative coronary angiographic (QCA) core laboratory (ISAResearch Center, Munich, Germany) using an automated edge detection system (QAngio XA version 7.3; Medis Medical Imaging Systems, Leiden, the Netherlands) by independent personnel unaware of the treatment allocation. Coronary lesion calcification was graded according to the angiographic classification of Mintz et al[7]. OCT acquisitions were performed with commercially available tools (ILUMIEN™ OPTIS™ system and Dragonfly™ OPTIS™ imaging catheter; both Abbott Vascular, Santa Clara, CA, USA) according to predefined standard operating procedures of the imaging core laboratory (ISAResearch Center). A detailed description of the protocols for acquisition and analysis of angiographic and OCT data is provided in **Supplementary Appendix 2**.

ENDPOINTS AND DEFINITIONS

The primary endpoint of the trial was stent expansion index, defined as minimum stent area divided by mean reference lumen area assessed with OCT, as previously described[4,8].

Key secondary endpoints were: i) angiographic success, defined as target lesion residual angiographic stenosis <30% in the presence of Thrombolysis In Myocardial Infarction (TIMI) 3 flow; ii) procedural success, defined as angiographic success without the occurrence of major adverse cardiac events (MACE, a composite of cardiac death, target vessel-related myocardial infarction [MI] and repeat revascularisation) up to 30 days; iii) strategy success, defined as procedural success using the assigned study device and stent, without additional devices for lesion preparation; iv) acute lumen gain, defined as minimal lumen diameter (MLD) after balloon angioplasty with the study devices minus baseline MLD; v) need for complementary lesion preparation with rotational atherectomy; vi) incidence of vessel perforation; vii) procedure duration, and viii) contrast volume.

SAMPLE SIZE CALCULATIONS AND STATISTICAL ANALYSIS PLAN

Absence of relevant differences in the primary endpoint among treatment groups was considered the null hypothesis. The alternative hypothesis was that the super high-pressure balloon would be superior to the scoring balloon with regard to achieving improved stent expansion index by OCT. Assuming a stent expansion index of 0.90±0.30 following preparation with a super high-pressure balloon and of 0.70±0.30 following preparation with a scoring balloon, with a two-sided alpha level of 0.05 and a power of 80%, we estimated that a sample size of 37 patients per group (74 patients in total) was required to account also for missing OCT imaging data. Sample size calculation was carried out using nQuery Advisor, Version 7.0 (Statistical Solutions, Cork, Ireland).

All statistical analyses were performed by an independent statistician. Primary and secondary endpoints were analysed on an intention-to-treat basis. Categorical data were expressed as counts and proportions. Differences between groups were checked for significance using the chi-square test (or Fisher's exact test when the expected cell value was <5). Continuous data were displayed as mean±standard deviation and compared using the Student's t-test or Mann-Whitney U test, as appropriate. Events were reported as crude incidence. No adjustment was made for the comparisons of primary and secondary endpoints. All tests were two-sided and a p-value <0.05 was considered statistically significant. Statistical analyses were performed in R, Version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

STUDY ORGANISATION

This was an investigator-initiated trial sponsored by Deutsches Herzzentrum München. The study was funded in part by an unrestricted research grant from SIS Medical AG and Boston Scientific. The authors are solely responsible for the design and conduct of the study, analyses, drafting and editing of the report, and its final contents. The ISAR-CALC trial committees are presented in **Supplementary Appendix 1**.

