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A Prospective, Multicenter, Open Label Study Investigating the Implementation of a Standardized Algorithm for Coronary CaLcificatiOn With PlaquE Modification Using UltraSound Guidance to Improve Procedural and Clinical Outcomes (CYCLOPES): Design and Rationale of the CYCLOPES Trial

Daniel O'Callaghan[1,2] | Rory Durand[1] | Colm G. Hanratty[1] | Thomas Cuisset[3,4] | Beatriz Vaquerizo[5] | Jan-Malte Sinning[6] | Peter O'Kane[7] | J. J. Coughlan[1,2] | Simon Walsh[8] | Róisín Colleran[1,2] | Himanshu Rai[1,2] | Osama Soliman[1,2] | Emanuele Barbato[9] | Barbara E. Stähli[10] | Robert A. Byrne[1,2]

[1]Department of Cardiology, Cardiovascular Research Institute (CVRI) and Mater Private Network, Dublin, Ireland | [2]RCSI School of Medicine and Health Sciences, Dublin, Ireland | [3]CHU Timone, Marseille, France | [4]CV2N, INSERM, INRAE, Aix Marseille University, Marseille, France | [5]Hospital del Mar, IMIM, Universidad Autónoma, Barcelona, Spain | [6]St. Vincent Hospital, Cologne, Germany | [7]Dorset Heart Centre, Royal Bournemouth Hospital, University Hospitals Dorset, Bournemouth, UK | [8]Belfast Health & Social Care Trust, Belfast, UK | [9]University Hospital Sant'Andrea, Rome, Italy | [10]University Hospital Zurich, Faculty of Medicine, University of Zurich, Zurich, Switzerland

Correspondence: Robert A. Byrne (Robertabyrne@rcsi.ie)

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ABSTRACT

Introduction: Moderate-to-severe calcification is present in ~20%–30% of patients undergoing coronary angiography. Coronary lesion modification is often necessary to facilitate optimal stent delivery and expansion, with several dedicated devices now approved for calcium modification before stent implantation. The CYCLOPES study aims to evaluate an intravascular ultrasound (IVUS) based calcium modification algorithm for the treatment of moderate-to-severely calcified coronary lesions.

Methods and Analysis: CYCLOPES is a prospective, international, multi-center, observational, single-arm study. 500 patients will be enrolled at 25 centers in Europe. Patients with planned percutaneous coronary intervention (PCI) to a native coronary artery lesion with moderate-to-severe calcification will be eligible. All PCI procedures will be IVUS guided, with drug-eluting stents implanted according to the study-specific algorithm.

The co-primary endpoints are the minimum stent area (MSA) at the site of maximum calcification at the end of the index procedure (as determined by core lab analysis), and target lesion failure (TLF) at 1-year post-procedure. Prespecified secondary endpoints include: the individual components of TLF at 1 month and 1 year; the MSA measured at the end of the index procedure; strategy success (defined as successful stent delivery with $\geq 80\%$ stent expansion and complete stent apposition with no significant edge dissection and full lesion coverage with $< 50\%$ plaque burden at proximal and distal references with TIMI 3 flow); as well as target vessel revascularization; target lesion revascularization; stent thrombosis; cardiovascular death; and acute kidney injury at 1 year. Coronary angiograms and IVUS images will be analyzed by an independent core Lab. Clinical follow-up will be performed at discharge, 30-days, and 1 year post PCI.

Daniel O'Callaghan and Rory Durand contributed equally, should be considered joint first authors.

Trial Registration: ClinicalTrials.gov identifier: NCT06678594.

1 | Introduction

Moderate-to-severe calcification, defined as visible densities seen on fluoroscopy affecting both sides of vessel wall with (moderate) or without (severe) heart motion, is present in ~20%–30% of patients undergoing coronary angiography [1–4]. Given the ageing population, and the fact that coronary calcification increases significantly with age, the prevalence of calcified lesions in patients undergoing percutaneous coronary intervention (PCI) is expected to rise [3, 5]. Moderate to severe coronary artery calcification is a marker of increased procedural complexity [3]. Calcified lesions may result in challenges with respect to device delivery and adequate stent expansion [6]. This may partly explain why PCI of moderate to severely calcified lesions is associated with worse long term clinical outcomes [7].

