



Barbato, E. et al. (2023) Management strategies for heavily calcified coronary stenoses: an EAPCI clinical consensus statement in collaboration with the EURO4C-PCR group. *European Heart Journal*, 44(41), pp. 4340-4356. (doi: [10.1093/eurheartj/ehad342](https://doi.org/10.1093/eurheartj/ehad342))

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<http://eprints.gla.ac.uk/299562/>

Deposited on 30 May 2023

Enlighten – Research publications by members of the University of Glasgow
<http://eprints.gla.ac.uk>

1 **Management strategies for heavily calcified coronary stenoses: an EAPCI**
2 **clinical consensus statement in collaboration with the EURO4C-PCR group**

3
4 Emanuele Barbato¹, Emanuele Gallinoro², Mohamed Abdel-Wahab³, Daniele Andreini⁴,
5 Didier Carrié⁵, Carlo Di Mario⁶, Dariusz Dudek⁷, Javier Escaned⁸, Jean Fajadet⁹, Giulio
6 Guagliumi¹⁰, Jonathan Hill¹¹, Margaret McEntegart¹², Kambis Mashayekhi¹³, Nikolasos
7 Mezilis¹⁴, Yoshinobu Onuma¹⁵, Krzysztof Reczuch¹⁶, Richard Shlofmitz¹⁷, Giulio
8 Stefanini¹⁸, Giuseppe Tarantini¹⁹, Gabor G. Toth²⁰, Beatriz Vaquerizo²¹, William Wijns²²,
9 Flavio Ribichini²³

- 10
11 1) Department of Clinical and Molecular Medicine, Sapienza University, Rome, Italy
12 2) IRCCS Galeazzi Sant’Ambrogio Hospital, Milan, Italy
13 3) Heart Center Leipzig at University of Leipzig, Leipzig, Germany
14 4) Centro Cardiologico Monzino, IRCCS, Milan, Italy & Department of Clinical Sciences and Community
15 Health, Cardiovascular Section, University of Milan, Milan, Italy
16 5) Service de Cardiologie B, CHU Rangueil, Université Paul Sabatier, Toulouse, France
17 6) Interventional Structural Cardiology Division, Department of Clinical & Experimental Medicine, Careggi
18 University Hospital, Florence, Italy
19 7) Institute of Cardiology, Jagiellonian University, Collegium Medicum, Krakow, Poland
20 8) Hospital Clínico San Carlos IDISCC, Complutense University of Madrid, Madrid, Spain
21 9) Clinique Pasteur, Toulouse, France
22 10) IRCCS Galeazzi Sant’Ambrogio Hospital, Milan, Italy
23 11) Department of Cardiology, Royal Brompton Hospital, London, United Kingdom
24 12) West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, UK & British
25 Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical
26 Sciences, University of Glasgow, Glasgow, UK.
27 13) Department of Internal Medicine and Cardiology, MediClin Heart Institute Lahr/Baden, Lahr & Division of
28 Cardiology and Angiology II, University Heart Center Freiburg - Bad Krozingen, Bad Krozingen, Germany
29 14) St. Luke’s Hospital, Cardiology Department, Thessaloniki, Greece
30 15) Department of Cardiology, Cardiovascular Center, Fujita Health University Hospital, Toyoake, Japan &
31 Department of Cardiology, National University of Ireland Galway
32 16) Institute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland
33 17) St Francis Hospital, Roslyn New York, US
34 18) Humanitas Clinical and Research Hospital IRCCS & Department of Biomedical Sciences, Humanitas
35 University, Milan.
36 19) Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Padua,
37 Italy
38 20) University Heart Center Graz, Medical University of Graz, Graz, Austria
39 21) Unidad de Cardiología Intervencionista, Hospital del Mar, Universidad Autónoma de Barcelona,
40 Barcelona, Spain
41 22) The Lambe Institute for Translational Medicine, the Smart Sensors Laboratory, Corrib Core Laboratory and
42 Curam, National University of Ireland Galway, Ireland
43 23) Cardiovascular Section of the Department of Medicine, University of Verona, Italy
44
45

1 *Corresponding author:*
2 Prof. Emanuele Barbato,
3 Department of Clinical and Molecular Medicine,
4 Sapienza University of Rome,
5 Email: emanuele.barbato@uniroma1.it
6

7 **Abstract**

8

9 Since the publication of the 2015 EAPCI consensus on rotational atherectomy, the number of
10 percutaneous coronary interventions (PCI) performed in patients with severely calcified coronary
11 artery disease has grown substantially. This has been prompted on one side by the clinical
12 demand for the continuous increase in life expectancy, the sustained expansion of the primary
13 PCI networks worldwide and the routine performance of revascularization procedures in elderly
14 patients; on the other side, the availability of new and dedicated technologies such as orbital
15 atherectomy and intravascular lithotripsy, as well as the optimization of the rotational
16 atherectomy system, have increased operators' confidence in attempting more challenging PCI.

17 This current EAPCI clinical consensus statement prepared in collaboration with the
18 EURO4C-PCR group describes the comprehensive management of patients with heavily
19 calcified coronary stenoses, starting with how to use non-invasive and invasive imaging to assess
20 calcium burden and inform procedural planning. Objective and practical guidance is provided on
21 the selection of the optimal interventional tool and technique based on the specific calcium
22 morphology and anatomic location. Finally, the specific clinical implications of treating these
23 patients are considered, including the prevention and management of complications, and the
24 importance of adequate training and education.

26 **Keywords**

27 Calcium; calcified lesions; intravascular imaging; plaque modification; atherectomy; lithotripsy;
28 cutting balloons.