Results

A total of 74 patients with severely calcific coronary lesions were enrolled. The study flow chart is shown in **Figure 1**. Baseline features of the study patients are shown in **Table 1**. There were no

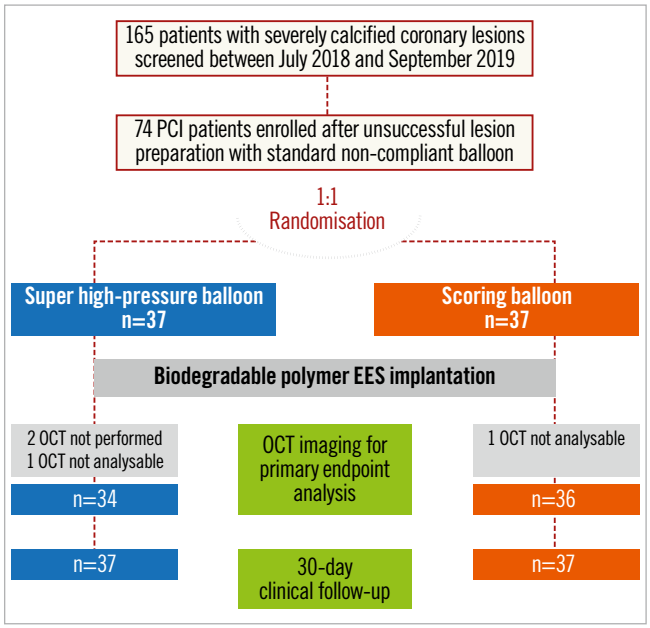

Figure 1. *Study flow chart. EES: everolimus-eluting stents; OCT: optical coherence tomography; PCI: percutaneous coronary intervention*

Table 1. Baseline characteristics.

	Super high-pressure balloon (n=37)	Scoring balloon (n=37)	*p*-value
Age, years	73.4±8.5	70.9±9.4	0.24
Male gender	86.5% (32/37)	83.8% (31/37)	>0.99
Height, cm	175±9	172±8	0.17
Weight, kg	81.3±15.0	78.1±15.8	0.37
Diabetes mellitus			
Non-insulin dependent	16.2% (6/37)	24.3% (9/37)	0.48
Insulin-dependent	13.5% (5/37)	13.5% (5/37)	
Hypertension	91.9% (34/37)	81.1% (30/37)	0.31
Hyperlipidaemia	78.4% (29/37)	75.7% (28/37)	>0.99
Current smoker	21.6% (8/37)	13.5% (5/37)	0.54
Prior myocardial infarction			
>90 days	10.8% (4/37)	13.5% (5/37)	>0.99
<90 days	5.4% (2/37)	8.1% (3/37)	
Prior revascularisation			
PCI	48.6% (18/37)	59.5% (22/37)	0.75
CABG	16.2% (6/37)	13.5% (5/37)	
Left main disease	24.3% (9/37)	18.9% (7/37)	0.78
Multivessel disease	91.9% (34/37)	81.1% (30/37)	0.26
Ejection fraction, %*	53.9±10.9	55.0±8.1	0.71
Creatinine, mg/dl	1.1±0.3	1.0±0.3	0.41

Values are n (%) or mean±standard deviation. *Baseline ejection fraction was available in 49 patients. CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention

Table 2. Angiographic* and procedural characteristics.