Adequate lesion modification prior to stent implantation is important to ensure optimal stent delivery, expansion, and apposition [6]. There are several dedicated coronary calcium modification devices available to operators [6]. These devices include non-compliant balloons, ultra high-pressure non-compliant balloons, scoring and cutting balloons, rotational atherectomy (RA), orbital atherectomy (OA), excimer laser coronary atherectomy (ELCA) and intravascular lithotripsy (IVL) [3, 4, 6, 8].

Intravascular ultrasound (IVUS) imaging allows for detailed assessment of the severity and distribution (concentric or eccentric, deep or superficial, calcium arc) of coronary arterial calcification, which may be useful to inform procedural planning and lesion preparation [9]. IVUS guidance has been associated with improved clinical outcomes after PCI in a wide variety of clinical settings [10, 11]. Given the wide variety of calcium modification devices available in contemporary catheterization laboratories, algorithms to guide optimal device selection may be useful. The CoronarY CaLcificatiOn with PlaquE Modification using UltraSound Guidance to Improve Procedural and Clinical Outcomes (**CYCLOPES**) study aims to evaluate the impact of the systematic utilization of this calcium modification algorithm on procedural and clinical outcomes in patients undergoing complex PCI.

The CYCLOPES study will evaluate a proposed calcium modification algorithm for coronary lesion preparation in a large cohort of patients with moderate to severely calcified coronary artery disease. This will provide evidence on the outcomes associated with an IVUS guided structured approach to the treatment of calcified coronary lesions. Further, secondary analysis of the IVUS data may enable identification of predictors of device efficacy and procedural success.

2 | Methods

2.1 | Study Design

The CYCLOPES study is an international, multi-center, observational, single-arm study. Five hundred patients will be enrolled at 25 centers in Europe. Patients will be screened before coronary angiography, and patients with planned PCI for moderate to severely calcified native coronary artery lesions will be eligible to enroll.

Coronary calcification is seen on coronary angiogram as radiopacities within the vessel wall, which can be classified as none/mild, moderate (radiopacities noted only during the cardiac cycle before contrast injection), and severe (radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen).

For the purpose of the study, we defined significant calcium at the target lesion site as defined as either:

1. The presence of radiopacities involving both sides of the arterial wall > 10 mm and involving the target lesion on angiography or,
2. The presence of $> 270°$ arc of superficial calcium on intravascular imaging with a length > 5 mm or the presence of 360° arc of calcium on intravascular imaging.

2.2 | Inclusion and Exclusion Criteria

Subjects will be assessed to ensure they meet all the inclusion criteria to be eligible for study enrollment. Inclusion criteria include: (1) Clinical indication for PCI in the setting of chronic coronary syndrome or non-ST-segment elevation myocardial infarction, due to symptoms or documented myocardial ischemia; (2) At least one moderate to severely calcified native coronary artery lesion confirmed by QCA and/or 60 MHz HD IVUS, with the presence of significant calcium, $\geq 70\%$ diameter stenosis by visual estimation (in a reference vessel diameter of ≥ 2.5 mm and ≤ 4.0 mm) and that is suitable for PCI; (3) It is possible to cross the calcified lesion with a coronary guidewire; (4) Age ≥ 18 years; (5) Patient is willing and able to comply with the study procedures and follow-up.

Subjects will also be assessed to ensure they do not meet any of the exclusion criteria in order to be eligible for study enrollment. Exclusion criteria include: (1) Patients with cardiogenic shock; (2) ST-segment elevation myocardial infarction; (3) Instent re-stenosis; (4) Stent thrombosis; (5) Coronary artery dissection; (6) Chronic total occlusion in a major artery; (7) Left ventricular ejection fraction $\leq 30\%$; (8) Need for coronary artery bypass graft surgery; (9) Documented allergy to everolimus or to any stent material; (10) Any contraindication for dual antiplatelet therapy with aspirin and a P2Y12 inhibitor for at least 3 months (except for patients on oral anticoagulation); (11) Pregnancy; (12) Life expectancy < 1 year; (13) Participation in another study with an investigational product; (14) Inability to provide informed consent.

2.3 | Study Procedures

All procedures will be performed by fully trained operators with at least 50 prior rotablation procedures and several years of interventional experience. All procedures will be performed

according to current guidelines and international standards using an everolimus-eluting stent [6]. In all patients, HD 60 MHz HD IVUS imaging will be performed according to a study-specific algorithm. Quantitative coronary angiography (QCA) images will need to be obtained at baseline (pre-procedure and post-procedure) displaying the coronary lesion in the projection demonstrating the severity of the lesion, after intracoronary administration of nitrate (recommended 100–200 μg, unless clinically contraindicated). At least two orthogonal, or near orthogonal views should be obtained. Quantitative analysis of the coronary angiographic images will be performed by an independent core laboratory for all subjects.