30 **Counts:**

31 Word counts manuscript text: 6242

32 Tables: 3

33 Figures: 5

34

1 **1. Introduction**

2 Since the publication of the 2015 EAPCI consensus on rotational atherectomy¹, the number of
3 percutaneous coronary interventions (PCI) performed in patients with severely calcified coronary
4 artery disease (CAD) has grown substantially². This has been prompted on one side by the
5 clinical demand for the continuous increase in life expectancy and the routine performance of
6 revascularization procedures in elderly patients. Prevalence of coronary calcification in fact is
7 age and sex dependent being more common in men older than 70 years (>90% in men vs. 67% in
8 women) and influenced by the imaging modalities adopted. If only coronary angiography is
9 used, the prevalence of moderate to severe calcification according to studies with core-laboratory
10 angiographic assessment is between 20-30%³⁻⁵. Therefore, advocating the need for adjunctive
11 plaque modification techniques likely in 2-3 out of 10 contemporary patients undergoing
12 coronary angiography.

13 The availability of new and dedicated technologies such as orbital atherectomy (OA) and
14 intravascular lithotripsy (IVL), as well as the optimization of the rotational atherectomy (RA)
15 system, have increased operators' confidence in attempting more complex and calcified lesions,
16 tailoring at times the device selection based on the calcification pattern. Calcification, in fact, can
17 occur in both intimal and medial coronary layers. When occurring at the intima, calcification can
18 lead to significant luminal obstruction and downstream ischaemia, while localisation of
19 calcification in the media and peri-adventitia results primarily in reduced vascular compliance⁶.
20 The mechanism of arterial calcification is complex and entails the apoptosis of macrophages
21 within the lipid core, the de-differentiation of vascular smooth muscle cells to an osteoblast
22 phenotype, resulting in the development of surrounding sheets or nodules of calcium. Fractures
23 in these calcified sheets can cause them to break through the overlying tissue and form nodules⁷.
24 Pathology and in vivo optical coherence tomography (OCT) studies have reported calcified
25 nodules as the culprit lesion in 2-10% of acute coronary syndrome (ACS) patients⁸⁻¹⁰. Calcified
26 plaques are less compliant than lipid plaques¹¹, and this can be associated with several technical
27 challenges during PCI, including difficult device delivery, equipment damage or entrapment,
28 stent under-expansion and complications, such as coronary rupture.

29 This current EAPCI clinical consensus statement prepared in collaboration with the
30 EURO4C-PCR group describes the comprehensive management of patients with heavily
31 calcified coronary stenoses, starting with how to use non-invasive and invasive imaging to assess

1 calcium burden and inform procedural planning, to providing practical guidance on the
2 appropriate device selection and adoption in order to optimize procedural outcome (**Graphical**
3 **Abstract** and **Supplementary Table 1**).

4 5 **2. Non-invasive imaging assessment**

6 Coronary computed tomography angiography (CCTA) is validated as an accurate non-invasive
7 method to detect coronary stenosis^{12,13} (**Supplementary Figure 1**). CCTA is able to assess
8 calcium distribution and quantification, providing a roadmap of all the coronary arteries¹⁴. CCTA
9 provides similar information to intravascular imaging, but with lower spatial resolution and a
10 systematic overestimation of calcific plaque volume especially when located peri-adventitial
11 with limited impact on luminal obstruction¹⁵. Calcium thickness remains challenging due to the
12 presence of blooming artefact; preliminary studies have shown that photon-counting detector
13 computed tomography (CT) may reduce this artifact improving the diagnostic performance of
14 CCTA¹⁶. Additional limitations in CCTA are related to the presence of arrhythmias or to motion
15 artefacts.

16 Heavy calcification of plaques at CCTA was associated with lower stent expansion and
17 higher rates of adverse events after PCI¹⁷. While visualization of a high calcium burden can
18 predict the use of calcium modification techniques during PCI with 71% sensitivity and 97%
19 specificity¹⁸, further refinement of the procedural approach may require intravascular imaging.
20 Lesion-based score of calcium severity may overcome some of the limitations encountered with
21 the traditional calcium scoring assessment¹⁸. In particular, a per-lesion calcium score ≥ 453 is a
22 predictor of an un-dilatable lesion and the need for dedicated devices such as RA¹⁸. Despite the
23 potential benefits for calcium assessment and procedural planning, CCTA is still underused in
24 clinical practice.

25 26 **3. Invasive imaging assessment of calcified lesion**

27 28 **3.1 Angiography**

29 On invasive coronary angiography, moderate or severe calcified lesions are detected as
30 radiopaque densities in the coronary arterial wall, seen with or without cardiac motion, and
31 visible prior to contrast injection (**Figure 1**)^{4,19-21}. These angiographic criteria do not necessarily

1 imply an intra-luminal obstruction, but are included in the SYNTAX score I assessment of lesion
2 complexity²².

3 Angiographically identified severe coronary calcification is a predictor of adverse clinical
4 outcomes after revascularisation with either PCI or bypass surgery^{4,19,20}. This may in part be
5 explained by its association with a number of comorbidities (age, male sex, diabetes mellitus,
6 chronic kidney disease), larger plaque burden, increased technical complexity of PCI, post-
7 procedural stent fracture and stent under-expansion⁴. In addition, recent pathological studies
8 have shown that severely calcified lesions were associated with delayed healing (i.e. higher
9 prevalence of uncovered struts) after implantation of new generation drug-eluting stents²³.

10

11 **3.2 Intravascular ultrasound and optical coherence tomography**

12 The sensitivity of angiography to detect calcified plaque as well as the inter- and intra-observer
13 reproducibility is suboptimal^{24,25}. Intravascular imaging has a higher calcium detection rate than
14 angiography,^{26,27} and thus should be used more liberally to avoid underestimation of
15 calcification. Intravascular ultrasound (IVUS) and OCT are catheter-based imaging tools, which
16 provide complementary morphometric and quantitative assessment of calcified lesions (**Figure 2**
17 **and Table 1**) and facilitate the selection of the most appropriate techniques and devices during
18 PCI. The inability to cross a calcified lesion with an imaging catheter often indicates the need for
19 an upfront dedicated plaque modification technique.