	Super high-pressure balloon (n=37)	Scoring balloon (n=37)	*p*-value
Angiographic characteristics			
Target lesion location			
Left anterior descending	56.8% (21/37)	51.4% (19/37)	0.66
Left circumflex	13.5% (5/37)	21.6% (8/37)	
Right coronary artery	29.7% (11/37)	27.0% (10/37)	
Bifurcation	40.5% (15/37)	37.8% (14/37)	>0.99
Moderate/severe tortuosity	13.5% (5/37)	21.6% (8/37)	0.74
Chronic total occlusion	2.7% (1/37)	5.4% (2/37)	>0.99
B2/C lesion	100% (37/37)	100% (37/37)	>0.99
Severe calcification	100% (37/37)	97.3% (36/37)	>0.99
Vessel diameter, mm	3.1±0.5	2.9±0.4	0.11
Lesion length, mm	23.3±11.5	24.8±12.1	0.58
Diameter stenosis, pre, %	69.1±10.2	70.6±10.7	0.53
Minimal lumen diameter, pre, mm	0.85±0.36	0.82±0.33	0.12
Procedural characteristics			
Guiding catheter			
6 Fr	43.2% (16/37)	41.7% (15/37)	>0.99
7 Fr	51.4% (19/37)	55.6% (20/37)	
Predilation¶			
Maximal predilation balloon diameter, mm	3.1±0.4	3.0±0.4	0.18
Maximal predilation balloon pressure, bar	33.8±6.5	17.0±4.0	<0.001
Large residual dissection (>5 mm)	8.1% (3/37)	13.5% (5/37)	0.71
Stent/lesion	1.5±0.8	1.6±0.7	0.88
Total stent length, mm	39.6±18.0	41.0±21.5	0.75
Minimal stent diameter, mm	3.2±0.5	3.1±0.5	0.38
Maximal stent diameter, mm	3.4±0.5	3.2±0.4	0.24
Maximal stent implantation pressure, bar	16.5±3.5	16.1±2.9	0.62
Post-dilation	78.4% (29/37)	83.8% (31/37)	0.77
Maximal post-dilation balloon diameter, mm	3.7±0.5	3.4±0.6	0.11
Maximal post-dilation balloon pressure, bar	21.3±7.9	19.9±3.8	0.38
Diameter stenosis, post, %	11.6±4.8	14.4±5.6	0.02
Minimal lumen diameter, post, mm	2.83±0.34	2.65±0.36	0.03
Acute lumen gain, mm	1.89±0.42	1.83±0.45	0.60
Compromised side branch	13.5% (5/37)	13.5% (5/37)	>0.99

Values are n (%) or mean±standard deviation. *As adjudicated by the angiographic core laboratory. ¶ Study device.

significant differences between the two groups at baseline. Of interest, the majority of participants were male and suffered from multivessel coronary disease.

Angiographic and procedural characteristics are provided in **Table 2**. There were no significant differences between the two groups at baseline. The angiographic core laboratory confirmed the presence of severely calcified target coronary lesions in all patients treated with the super high-pressure balloon and in all but one patient treated with the scoring balloon.

Target lesions were most frequently located in the left anterior descending artery and involved a bifurcation in approximately 40% of cases. Lesion length and the degree of baseline diameter stenosis did not differ between treatment groups. In the super high-pressure balloon group, the investigational device had a mean diameter of 3.1±0.4 mm and was inflated at a mean pressure of 33.8±6.5 bar. In the scoring balloon group, the control device had a mean diameter of 3.0±0.4 mm and was inflated at a mean pressure of 17.0±4.0 bar. After lesion predilation with the study devices, approximately one third of patients assigned to the scoring balloon received additional dilation with a standard non-compliant balloon (5.4% vs 32.4%, in the super high-pressure balloon and scoring balloon groups, respectively; p=0.012). Of note, three patients per group required rotational atherectomy for complementary lesion preparation due to inability to advance the assigned study device through the target lesions. A total of four lesions (5.4%) could not be treated with the DES selected per protocol due to unavailability; these lesions were treated with a XIENCE everolimus-eluting stent (Abbott Vascular). After DES implantation, the majority of patients received post-dilation with a standard non-compliant balloon without differences in terms of proportions (78.4% vs 83.8%; p=0.77) and maximal dilation pressures (21.3±7.9 bar vs 19.9±3.8 bar; p=0.38) between the super high-pressure balloon and scoring balloon groups.

According to core laboratory analysis, there was no significant difference in terms of acute lumen gain between the super high-pressure balloon and the scoring balloon (1.89±0.42 mm vs 1.83±0.45 mm; p=0.60). Of note, lesion preparation with the super high-pressure balloon significantly increased the final MLD (2.83±0.34 mm vs 2.65±0.36 mm; p=0.03) and reduced the residual diameter stenosis (11.6±4.8% vs 14.4±5.6%; p=0.02) as compared to the scoring balloon.

OCT DATA ANALYSIS

OCT data after DES implantation were available for 70 patients (94.6%) and are reported in **Table 3**. Three patients had no available OCT in the super high-pressure balloon group due to technical reasons (n=2) or because OCT pullbacks had insufficient quality for analysis (n=1), whereas one patient did not receive OCT in the scoring balloon group due to technical reasons.