The study protocol is based on three main steps; 1. Define, 2. Modify and 3. Confirm. The algorithm workflow is demonstrated in Figure 1.

2.4 | Step 1. Define

The algorithm is guided by intravascular ultrasound with mechanical pullback, using HD IVUS. The IVUS 1, 2, 3 Essentials Workflow should be performed for the first and final HD IVUS acquisition [12].

Having met the eligibility criteria, the set-up step is initiated. This involves crossing the calcified lesion with a coronary guidewire and attempting to cross the lesion with the imaging (IVUS) catheter. If the imaging catheter does not pass through the lesion, the lesion should be predilated with an angioplasty balloon to facilitate crossing the lesion with the imaging catheter at a second attempt. For "balloon uncrossable" lesions, an upfront rotational atherectomy strategy will be required to proceed.

Once the IVUS catheter is passed distal to the lesion, the first step of the CYCLOPES algorithm, "Define" is performed. The first HD IVUS acquisition takes place to define the potential characteristics of coronary calcification seen with intravascular imaging. The six main features to assess are circumferential calcium, long segments of calcification, vessel sizing and reference vessel diameter (RVD), wire bias, calcific nodule, and reverberations. Circumferential calcium refers to the presence or absence of circumferential calcium. A long segment of calcification is assessed by the operator as a segment of calcified disease >20 mm. Vessel sizing, including reference vessel diameter (RVD), is assessed and recorded by the operator using the IVUS 123 Essentials workflow method [12]. Wire bias is defined as wire bias toward calcium or away from calcium. Calcific nodule refers to the presence or absence of a calcified nodule on HD IVUS. Reverberations refer to the presence of reverberations seen on HD IVUS. Examples of these potential IVUS findings are highlighted in Figure 2.

2.5 | Step 2. Modify

Once the lesion has been defined, the operator then moves to the "Modify" step. The first part of this step involves attempting to pre-dilate the lesion with a non-compliant balloon or cutting balloon. For non-compliant balloon dilatation, ideally a balloon sized in a 1:1 ratio to the reference vessel diameter should be used. For cutting balloon dilatation, the cutting balloon size should be 0.5 mm smaller than the media-to-media measurement of the vessel size as determined by intravascular imaging. It is strongly recommended that cutting balloon therapy be delivered to the target lesion at high pressure (e.g., ~18–20 atmospheres), as this has been shown to be safe and effective in prior studies [13].

If 1:1 balloon expansion is achieved with angiographic evidence of complete balloon expansion, then the lesion may be sufficiently prepared and additional calcium modification may not be required; if so the operator can proceed to Step 3, "Confirm (Part 1)." If there is incomplete or asymmetric balloon expansion, then additional calcium modification methods may be required. Using the characteristics assessed with HD IVUS in the "Define" step, the operator can then choose an additional advanced modality for calcium modification. It should be noted that calcium morphologies are often heterogenous, with multiple morphologies present within the one treated segment.

The choice of calcium modifying modality is at the discretion of the operator. However, some suggestions based on potential observed morphologies are provided to guide the operators. Suggested ideal calcium characteristics for rotational atherectomy include balloon uncrossable lesions, long calcific lesions and calcified nodules if the wire is biased toward the nodule. The atherectomy burr size should be approximately 0.5 x mean RVD. Suggested ideal calcium characteristics for intravascular lithotripsy include the presence of a calcium arc $>270°$ in large vessels. IVL may also be considered for eccentric or nodular calcium when the wire is biased away from the nodule (as in this setting, rotational atherectomy is unlikely to be effective).

2.6 | Step 3. Confirm

2.6.1 | Confirm (Part 1)

Once the chosen modality for calcium modification has been used, the operator moves to the "Confirm" step, which involves post calcium modification HD IVUS imaging to assess the outcome of the "Modify" step. Part 1 of the confirm step is to confirm that adequate calcium modification has been achieved prior to proceeding to stent implantation. This post lesion preparation HD IVUS recording assesses for calcium fractures, increased reverberations and luminal gain in comparison to the baseline IVUS recording. If signs of calcium modification are present, defined as the presence of calcium fractures or increased reverberations visualized on HD IVUS, then the algorithm directs the operator to DES insertion and optimization.