20 On IVUS, calcified plaque is detected as an area with high-echogenicity, brighter than the
21 reference adventitia, with acoustic shadowing of deeper vessel structures. With thinner calcium,
22 IVUS detects a smooth surface with reverberations, whereas with thick calcium, IVUS detects an
23 irregular surface without reverberations.^{24,28} (**Figure 3**). Calcified plaque attenuates the
24 ultrasound signal and thus does not allow quantification of calcium thickness behind the leading
25 edge²⁴. IVUS can therefore quantify calcification by the size of the circumferential arc and by the
26 length of the calcified segment. IVUS can also determine whether calcium is nodular, superficial
27 or deep. In post-mortem validation studies, IVUS demonstrated a high sensitivity (89%) and
28 specificity (100%) for identification of dense calcified plaque or clusters of micro-calcifications,
29 with a lower accuracy for isolated micro-calcifications^{29,30}. IVUS detected calcification and
30 derived scoring system are known to predict stent under-expansion³¹.

1 OCT, infra-red light-based intravascular imaging, provides higher resolution than IVUS
2 and detects calcified plaque as a low-intensity area with clear delineation (**Figure 3**). Since the
3 tissue penetration of low-coherence light is less attenuated by calcium, the far side of the
4 calcified plaque is detectable, and thus the full extent of the calcium plaque can be visualized.
5 OCT can therefore quantify calcification by the size of the circumferential arc, thickness,
6 longitudinal length, depth, area and 3-dimensional volume. However, it should be noted that
7 when calcium becomes very thick the far side of the plaque cannot be detected. An OCT calcium
8 scoring system has been shown to predict stent under-expansion¹⁷ (**Figure 3**).

9 Evidence of calcium fracture following lesion preparation seen either by IVUS or OCT is
10 associated with improved stent expansion¹⁷. Following stent implantation, the result should be
11 optimised using IVUS or OCT guidance³².

14 **4. Interventional tools for coronary calcified lesion treatment**

16 **4.1 Vascular access and guiding catheters**

17 Considerations regarding vascular access include: 1) high bleeding risk profile of the patients
18 (often related to advanced age); 2) frequent calcification in larger arteries; and 3) need to use 7 or
19 8F guiding catheters (GC) in some cases (**Table 2**). Access-site complications can be reduced
20 with the use of 6F GC via radial access, compatible with OA, small size excimer laser, IVL, and
21 1.25 to 1.5 mm RA burrs (Note, although 1.75 mm RA burr is accommodated in 6F GC,
22 advancement can be extremely difficult especially when there is peripheral vascular tortuosity).
23 Slender sheaths permit the use of 7F GC through radial access if deemed necessary. Use of the
24 ulnar artery, which has generally a larger diameter and fewer loops could be an alternative
25 option³³ (e.g. doi: 10.1016/j.ijcard.2010.12.022). Selection of a GC that facilitates coaxial
26 alignment and maximizes support is important. GC support can be enhanced further by using
27 guide-extension catheters, particularly in tortuous coronary anatomy or when treating calcified
28 lesions in the mid or distal vessel.

29 Peripheral IVL has been used to facilitate large bore sheath/catheter delivery through the
30 ilio-femoral vessels for both coronary and aortic valve interventions, and insertion of
31 haemodynamic support devices.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

4.2 Balloon-Based Techniques

4.2.1 Cutting balloons and scoring balloons

Cutting balloons and scoring balloons are commonly used for the preparation of calcified lesions³⁴⁻³⁶. The cutting balloon (Wolverine™ Cutting Balloon™ - Boston Scientific) is a non-compliant balloon with 3 or 4 micro-blades longitudinally arranged on its surface. Scoring balloons are semi-compliant (AngioSculpt® - Philips; NSE Alpha™ – Braun) or non-compliant (ScoreFlex™ NC – Orbusneich) balloons with scoring elements on the surface. The presence of cutting/scoring elements on the balloon surface allows effective dilation with a lower inflation pressure³⁷. A recent randomised trial comparing super high-pressure (SHP) balloon versus scoring balloon for preparation of calcified coronary lesions revealed comparable stent expansion on intravascular imaging³⁸.

4.2.2 High- and super high-pressure balloons

High-pressure balloons (HPB) have a more uniform and limited expansion profile than semi-compliant balloons, avoiding the dog-boning effect with both under and over-expansion that can result in vessel perforation or dissection^{34,39}. A twin-layer non-compliant (NC) SHP balloon (OPN, SIS Medical AG) allows the use of inflation pressures up to 35 atm, that may be cautiously increased up to 40-50 atm in selected cases without eccentric calcification. The main limitation of HPB and SHP balloons is their stiffness, which can make crossing and recrossing difficult.

4.3 Atherectomy techniques

Atherectomy is an important technique for plaque modification to facilitate adequate stent expansion, but also importantly to allow crossing of tight calcific stenoses. The basic principle of these techniques is the ablation of calcific atherosclerotic plaque within the vessel lumen, while also creating fractures and fissures (**Table 3**). While intravascular imaging may help select the most appropriate technique, in some cases it will not be possible to cross the lesion with an imaging catheter before modification⁴⁰, and in some geographic locations the use of imaging and device choice may be limited.

1

2 **4.3.1 Rotational atherectomy**

3 RA, first described in 1987⁴¹ and utilised in more than 1 million patients¹, has survived all
4 subsequent developments due to its unique advantages in treating calcified coronary lesions. The
5 main component of RA is a rapidly rotating olive-shaped metallic burr coated with small
6 diamond crystals on its distal end (burr diameter ranges between 1.25 to 2.5 mm). Rotation is
7 achieved by converting highly pressurized air to rotational energy, and the system has recently
8 been upgraded (Rotapro, Boston Scientific) resulting in an improved ease of use⁴². RA is
9 performed on a dedicated 0.014" guidewire, commercially available in two different designs,
10 floppy (ROTAWIRE™ Drive Floppy) and extra support (ROTAWIRE™ Drive Extra Support).
11 Plaque debulking is achieved based on the physical principle of differential cutting, which
12 enables the burr to preferentially ablate inelastic tissue. Wire bias may influence the trajectory of
13 atherectomy but this can potentially be adjusted by using a floppy wire or bigger burrs. The
14 microparticles of plaque generated are less than 5 µm in diameter and can therefore pass through
15 the capillary bed into the systemic venous circulation and be engulfed by the reticulo-endothelial
16 system. Key procedural steps to avoid microcirculatory disturbances leading to no-or-slow flow
17 include pharmacological measures to avoid coronary spasms and hypotension, and technical
18 measures (e.g. short burr runs, appropriate rotational speed, avoidance of decelerations), the
19 details of which are beyond the scope of this document¹.