In relation to the primary endpoint of the trial, stent expansion index was comparable in both treatment groups (0.72±0.12 vs 0.68±0.13; p=0.22) **(Figure 2)**. There was no significant difference with respect to other OCT parameters.

Table 3. Optical coherence tomography measurements* after stent implantation.

	Super high-pressure balloon (n=34)	Scoring balloon (n=36)	*p*-value
Minimal lumen area, mm²	6.40±2.15	5.77±1.91	0.20
Maximal lumen area, mm²	11.5±2.97	11.1±3.05	0.62
Average lumen area, mm²	8.59±2.18	8.14±1.95	0.37
Mean reference area, mm²	10.0±2.52	9.64±2.39	0.50
Minimal stent area, mm²	6.33±2.08	5.67±1.88	0.17
Maximal stent area, mm²	10.8±2.87	10.6±2.90	0.79
Average stent area, mm²	8.36±2.13	7.98±1.92	0.44
*As adjudicated by the imaging core laboratory.			

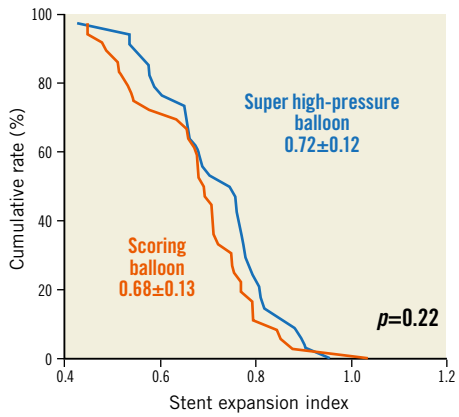

Figure 2. *Stent expansion index in patients assigned to either a super high-pressure balloon or a scoring balloon. Cumulative rate distribution for stent expansion index as assessed with optical coherence tomography.*

PROCEDURAL AND CLINICAL OUTCOMES

Large residual dissections, coronary perforations with need for covered stents and compromised side branches were observed in a minority of patients among those enrolled, without significant differences between groups. Angiographic success was comparable with either the super high-pressure balloon or the scoring balloon (100% vs 97.3%; p>0.99). Strategy success (91.9% vs 83.8%; p=0.48) and procedural success (100% vs 89.2%; p=0.12) were numerically more frequent with the super high-pressure balloon versus the scoring balloon, without statistical significance. Two patients in the scoring balloon group suffered from an MI due to acute stent thrombosis, which required repeat revascularisation and stenting. No adverse event occurred in the super high-pressure balloon group. The complete list of procedural and in-hospital outcomes is shown in **Table 4**. The cumulative incidence of 30-day clinical outcomes is reported in **Supplementary Table 2**. There was no adverse event between discharge and 30-day follow-up.

Table 4. Procedural and in-hospital outcomes.

	Super high-pressure balloon (n=37)	Scoring balloon (n=37)	*p*-value
Angiographic success	100% (37/37)	97.3% (36/37)	>0.99
Final TIMI flow grade <3	0	2.7% (1/37)	>0.99
Residual diameter stenosis >30%*	0	2.7% (1/37)	>0.99
Strategy success	91.9% (34/37)	83.8% (31/37)	0.48
Stent deployment failure	0	2.7% (1/37)	>0.99
Complementary rotational atherectomy	8.1% (3/37)	8.1% (3/37)	>0.99
Procedural success	100% (37/37)	89.2% (33/37)	0.12
In-hospital MACE	0	10.8% (4/37)	0.11
Cardiac death	0	0	–
Target vessel myocardial infarction	0	5.4% (2/37)	0.49
Repeat revascularisation	0	8.1% (3/37)	0.24
Procedure duration, min	56.2±32.2	55.8±38.5	0.96
Fluoroscopy time, min	25.3±22.7	24.1±15.5	0.79
Contrast volume, ml	273±108	248±107	0.32
Coronary perforation	2.7% (1/37)	2.7% (1/37)	>0.99
Covered stent implantation	2.7% (1/37)	2.7% (1/37)	>0.99
*As adjudicated by the angiographic core laboratory. The cumulative incidence of MACE up to 30 days is reported in Supplementary Table 2. MACE: major adverse cardiac events; TIMI: Thrombolysis In Myocardial Infarction			