If at the "Confirm" step signs of calcium modification are absent, then the algorithm re-directs back to the modify step. At this point, the choice of calcium modification modality is again at the operator's discretion. Multiple modalities may be used. The "Confirm" step must be completed after repeating the "Modify" step.

If the individual operator is satisfied that optimal lesion preparation has been achieved by the presence of calcium fractures, increased reverberations or acceptable luminal gain (or at the clinical discretion of the operator), they can proceed to treat the lesion with an appropriate stent type for the individual patient and lesion characteristics (Figure 3). If optimal lesion

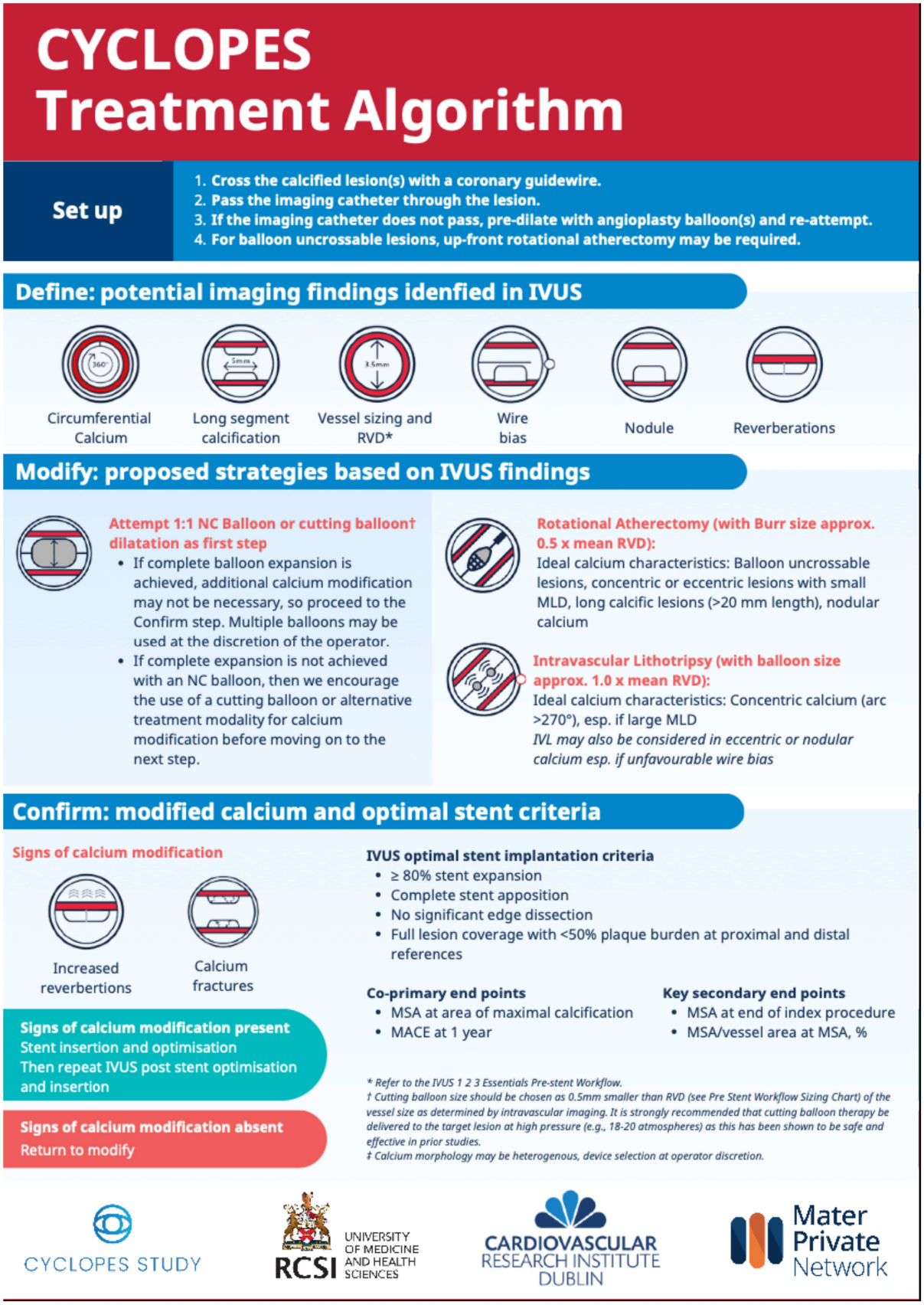

FIGURE 1 | The CYCLOPES treatment algorithm. [Color figure can be viewed at wileyonlinelibrary.com]