20 Data from the PREPARE-CALC and the ROTAXUS trials suggested that RA before
21 stent implantation is feasible and effective nearly in all patients with heavily calcified lesions.
22 Despite the fact that a RA strategy did not result in a better angiographic outcome compared to a
23 balloon-based strategy, RA is recognized as an enabling tool to facilitate balloon and stent
24 delivery and adequate stent expansion in calcified coronary lesions, particularly when a balloon-
25 based lesion preparation strategy has failed. In randomised clinical trials, up to 20% of calcified
26 coronary lesions required bailout RA to achieve procedural success^{43,44}. When optimal
27 atherectomy techniques are applied, complication rates are low and not significantly different
28 compared to balloon-based strategies^{43,44}. Importantly, RA is used to modify lesion morphology
29 by creating a polished channel that allows adequate balloon dilatation, calcium fracture, and
30 optimal stent expansion and is therefore utilised for limited (rather than aggressive) debulking
31 (burr/artery ratio <0.7). Despite a recommended rotation speed between 135,000 and 180,000

1 rpm¹, greater calcium debulking has been shown with speeds lower than 150.000 rpm in a small
2 OCT study⁴⁵.

3 Data on the relative efficacy of RA compared to OA or IVL are not yet available. Identifying RA
4 as the initial PCI strategy in a given patient, with the potential of reducing radiation, procedural
5 time, contrast dose and cost⁴⁶, can be facilitated by using the RotaScore, which integrates four
6 variables (degree of calcification, lesion length, tortuosity, and involvement of a bifurcation) for
7 upfront prediction of the need for RA^{47,48}.

8

9 **4.3.2 Orbital atherectomy**

10 OA (Cardiovascular Systems, Inc., St. Paul, MN) uses a differential sanding mechanism to
11 reduce the calcified plaque^{49,50}. A drive shaft eccentrically mounted-diamond-coated crown
12 modifies plaque and increases luminal size and compliance. OA is performed on a dedicated
13 0.014” guidewire (VIPERWIRE Advance®). In contrast to RA, OA uses a single crown with its
14 orbital diameter expanding radially via centrifugal force when a high rotational speed is selected;
15 this orbital rotation also reduces the limitations of wire bias. A key aspect of OA is that it works
16 bi-directionally, ablation plaque while being advanced and retracted. OA has been shown to
17 modify calcified plaque, changing its morphology and compliance, and ultimately facilitating
18 stent expansion⁵¹.

19 The OA device has two speed settings. Low speed (80.000 rpm) should be used for the
20 initial pass, with only some lesions requiring high speed (120.000 rpm). It is advised to avoid
21 high-speed in tortuosity, severe angulation, and vessels smaller than 3.0 mm, as it might be
22 associated with increased risk of vessel perforation⁵², limiting its use only to larger straight
23 vessel segments if insufficient ablation or compliance change have been achieved after two or
24 more runs at low speed.

25 Two prospective multicenter studies, ORBIT (Orbital Atherectomy System in Treating
26 De Novo, Severely Calcified Coronary Lesions) I and II, have compared PCI with or without OA
27 in patients with calcified stenoses^{50,53}. ORBIT II reported in 443 patients an in-hospital major
28 adverse cardiac event (MACE) rate of 10%, and 23% at 3-year follow-up⁵⁴. In addition, a real-
29 world retrospective registry on the use of OA has been published⁵⁵. The ongoing ECLIPSE trial
30 (Clinicaltrials.gov identifier NCT03108456) is the largest randomised trial to date studying

1 coronary atherectomy for severely calcified *de novo* lesions, assessing OA vessel preparation
2 compared to HPB angioplasty and/or cutting balloon.

4 **4.3.3 Excimer laser coronary atherectomy**

5 Excimer laser coronary angioplasty (ELCA) is based on the emission of monochromatic coherent
6 light in the ultraviolet range (wavelength 308 nm) able to ablate inorganic material and break
7 molecular bonds. While laser is thought to be more effective on thrombus and other soft or
8 fibrotic plaques, it can be useful in calcified lesions,⁵⁶ alone or in combination with or after
9 failed RA⁵⁷. Another specific application is within under-expanded stents, where laser can be
10 activated during slow contrast infusion (although data concerning its safety are still lacking and
11 the indication is off-label)⁵⁸.

13 **4.4 Intravascular Lithotripsy**

14 IVL has emerged as a novel therapy for the treatment of vascular calcification. The Shockwave
15 Medical (Santa Clara, CA) coronary IVL catheter consists of a 0.014 inch guidewire-compatible,
16 fluid-filled balloon angioplasty catheter with two spark gap-based lithotripsy emitters
17 incorporated into the shaft of the 12 mm long balloon⁵⁹. The coronary IVL system is delivered
18 on a rapid exchange catheter and is available in 2.5, 3.0, 3.5 and 4.0 mm diameters to allow 1:1
19 sizing to the reference vessel diameter. When the balloon is positioned at the target lesion and
20 inflated to 4 atm, 10 IVL pulses are delivered, followed by an optional brief balloon inflation to
21 6 atm. IVL treatment cycles are continued until full balloon expansion is achieved (up to 80
22 pulses per balloon or 120 with the latest generation Shockwave C²⁺ system) with interval
23 deflation to allow for distal perfusion. An IVL pulse is produced when lithotripsy emitters create
24 vapour bubbles within the integrated balloon resulting in the formation of acoustic shockwaves
25 with peak acoustic pressures of ~50 atm that propagate circumferentially and transmurally
26 through soft tissue with minimal effect while imparting compressive stress on calcified plaque as
27 the primary mechanism of calcium fracture⁵⁹ (**Supplementary Figure 2**).