Discussion

The ISAR-CALC trial represents the first multicentre investigation of the comparative performance of two balloon-based techniques to prepare severely calcified coronary artery lesions before stenting. After unsuccessful preparation with a standard non-compliant balloon at maximal pressure, patients enrolled were randomly

assigned to preparation with either a super high-pressure balloon or a scoring balloon before implantation of a latest-generation, thin-strut, everolimus-eluting stent. The principal findings of this trial are that:

– A super high-pressure balloon versus a scoring balloon led to comparable stent expansion index as assessed with OCT imaging.
– There was a trend towards improved angiographic performance with the super high-pressure balloon versus the scoring balloon (namely, increased final MLD and reduced residual stenosis), although angiographic success did not differ between groups.
– The rates of procedural complications and adverse clinical events up to 30 days reflect the anatomical and procedural complexity.

Adequate lesion preparation before stenting is crucial for PCI success: dilatation of fibrocalcific plaque favours stent delivery and allows more homogeneous stent expansion, which, in turn, impacts on acute and long-term outcomes from stenting[9]. These aspects are of particular importance in the case of PCI for severely calcified coronary lesions, which are associated with higher anatomical complexity, more frequent procedural complications, and stent failure[10].

The use of balloon-based techniques to prepare severely calcified coronary lesions offers several potential advantages over ablation- or debulking-based techniques: there is minimal additional training, no extra staff or instrumentation required in the catheterisation laboratory and less risk of downstream embolisation of atheromatous material[1]. Notably, more than 90% of patients included in the ISAR-CALC trial achieved a strategy success with assigned devices, with rotational atherectomy required only in a minority of patients.

Stent underexpansion is a powerful predictor of stent thrombosis[11] and restenosis[12]. Although not specifically validated for calcific coronary lesions, we chose stent expansion index as the primary endpoint of this trial, deriving the cut-off value for sample size calculations from available evidence[4]. We found that preparation of severely calcified lesions with a super high-pressure balloon was not superior to a scoring balloon in terms of stent expansion. In relation to this finding, a couple of issues should be mentioned. In contrast to previous investigations[13,14], this trial focused on balloon-based techniques for preparation of severely calcified coronary lesions undilatable with standard non-compliant balloons at maximal pressures. The use of a super high-pressure balloon for preparation of these highly complex lesions is probably insufficient to achieve optimal stent expansion as measured by intravascular imaging. However, in contrast with the scoring balloon, a super high-pressure balloon is an established tool for stent optimisation[15]. Further studies are required to determine whether a super high-pressure balloon is superior to other balloon-based strategies when used for both preparation of calcific lesions and stent optimisation, under the guidance of intravascular imaging.

In this trial, the implementation of a super high-pressure balloon versus a scoring balloon in severely calcified lesions before coronary stenting was associated with larger final MLD and lower residual diameter stenosis according to independent core laboratory analysis. This fact is important; although the overall angiographic success did not differ with either the super high-pressure balloon or the scoring balloon, vessel size and residual diameter stenosis are highly predictive of DES failure[16]. In addition, although the magnitude of treatment effect for vessel size and diameter stenosis observed with the super high-pressure balloon was modest, the marginal gain may be of clinical relevance in this particular population that is prone to stent failure. However, the current findings are hypothesis-generating and require validation in studies powered for angiographic measures of efficacy.