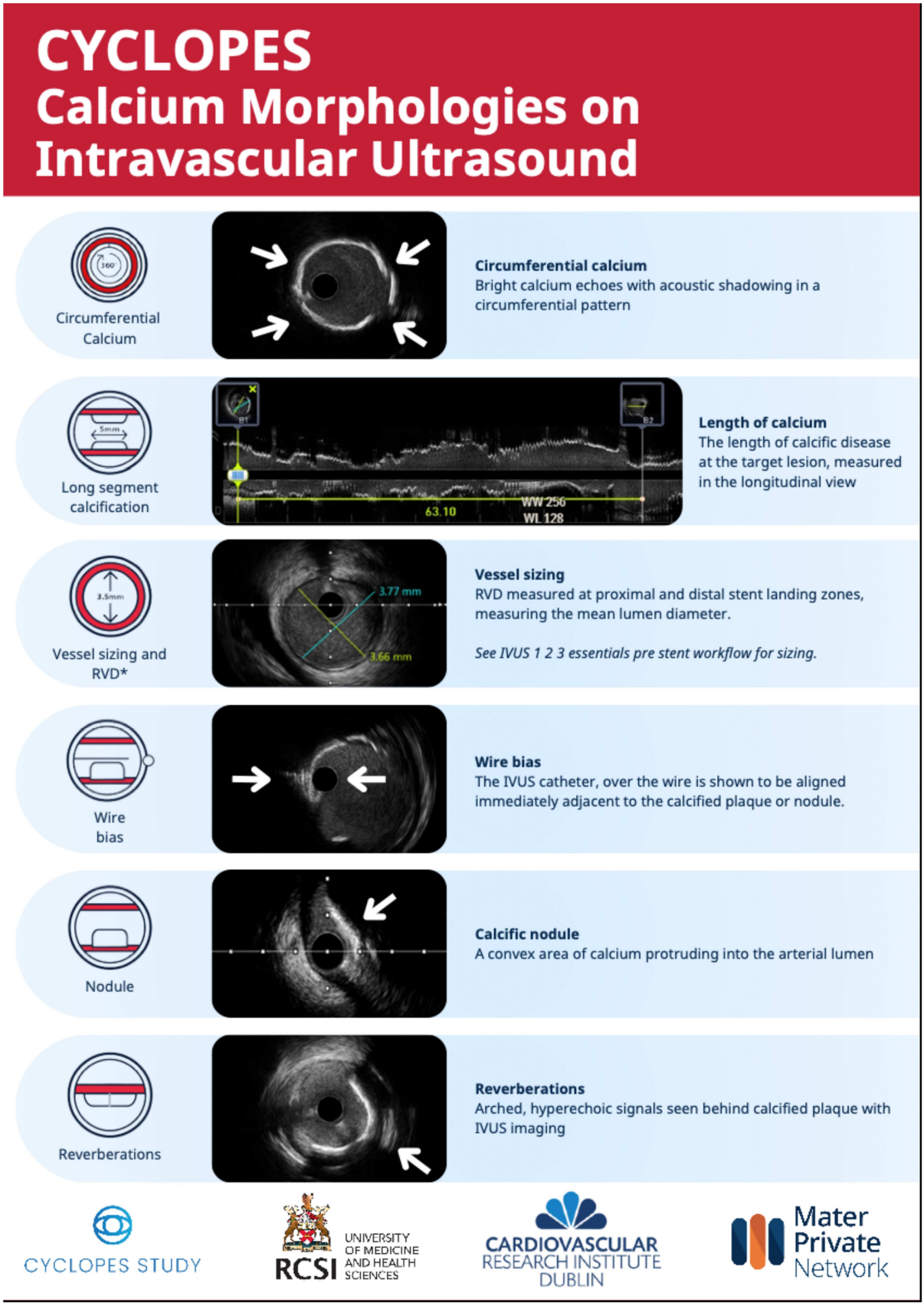

FIGURE 2 | IVUS defined patterns of calcification for CYCLOPES. [Color figure can be viewed at wileyonlinelibrary.com]