28 Clinical outcomes of IVL for the treatment of severely calcified *de novo* coronary
29 stenoses have been reported across three prospective studies^{21,60,61}. Pooled results from the
30 Disrupt CAD studies were evaluated in a patient-level pooled analysis of 628 patients enrolled
31 across 72 sites from 12 countries⁶². The primary safety endpoint of the pooled analysis (30-day

1 MACE) was 7.3% and was driven primarily by the rate of in-hospital non-Q-wave myocardial
2 infarction (5.7%). The primary effectiveness endpoint of procedural success, defined as stent
3 delivery with angiographic core lab assessed residual in-stent stenosis $\leq 30\%$ without in-hospital
4 MACE, was achieved in 92.4% of the cases, with low rates of flow-limiting dissection (0.2%)
5 and perforation (0.2%) and no slow flow or no-reflow events at the end of the procedure⁶².

6 Acute outcomes following IVL treatment have been promising, and with 1-year outcomes
7 confirming safety and effectiveness, the simplicity of use is prompting widespread adoption⁶².
8 No randomised clinical trials comparing IVL with other calcium-modifying therapies have
9 currently been reported⁶³.

10 11 **5. Optimal management of calcified lesion**

12 13 **5.1 Management of calcified lesions based on pre-procedural CCTA**

14 When available, CCTA may facilitate pre-procedural planning of PCI by assessing the global
15 calcium burden, coronary anatomical complexity⁶⁴⁻⁶⁷, distribution of calcium at each coronary
16 segments, remaining lumen, morphology and dimension of the aortic root, and extension of
17 calcification at the left main or right coronary ostia. Fractional flow reserve CT (FFR_{CT}), in
18 addition, can provide a hemodynamic assessment of the severity of the lesions (**Supplementary**
19 **Figure 3**). Specifically, a detailed CT assessment of the aortic root and coronary anatomy can
20 guide the interventional cardiologist on the most suitable guiding catheter and best angiographic
21 view for lesion visualization and stent placement⁶⁸. Extensive calcification on CCTA (defined as
22 a cross section with calcium $>270^\circ$) could anticipate the need for adjunctive devices, and thus
23 facilitate logistical and case planning in busy interventional cardiology programs. Finally, CCTA
24 can be useful for PCI of coronary chronic total occlusions (CTOs) providing information on the
25 vessel course, tortuosity, length of occluded segment, quality of the distal landing zone, in
26 addition to extent and distribution of calcification⁶⁹.

27 28 **5.2 Optimal management based on angiography**

29 In centers with limited or no access to intravascular imaging, angiography is used to guide PCI
30 procedures (**Figure 4**). Angiography can be used for detection of calcium, a qualitative
31 assessment of severity, and balloon and stent expansion; the latter is further facilitated by

1 acquisition of computer assisted X-ray image enhancing metallic structure (e.g. stent boost)⁷⁰.
2 The adequacy of lesion preparation is evaluated by the visual expansion of a balloon
3 appropriately sized to the vessel. Eccentric calcification may not be detected in a single
4 angiographic view and can result in subsequent asymmetric stent expansion⁷¹; therefore,
5 angiographic evaluation of balloon expansion in multiple views during lesion preparation is
6 essential.

7 8 **5.3 Optimal management based on intravascular imaging**

9 Intravascular imaging can be used to guide each step of complex PCI (at baseline, after lesion
10 preparation, and post-stent implantation), informing decisions regarding the most appropriate
11 technique for calcium modification and confirming optimal stent expansion (**Figure 5**). IVUS
12 and OCT allow the assessment of calcium in both cross sectional and longitudinal views. When a
13 stenosis fulfils the criteria for high calcification burden with significant luminal narrowing, the
14 use of an adjunctive device (e.g. RA, OA, IVL) should be considered^{17,68}. When calcium is
15 deeper in the plaque or vessel wall, IVL may be preferred, whereas with superficial calcification,
16 atherectomy may be more effective (**Figure 5**). After plaque modification, intravascular imaging
17 can be repeated, with the detection of calcium fractures and/or sufficient lumen gain indicating
18 that a stent can be implanted (**Supplementary Figure 3B-D**). Post-stent intravascular imaging
19 can confirm that optimal stent expansion has been achieved according to the EAPCI consensus
20 guidelines⁷² (**Figure 5**). It should be noted that in OCT studies of severe calcified lesions, mean
21 final stent expansions of 68 to 84% were reported, highlighting the challenge of achieving these
22 optimal stent expansion goals in resistant lesions^{38,40,61,73}. If stent under-expansion occurs,
23 additional post dilatation with HPB or off-label use of IVL can be performed.

24
25 When dealing with a calcified lesion, stent choice is a crucial step to achieve successful
26 revascularization. The ideal stent, in this scenario, should have the following characteristics: 1)
27 high deliverability to be advanced through tortuous and calcified segments; 2) high radial force
28 to achieve an adequate expansion even in the presence of calcium; 3) flexibility to conform to the
29 vessel.