There is concern regarding the potential risk of coronary perforation with super high-pressure balloons due to excessive mechanical vascular trauma associated with high dilation pressures in calcified lesions[1]. Although this trial was not powered to address such rarely occurring clinical endpoints, the overall incidence of adverse events was low in both treatment groups. However, in line with previous data[14], we found that adverse events were numerically more frequent among patients treated with a scoring balloon. Approximately one third of patients assigned to a scoring balloon received complementary lesion preparation with repeat, additional non-compliant balloons before stenting. In contrast, the super high-pressure balloon was the sole therapy used for lesion preparation in the majority of cases. The variance in complementary lesion preparation is probably due to the unsatisfactory angiographic appearance after scoring balloon dilation as per the visual estimation of operators. However, the angiographic core laboratory analysis found no significant difference in terms of acute gain between treatment groups.

Study limitations

This trial has several limitations, which deserve discussion.

– The hypothesised superiority of a super high-pressure balloon versus a scoring balloon in terms of stent expansion index could not be demonstrated. In this regard, any consideration regarding other endpoints should be interpreted with caution and remains exploratory in nature.
– Since randomisation occurred after unsuccessful lesion preparation with a standard non-compliant balloon, baseline OCT pullbacks were not routinely performed, which represents a major limitation of the present study. However, the value of baseline imaging such as OCT[17] to guide the selection of interventional techniques and predict the relative performance in calcific coronary lesions remains undisputed, and the threshold for imaging-guided interventions in this setting should be as low as possible.
– The present results cannot be extrapolated to balloon-based technologies or DES platforms different from those selected for this trial. Amongst others, the novel option of intravascular lithotripsy, which uses acoustic shock waves in a balloon-based system to fracture severe calcifications in the vessel wall, is promising[18]. Whether this latter technology is alternative or

complementary to a super high-pressure balloon in the contemporary algorithm for the imaging-guided management of severe coronary calcifications undilatable with conventional non-compliant or scoring balloons (as suggested from the study of Kassimis et al[19]) warrants further investigation in properly designed head-to-head comparisons.

– This trial enrolled selected patients, excluding, amongst others, those with a history of MI within seven days. This aspect limits the external validity of the current findings.

Conclusions

The preparation of severely calcified coronary lesions with either a super high-pressure balloon or a scoring balloon was associated with comparable stent expansion on intravascular imaging and a trend towards improved angiographic performance. The role of the super high-pressure balloon for lesion preparation and imaging-guided optimisation of drug-eluting stents in severely calcified coronary lesions warrants further investigation.

Impact on daily practice

Percutaneous treatment of severely calcified coronary lesions is associated with procedural complications and adverse clinical events. So far, there has been no randomised comparison of balloon-based techniques to prepare severely calcified coronary lesions. In this randomised trial, the preparation of severely calcified coronary lesions with either a super high-pressure balloon or a scoring balloon was associated with comparable stent expansion on intravascular imaging and a trend towards improved angiographic performance.

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Conflict of interest statement

A. Allali reports personal fees from Boston Scientific, outside the submitted work. M. Ayoub reports personal fees from Boston Scientific, outside the submitted work. F. Cuculi reports personal fees from SIS Medical AG, outside the submitted work. M. Bossard reports grants from SIS Medical Switzerland, and personal fees from Abbott Vascular, during the conduct of the study. S. Kufner reports personal fees from AstraZeneca and personal fees from Bristol-Myers Squibb, outside the submitted work. M. Fusaro reports personal fees from SIS Medical AG, outside the submitted work. M. Joner reports personal fees from Biotronik, personal fees from OrbusNeich, grants and personal fees from Boston Scientific, grants and personal fees from Edwards, personal fees from ReCor, personal fees from AstraZeneca, and grants from Amgen, outside the submitted work. R.A. Byrne reports grants to the institution of prior employment from SIS Medical and from Boston Scientific related to the conduct of the study, and grants from CeloNova Biosciences to the institution of prior employment, outside the submitted work. S. Cassese reports personal fees and grants to the institution from SIS Medical AG, outside the submitted work. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. ISAR-CALC trial committees.