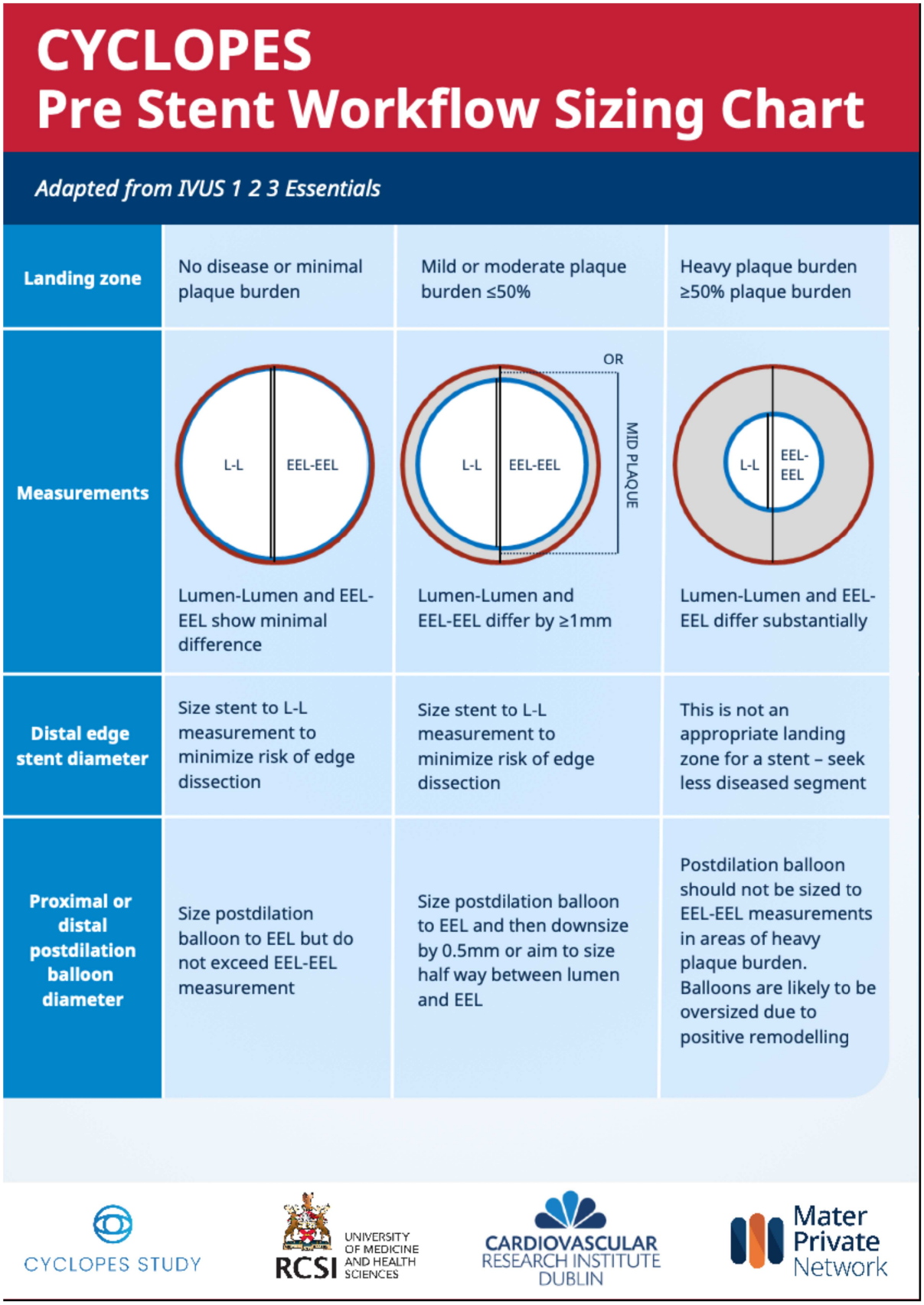

FIGURE 3 | IVUS recommended sizing in CYCLOPES. [Color figure can be viewed at wileyonlinelibrary.com]

preparation has not been achieved by the above criteria, then further lesion preparation is recommended by the calcium modification algorithm. Each time that further calcium modification is performed using a different modality of calcium modification (e.g., NC balloon, cutting balloon, IVL or rotational atherectomy), an additional HD IVUS recording is required to assess for optimal lesion preparation prior to stent implantation.

Once optimal lesion preparation is achieved, the operator will then proceed to stent insertion. Pre-dilatation and post-dilatation may be performed by the operator as per their usual practice. Should the operator opt to avoid stent insertion during the index procedure based on their clinical decision, no further HD IVUS recordings will be required at this time point. Should a staged procedure be planned, and a stent inserted later, the final result should be assessed with IVUS, and recordings uploaded as part of the study.