30
31

1 **Consensus statements:**

- 2 1) With high coronary stenosis calcium score (i.e. ≥ 453 or cross-section calcium $> 270^\circ$) on
3 CCTA (when available), PCI with advanced plaque modification techniques (e.g. IVL
4 and/or atherectomy devices) should be considered before stent implantation.
- 5 2) Coronary angiography underestimates the severity of coronary calcification. Response to
6 PCI in angiographically ambiguous or calcified stenoses might be unpredictable,
7 therefore direct stenting (especially in ACS patients) should be discouraged.
- 8 3) Target calcified lesions are best evaluated in multiple angiographic projections.
- 9 4) Failure to dilate the lesion with a semi or non-compliant balloon inflated at high pressure
10 (i.e. Dog-boning or asymmetric balloon expansion in at least two projections) should
11 prompt the use of intracoronary imaging and/or the adoption of advanced plaque
12 modification techniques (e.g. IVL and/or atherectomy devices) rather than the use of
13 more aggressive balloon dilatation.
- 14 5) Liberal use of angiographic enhancement systems (e.g. stent boost, etc.) is advised pre-
15 and post-stenting, to facilitate visualization of stent expansion.
- 16 6) Inability of intravascular imaging tools to cross a coronary stenosis suggests the need for
17 dedicated plaque modification tools and techniques.
- 18 7) The adjunctive use of advanced plaque modification techniques (e.g. IVL and/or
19 atherectomy devices) before stent implantation is advised when the calcified lesion fulfils
20 the IVUS or OCT criteria of high calcification burden (**Figure 5**) with lumen narrowing.
- 21 8) Transradial arterial access is advised in PCI of calcified coronary lesions to reduce
22 bleeding risk.
- 23 9) Cutting balloons are suitable for: a) proximal lesions; b) aorto-ostial lesions; c) straight
24 coronary segments; d) after RA, OA or IVL ⁷⁴.
- 25 10) Scoring balloons are suitable for: a) proximal and distal lesions; b) aorto-ostial lesions; c)
26 tortuous coronary segments; d) after RA, OA or IVL.
- 27 11) High and super high-pressure balloons are suitable for: a) crossable un-dilatable calcified
28 stenosis (excluding eccentric calcification pattern); b) under-expanded stent
- 29 12) RA is suitable for: a) undilatable and/or balloon uncrossable lesions; b) superficial or
30 nodular calcification (by intravascular imaging); c) very tight calcified stenosis; d) long

1 calcified lesions; e) selected calcified bifurcation lesions, if side-branch wire protection is
2 not mandatory.

3 13) OA is suitable for: a) undilatable lesions; b) superficial or nodular calcification (by
4 intravascular imaging).

5 14) IVL is suitable for: a) deep calcification and calcified nodules; b) large vessels; c) stent
6 under-expansion (currently off-label indication); d) bifurcation lesions, if side-branch
7 wiring protection is mandatory; e) aorto-ostial calcified stenosis.

8 15) ELCA is suitable for: a) microcatheter uncrossable fibro-calcific lesions; b) stent under-
9 expansion.

10 **6. Specific clinical and anatomical settings**

11 **6.1 Acute coronary syndromes/thrombotic lesions**

12
13 A recent OCT analysis found that 13% of patients with ACS have a calcified plaque as the
14 culprit lesion, with three sub-types described: superficial calcific sheets (67%), eruptive calcified
15 nodules (26%), and calcified protrusions (7%)⁷⁵. In addition, when the culprit lesion was a
16 calcified plaque, non-culprit lesions had a higher calcium burden and less vulnerability than in
17 patients presenting with a plaque rupture or erosion as the culprit lesion⁷⁶. A pooled analysis
18 from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) and
19 HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute
20 Myocardial Infarction) trials found that 32% of patients had angiographic moderate or severe
21 calcium, which was an independent predictor of stent thrombosis and ischemic target lesion
22 revascularization at 1 year⁴.

23
24 Therefore, in patients with ACS there should be no exception to proper lesion preparation
25 before stent implantation. More specifically in ACS patients direct stenting should be
26 discouraged to prevent stent under-sizing (a consequence of vessel hypoperfusion downstream to
27 the coronary occlusion or stenosis, along with vasoconstriction) and/or under-expansion (due to
28 unanticipated underlying calcification). In the case of an uncrossable or undilatable lesion, we
29 advise that the threshold for ad-hoc plaque modification techniques (including RA or OA) is
30 lowered even during primary PCI procedures ([https://www.pcronline.com/Cases-resources-
31 images/Cases/Euro4C/2021/How-manage-uncrossable-lesions-ACS?auth=true](https://www.pcronline.com/Cases-resources-images/Cases/Euro4C/2021/How-manage-uncrossable-lesions-ACS?auth=true)). Concerns

1 regarding possible risk of increased distal thrombotic embolization with ablative techniques are
2 largely offset by the achievement of an optimal acute stenting result and by the available
3 antithrombotic treatment strategies. This also avoids the need for a staged procedure and possible
4 subsequent rehospitalization. If an operator has limited experience with plaque modification
5 techniques, deferral of stenting is advised after achieving coronary TIMI-3 flow with balloon
6 angioplasty. Nevertheless, full training on plaque modification techniques is advised for the
7 interventional cardiologist participating in an emergency PCI program to enable optimal and
8 timely treatment of heavily calcified lesions also during the acute procedure.

10 **6.2 Chronic total occlusions**

11 Severe calcification is one of the main characteristics of increased complexity during CTO PCI.
12 This in turn contributes significantly to the lower success rates in calcified CTO lesions,
13 reflected by its inclusion in all the major CTO complexity scores^{77,78}. Based on histopathological
14 findings, calcium is predominantly located at the proximal cap⁷⁹. To overcome proximal cap
15 calcification, high penetration-force (>9 g) tapered-tip CTO wires have been developed to be
16 used with a single or double-lumen microcatheter to further increase the penetration force. In
17 cases of an impenetrable cap, alternative dissection algorithms, such as the "move-the-cap"
18 technique, are often effective, but may not be applicable for occlusions involving bifurcations or
19 with an ostial location^{80,81}. The occlusive segment can be crossed intra- or extra-plaque, as
20 defined in the CTO-ARC consensus⁸². In heavily calcified CTOs intentional "extra-plaque
21 tracking" with knuckle wire dissection is often necessary to overcome long calcified segments.
22 Special caution should be taken during plaque modification after "extra-plaque tracking" to
23 avoid severe and longitudinal perforation in large dissection planes. Balloon inflation pressures
24 over 14-16 atm and RA or OA are generally not advised after "extra-plaque tracking". There are
25 limited data on the use of IVL during CTO PCI⁸³, and for ECLA on impenetrable proximal caps
26 or microcatheter or balloon uncrossable lesions⁸⁴.