Supplementary Appendix 2. Detailed description of the protocols for acquisition and analysis of angiographic and OCT data.

Supplementary Table 1. Inclusion/exclusion criteria of the ISAR-CALC trial.

Supplementary Table 2. Cumulative 30-day clinical outcomes.

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Supplementary data

Supplementary Appendix 1. ISAR-CALC trial committees

- **Steering committee**: Robert A. Byrne (Chair); Salvatore Cassese (Principal Investigator); Michael Joner (Sub-Principal Investigator); Mohamed Abdel-Wahab (Sub-Principal Investigator).
- **Clinical project manager**: Tobias Rheude.
- **Clinical event adjudication committee**: Gjin Ndrepepa (Chair); Andreas Stein; Giulio Stefanini.
- **Patient follow-up and data coordination at the *ISAResearch Center, Munich, Germany***: Stefanie Brunner, Nonglag Rifatov, Felix Voll, Barbara von Merzljak, Jens Wiebe.
- **Angiographic and intravascular imaging core laboratory at the *ISAResearch Center, Munich, Germany***: Susanne Pinieck, Silvia Hurt (quantitative angiographic core laboratory analysis), Himanshu Rai, Erion Xhepa (optical coherence tomography core laboratory analysis).

Contract research organisation for independent data monitoring and audit: KCRI, Krakow, Poland.

Supplementary Appendix 2. Protocol for acquisition and analysis of quantitative coronary angiography data

Coronary angiograms were digitally recorded, stored offline and analysed by independent personnel unaware of treatment allocation in the quantitative coronary angiographic (QCA) core laboratory (ISAResearch Center, Munich, Germany) using an automated edge detection system (QAngio XA version 7.3; Medis Medical Imaging Systems, Leiden, the Netherlands) and a predefined standard operating procedure. The analysis was based on digitisation of coronary angiograms, image calibration and arterial automatic contour detection, as previously described. At least a 6 Fr guiding catheter with good support and co-axial alignment was requested for all coronary angiograms. A baseline angiography of the target vessel with and without contrast (filled/empty, approximately 3-4 cardiac cycles) served for quantification of coronary calcium at the level of the target lesion and qualitative evaluation of baseline angiographic features. During the acquisition, a minimum of 3 cm of the non-tapered distal, dye-filled catheter should be visible for calibration purposes. Baseline coronary angiograms were selected before guidewire advancement to avoid artefacts. Baseline QCA measures comprised, but were not limited to, minimal luminal diameter (MLD, the smallest lumen diameter in the segment of interest), reference vessel diameter (RVD, the averaged diameter of the coronary assumed without atherosclerotic disease), lesion length (length of the stenosis as measured by two points where the coronary margins change direction, creating a shoulder between the angiographically normal sub-segment and the diseased sub-segment), and diameter stenosis ([RVD-MLD]/RVD*100). The failure of lesion preparation with a standard non-compliant balloon at maximal pressure was recorded and documented in the intervention protocol transmitted for all patients enrolled for source verification. For evaluation of acute luminal gain (MLD after balloon angioplasty with the study devices minus baseline MLD), the coronary angiograms with study balloon inflation (at maximal pressure) were recorded and the sequence was indicated in the intervention protocol (omitting any information regarding the type of device used). After lesion preparation with the assigned study device, any other device used for complementary lesion preparation was recorded (standard non-compliant balloon at maximal pressure or any rotablation run, if necessary) and documented in the intervention protocol for source verification. For the stent implantation, the stent-balloon inflation (at maximal pressure) was recorded. Baseline QCA measurements were performed using the coronary angiograms with the single worst view projection of the target lesion; the same view projection was used for measurements after intervention. Final angiographic results were measured before OCT pullback (performed for the assessment of the primary endpoint) or after OCT pullback and guidewire removal in case of no additional coronary interventions. Pre- and post-PCI coronary angiograms were obtained at the same magnification and the same view projection. All measurements were performed on coronary angiograms recorded after the intracoronary administration of nitroglycerine (200 mcg).