2.6.2 | Confirm (Part 2)

Following stent insertion, a final IVUS recording of the target lesion will be performed. If additional stent optimization, such as with further post-dilatation with non-compliant angioplasty balloon is required, this is permitted and must be followed by another IVUS recording such that the final IVUS recording shows the final optimized result. The final HD IVUS acquisition will be used to assess if the operator has achieved optimal stent implantation criteria. These criteria include at least 80% stent expansion, complete stent apposition, no edge dissection and full lesion coverage, with less than 50% plaque burden at the proximal and distal references.

2.7 | Data Collection

Baseline characteristics, vital signs, concomitant co-morbidities, cardiovascular risk factors, medication, routine laboratory analyses, ECG data, coronary angiography, and procedural data (coronary angiogram, HD IVUS images, procedural characteristics, and periprocedural complications), and follow-up data will be collected.

Baseline variables will include:

- Demographic characteristics
- Medical history
- Past and concomitant anti-thrombotic medications
- Clinical status at study entry
- Baseline lesion characteristics

2.8 | Primary Outcomes

The co-primary end points are minimum stent are (MSA) at the site of maximum calcification at the end of the index procedure (as assessed by 60 MHz HD IVUS imaging) and rates of target lesion failure (TLF), a composite of cardiovascular death, non-fatal myocardial infarction related to the target vessel, and unplanned ischemia-driven target lesion revascularization, at 1 year.

2.9 | Secondary Outcomes

Secondary endpoints will include: (1) the individual components of TLF at 1 month and 1 year; (2) the minimum stent area (MSA) measured at the end of the index procedure; (3) Strategy success defined as successful stent delivery with $\geq 80\%$ stent expansion and complete stent apposition with No edge dissection and full lesion coverage with $< 50\%$ plaque burden at proximal and distal references with TIMI 3 flow; (11) Procedure time; (12) Fluoroscopy time; (13) Radiation exposure (dose-area-product); as well as (4) Target vessel revascularization (TVR); (5) Target lesion revascularization (TLR); (6) Stent thrombosis; (7) Stroke; (8) Cardiovascular death; (9) Acute kidney injury; (10) Major bleeding, categorized as class 3–5 according to the Bleeding Academic Research Consortium [BARC] at 1 year. Further, cost effectiveness analyses will be performed.

2.10 | Study Conduct

Coronary angiograms and HD IVUS images will be analyzed by an independent angiography and HD IVUS Core Lab. Follow-up will be performed at discharge, at 30-days, and at 1 year.

The study will be conducted in accordance with the investigation plan, the current version of the Declaration of Helsinki, and national legal and regulatory requirements [14].

The study's expected duration is about 36 months. Enrollment will take place over 18 months. Follow up is planned for 12-months. There will be an additional 6-months for data freeze, core lab analysis and statistical analysis.

2.11 | Statistical Analysis

The statistical analysis plan will be finalized prior to data freeze and will include an in-depth technical description of the statistical analyses described in this section. All potentially eligible subjects meeting the general inclusion and exclusion criteria, who have signed an informed consent form, have had the index procedure, and have been entered into the eCRF will be included.

The study design is a single armed, prospective, observational analysis. No statistical hypothesis has been formulated. Statistical analysis methodology will be described in detail in the statistical analysis plan (SAP), which will be finalized prior to database lock.

Descriptive statistics and graphical displays will be used to summarize the study findings and outcomes. Distribution of continuous variables will be assessed by the Shapiro-Wilk test, which will be summarized by the arithmetic mean $\pm$ standard deviation (SD) for normally distributed data and by the median and interquartile range for non-normally distributed data, unless otherwise stated. Frequency tables presenting counts and percentages will be generated for categorical variables. Group comparisons will be performed using the Pearson χ^2 test or Fisher's exact test, as appropriate. Unless otherwise specified, percentages will be calculated using the number of non-missing observations as the denominator.

Time-to-event analyses will be performed using the Kaplan-Meier method to estimate the cumulative incidence of primary clinical and secondary clinical endpoints over time from the

time of index PCI. Patients will be censored at the time of last follow-up or study end, whichever occurs first. Cumulative incidence curves will be generated to visualize the probability of event occurrence over time, accounting for censoring.