27 IVUS is an indispensable tool during CTO PCI to understand the position of the wire, the
28 composition and morphology of the occlusive plaque, and to identify calcified nodules that are at
29 high risk for perforation during intensive plaque modification.

6.3 Bifurcation lesions

The presence of calcification in coronary bifurcation lesions increases the complexity of these already challenging PCI procedures⁸⁵. Data from the COBIS II (COronary Bifurcation Stent) registry showed that severe calcification in bifurcation lesions was associated with a higher rate of target lesion failure (TLF) after PCI as compared to mild or no calcification^{86,87}. An OCT study revealed that the presence of calcium at a bifurcation segment of the main branch is an independent predictor of side branch stenosis after main branch stenting⁸⁸. The sub-analysis of the PREPARE-CALC (Comparison of Strategies to PREPARE Severely CALCified Coronary Lesions) trial reported that, when comparing RA to scoring/cutting balloon (SCB) in calcified bifurcation lesions, side branch compromise (i.e. any significant stenosis, dissection, or TIMI flow <3) was more frequently observed after lesion preparation with SCB⁸⁹. In addition, a multicenter retrospective registry of 1156 patients treated with OA for calcified lesions, reported that patients treated for bifurcation lesions had comparable outcomes to those treated for non-bifurcation lesions, demonstrating that atherectomy devices appear to be both safe and effective for calcium modification in bifurcation lesions⁹⁰.

However, further data concerning the optimal management of calcium in bifurcation lesions are lacking. Plaque modification is critically important in this lesion subset before stent implantation⁹⁰. Once adequate lesion preparation is achieved in the main vessel, plaque modification with atherectomy is only advised in the side branch if a 2-stent strategy is decided upfront and the vessel has moderate-to-severe calcification⁹¹. Of note, while the side-branch wires should be removed for RA or OA to avoid wire fracture or burr entrapment, protective wires can be maintained throughout the procedure when using IVL. For atherectomy, sequential rota- or viper-wiring of the branches can be performed if needed.

6.4 Calcified coronary lesions in patients with aortic stenosis

Degenerative aortic stenosis (AS) and CAD are the most prevalent cardiovascular diseases in developed countries, and they coexist in around 40% to 75% of the patients⁹². The pathophysiological basis behind both degenerative AS and calcified CAD is atherosclerosis. The association is so strong that calcification of the aortic valve has been proposed as a surrogate marker of CAD⁹². There are limited data regarding the indication for and timing of PCI in stable patients planned for transcatheter aortic valve implantation (TAVI),⁹³ particularly in patients

1 with complex calcified CAD. The feasibility, efficacy and safety of RA after TAVI has been
2 reported⁹⁴. When revascularization is indicated in patients with AS, anticipating the presence of
3 calcified lesions, optimal plaque modification techniques using dedicated devices should be
4 employed as in patients without AS.

6 **6.5 Role of mechanical circulatory support**

7 PCI in heavily calcified coronary arteries are technically challenging, due to the need for
8 meticulous vessel preparation and stent optimization that may lead to hemodynamic compromise
9 and/or life-threatening complications (e.g. sustained hypotension, malignant arrhythmias,
10 coronary rupture, no reflow), especially in patients with multiple comorbidities and severely
11 reduced left ventricular ejection fraction⁹⁵.

12 The potential benefit of mechanical circulatory support (used upfront or as bail-out) is
13 related to the maintenance of an adequate blood pressure, the unloading of the left ventricle, and
14 increased coronary perfusion pressure, in the presence of severe CAD.⁹⁶

15 However, definitive demonstration of benefit remains weak and hampered by an
16 increased rate of vascular complications; their use therefore should be carefully weighed within
17 the heart team discussion.

19 **7. Clinical implications**

21 **7.1 Pharmacologic treatment**

22 Since calcified coronary lesions may be involved in both acute and chronic coronary
23 syndromes⁴⁸, optimal pharmacological treatment should be given to patients according to their
24 clinical presentation and respective standard protocols.

25 The use of glycoprotein IIb/IIIa inhibitors, previously demonstrated in small studies to
26 reduce periprocedural cardiac enzymes elevation and slow-/no-reflow, should be limited to bail-
27 out situations of thrombotic complications⁹⁷. In PCI for chronic coronary syndrome, potent
28 P2Y₁₂ inhibitors failed to demonstrate in recent studies a benefit over clopidogrel in terms of
29 myocardial necrosis or clinical outcome^{98,99}. In the specific setting of RA for calcified lesions,
30 ticagrelor failed to demonstrate a reduction of peri-procedural necrosis over clopidogrel¹⁰⁰

1 (NCT02505399). Thus, data do not support systematic use of potent P2Y₁₂ inhibitors over
2 thienopyridines for calcified lesions PCI in chronic coronary syndrome.

3 4 **7.2 Prevention and management of procedural complications**

5 The presence of calcified lesions increases the complexity of PCI and, therefore, is associated
6 with an increased risk of procedural complications^{4,19,99}. These include vascular, coronary and
7 renal complications and are often related to the inherent complexity of the patient and lesion
8 setting. Implementing all possible measures to prevent these complications and to promptly
9 recognize and manage them is of paramount importance. An in-depth description of prevention
10 and treatment of periprocedural complication is beyond the scope of this document and can be
11 found elsewhere; the main recommendations are summarised in **Table 3**.