Protocol for acquisition and analysis of OCT data

OCT pullbacks were stored offline and analysed using Windows-based QIvus 3.1.12.0 software (Medis Medical Imaging Systems) by independent personnel unaware of treatment allocation in the imaging core laboratory (ISAResearch Center, Munich, Germany) using a predefined standard operating procedure. At least a 6 Fr guiding catheter (ideally without side

holes) with good support and co-axial alignment was requested for all OCT pullbacks. After infusion of intracoronary nitroglycerine (200 mcg) and after ensuring that the OCT catheter lumen was purged by injection of at least 1-2 ml of pure contrast, the OCT catheter was advanced into the target vessel such that the scanning crystal lay ca. 10 mm distal to the distal stent edge and such that the end of the pullback was 10 mm proximal to the proximal stent edge. In case of long lesions, more than one OCT pullback was permitted. The automatic pullback was started while 20 ml of contrast was infused at a rate of 5 ml/s (left coronary artery) or 16 ml of contrast at a rate of 4 ml/s (right coronary artery). The unitary acquisition length for OCT pullbacks was 75 mm or 54 mm, the axial scanning rate was 100 Hz and the rate of pullback acquisition was 36 mm/s or 18 mm/s. Morphometric analysis of contiguous cross-sections within the stented segment was performed for each 1 mm longitudinal interval. Software-aided automatic strut detection was performed, adjusted in case of anomalies and later connected to identify stent contour. Stent area in each analysed frame was defined as the circumferential area limited by the stent contour. In frames with stent overlap and visible strut crowding, the layer of stent struts closest to the vessel's endoluminal surface was used to extrapolate the stent contour. Software-aided automatic lumen contour detection was performed within 5 mm from the distal and proximal stent edge (reference segments) in order to identify proximal and distal reference lumen areas. Reference lumen area is defined as a representative, preferably disease-free, frame contained within the reference segment. Mean reference lumen area was calculated using the following formula: (distal reference lumen area + proximal reference lumen area) / 2. If the pullback lacked analysable reference segments, the proximal or distal reference area was extrapolated from the most analysable proximal or distal stent area. To account for natural vessel tapering in case of long lesions (>70 mm), stented segments were split into two equal segments and analysed separately. In the case of long lesions requiring two or more OCT pullbacks for the stented segment, anatomical landmarks (e.g., side branches) were used as bookmarks for splitting the analysis. Additional coronary interventions following OCT imaging were permitted in case of evidence of suboptimal procedural results (i.e., residual dissection) at the discretion of the operator. In addition, further OCT pullbacks were allowed at the operator's discretion without being considered for primary endpoint evaluation.

Supplementary Table 1. Inclusion/exclusion criteria of the ISAR-CALC trial.

Inclusion criteria
- Age above 18 years and consentable - Persistent angina despite optimal medical therapy and/or evidence of inducible ischaemia - Angiographically proven coronary artery disease - De novo lesion in a native coronary artery - Target reference vessel diameter between 2.25 and 4.00 mm by visual estimation - Severe calcification of the target lesion as determined by visual estimation at coronary angiography - Unsuccessful lesion preparation with standard non-compliant balloon (<30% reduction of baseline diameter stenosis at maximal pressure) - Written informed consent.
Exclusion criteria
- Myocardial infarction (within 1 week) - Target lesion is located in a coronary artery bypass graft - Target lesion is an in-stent restenosis - Target lesion is aorto-ostial - Target vessel thrombus - Limited long-term prognosis due to other comorbid conditions.

Supplementary Table 2. Cumulative 30-day clinical outcomes.

	Super high-pressure balloon (n=37)	Scoring balloon (n=37)	*p*-value
MACE	-	10.8% (4/37)	0.11
Cardiac death	-	0	-
Target vessel myocardial infarction	-	5.4% (2/37)	0.49
Repeat revascularisation	-	8.1% (3/37)	0.24