There is no planned/pre-specified subgroup analysis. However, potential differences in terms of primary and secondary outcomes will be investigated after dichotomizing/stratifying the study population into sub-groups of interest including, but not limited to:

1. Diabetes status (Yes/No)
2. Hypertension status (Yes/No)
3. Bifurcation status (Yes/No)
4. Indication (ACS/CCS)
5. Sex (Female/Male).
6. Age (< 75 years/≥ 75 years).
7. Vascular access site (radial/femoral/other).

For comparisons between the subgroups of interest, Kaplan-Meier curves will be constructed for study-specific primary and co-primary clinical endpoints at predefined time points (e.g., 30 days, 1 year). Differences between groups will be assessed using the log-rank test, and hazard ratios (HRs) with 95% confidence intervals (CIs) will be estimated using Cox proportional hazards models.

All statistical analyses will be conducted using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

2.12 | Ethics and Dissemination

This study will be run according to the ethical principles of the Declaration of Helsinki (2013) [14]. Further the study will be run in compliance with ISO 14155 (CEN 2020; ISO 2020). Both investigators and Sponsor will conduct this study in accordance with any applicable local or regional laws and regulations. Investigators will neither conduct procedures specific to the study nor collect subject data without prior approval or favorable opinion of any IEC under whose jurisdiction the conduct of this study falls.

During study activity, the investigators and the Sponsor shall act in accordance with any further requirements imposed by an IEC or regulatory agency.

2.13 | Consent Process

Prior to participation in this study, and before collection of any study specific data, the patient must complete an informed consent process involving reading the study information leaflet and then signing and dating the consent form. The patient will be given the opportunity to discuss the study with the investigator, including any medical aspect of their disease or the study treatment. No patient will be enrolled without signing the informed consent. Any new significant information on the study algorithm or procedure that may be relevant to the subject's willingness to participate or to continue participation in the study will be provided to new and existing subjects throughout the clinical investigation. If new information that can significantly affect a subject's future health and medical care becomes available, this information shall be provided to the subjects affected. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

Any new information or protocol amendment that substantially alters the scientific validity of the study or affects the subjects' rights, safety, welfare, or their willingness to continue participation in the study, will result in the re-consenting of currently active patients on an updated and approved (as required by local law and regulation) ICF.

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Subject names will not be supplied to the Sponsor.

2.14 | Dissemination

The Institution and/or Investigator will publish relevant parts of the Study Information. It is the intention that the publication of the primary endpoints will be submitted to a peer-reviewed journal within 6 months of the outcome of all the primary measures being met (i.e., within 6 months of all patients having completed 1-year follow-up). If the study is terminated early, manuscript submission will occur within 90 days of study termination.

3 | Discussion

While several calcium modification algorithms proposing integration of lesion assessment with intravascular imaging for optimal calcium modification device selection have been published, none of these have been prospectively validated [15–18]. Limited uptake of intravascular imaging in interventional practice remains an issue, with substantial variability in practice patterns according to geographic region and interventional experience [19, 20].

The CYCLOPES study aims to evaluate the impact of systematic utilization of a calcium modification algorithm on procedural and clinical outcomes in patients undergoing complex PCI. We hope that this will provide user friendly principles to guide interventional cardiologists in their treatment of calcific coronary disease, whilst also assessing the feasibility and safety of an intravascular imaging guided approach.

Separately, the IVUS data collated from this study will provide a rich database of treated calcific lesions using the various tools in the contemporary armamentarium. This may ultimately provide an opportunity to evaluate the effectiveness of individual steps and devices for specific patterns of calcification. As this is a single arm, observational study, casual inferences will be limited. However, this study may act as a precursor to future randomized trials directly comparing different treatment approaches for plaque modification in coronary calcification.

Acknowledgments

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Ethics Statement

Informed consent will be obtained from participants and ethical approval from local institutions will be obtained prior to enrollment. The primary analysis will be submitted for publication after patients have completed 1-year follow-up.

Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: all authors had financial support from "Boston Scientific" in the form of a research grant to fund this clinical trial, C.H. has received honorariums from Boston Scientific, T.C. has received consultancy and honorariums from Boston Scientific, P.O.'K. has received honorariums from Boston Scientific, S.W. does consultancy for Boston Scienfitic, B.E.S. has received a research grant and honorariums from Boston scientific, R.A.B. has received research funding from Boston Scientific without impact on personal remuneration; no other relationships or activities that could appear to have influenced the submitted work.

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