12 Coronary rupture or perforation may occur after atherectomy, high atmosphere balloon
13 inflation, and occasionally after IVL. Coronary rupture may require urgent pericardiocentesis if
14 associated with cardiac tamponade. Treatment can be surgical or percutaneous with covered stent
15 implantation. Small perforations may be treated with a prolonged balloon inflation with or
16 without covered stent implantation. In case of distal perforation, occlusion of the distal vessel
17 with coils, fat or microsphere are effective treatments. In all cases serial echocardiograms should
18 be performed to assess for hemopericardium or tamponade. The risk of perforation and coronary
19 rupture can be minimized by performing careful RA and OA techniques, and by avoiding
20 excessive HPB inflations.

21 Late pericardial tamponade can occur following temporary pacemaker implantation,
22 during RA/OA of a right coronary artery or dominant left circumflex artery. Following the use of
23 a temporary pacemaker, an echocardiogram is recommended 2 hours after the procedure. Some
24 operators have abandoned the systematic use of temporary pacemakers, by administering
25 intraprocedural atropine or using wire pacing.

26 The treatment of periprocedural myocardial infarction is described in dedicated
27 guidelines¹⁰¹; this complication can usually be mitigated by using appropriate periprocedural
28 antithrombotic treatment, careful RA technique and low speed OA to reduce distal embolization
29 of debris and plaque microparticles. Periprocedural myocardial infarction has also been
30 described with IVL in up to 6.8% of the cases, possibly related to the treatment of longer
31 calcified lesions⁵⁴.

1 Slow flow/no reflow phenomena can be related either to embolization of plaque material
2 to the distal coronary bed or due to microvascular dysfunction and or arteriolar spasm. After
3 excluding other causes of no reflow (i.e. thrombosis, air embolization, dissection, intramural
4 haematoma) various pharmacological treatment can be used such as adenosine, nitroprusside,
5 nicardipine, verapamil, injected through the guiding catheter or distally through a microcatheter.
6 Yet, the comparative effectiveness of these agents has never been tested. In order to avoid this
7 complication, it is recommended to: a) optimize systemic blood pressure allowing a sufficient
8 coronary perfusion pressure during the PCI; b) keep the activated clotting time value >250 s; c)
9 perform short runs of RA or OA; d) use vasodilator in the flushing saline solution.

10 IVL can be associated with mechanical ventricular captures often with transient drop in
11 systemic blood pressure. IVL-induced ventricular capture has been associated with episodes of
12 non-sustained tachyarrhythmias⁵⁹.

14 **8. Education and training**

15 To safely and effectively perform PCI in the setting of calcified coronary stenoses it is
16 paramount to: first, identify and quantify the calcium; and second, understand the application of
17 plaque modification tools and techniques. Accordingly, education should start with training in
18 intravascular imaging that can be done both intra-procedurally and offline to boost caseload.
19 Training should start with the theory on the state-of-the-art use of tools and techniques, but also
20 focus on algorithms for potential pitfalls, trouble-shooting and bail-out situations. This can be
21 best acquired through structured educational platforms, such as dedicated seminars or webinars.
22 Practical training with specific plaque modification devices can be acquired through simulation-
23 based learning and should include significant initial experience as second operator (at least 20 to
24 30 cases) followed by senior-assisted cases as first operator (at least 20 to 30 cases). Extensive
25 experience with one device (e.g. RA) can facilitate training with another (e.g. OA). Considering
26 that operator volume is an independent predictor of outcome in complex procedures¹⁰², sharing
27 experience by working with two operators might be a favourable approach, whenever logistically
28 possible.

1 **Consensus statements:**

- 2 1) In calcified CTOs crossed with “extra-plaque tracking”, balloon inflation pressures over
3 14-16 atm and rotational, orbital or laser atherectomy are not advised.
- 4 2) In bifurcation lesions, protective side-branch wiring should be avoided during rotational
5 or orbital atherectomy of the main branch.
- 6 3) PCI of calcified left main coronary lesions is best guided by intravascular imaging.
- 7 4) Advanced plaque modification techniques, if required, can be safely used in TAVI
8 patients undergoing PCI of calcified lesions.
- 9 5) Patients undergoing complex high-risk PCI of calcified coronary stenosis with severely
10 reduced left ventricular function or where an adequate blood pressure cannot be
11 maintained might benefit from mechanical circulatory support.
- 12 6) Procedural pharmacologic treatment of patients undergoing complex PCI of calcified
13 coronary stenosis should be guided by the clinical presentation.
- 14 7) Given the risk of severe complications in PCI of complex and calcified lesions, each
15 centre should establish dedicated protocols for the management of complications that
16 must include availability of dedicated materials and resources. In some cases, especially
17 elective complex procedures, these protocols should also include the possibility of
18 standby emergency cardiac surgery.
- 19 8) Interventional teams performing 24/7 emergency PCI in ACS should be proficient in
20 dealing with complex and calcified lesions using dedicated technologies, enabling ad-hoc
21 optimal revascularization also during off-hours. In case of limited experience with plaque
22 modification techniques, deferral of stenting after achieving coronary TIMI 3 flow with
23 plain balloon angioplasty is advisable.

24 **9. Limitations**

25 Although the treatment of heavily calcified lesions remains challenging, the broad
26 armamentarium of dedicated tools has improved the therapeutic approach to these patients over
27 the last years. Some limitations of the present document should be acknowledged. First, the
28 studies and the registries available in the literature have clearly shown the indispensable
29 adjunctive value of these dedicated tools to achieve a successful PCI. Nevertheless, none of these
30
31

1 studies was designed to detect differences in terms of hard endpoints on long-term follow-up
2 (**Supplementary Table 2**). Second, especially in the context of an elective PCI, before
3 embarking on a potentially complex and demanding procedure, a careful evaluation aimed at
4 balancing the risks, benefits and costs should always be performed. Third, the consensus points
5 provided are based on expert operator opinions, best practices, and the available evidence, but do
6 not represent clinical recommendations which can be provided by Scientific Societal guidelines.
7 ~~after the availability of more solid data derived from randomized clinical trials.~~

8 9 **10. Conclusion**

10 The availability of imaging tools to anticipate and refine the accurate assessment of calcified
11 lesions, along with a broader armamentarium of devices, currently enables the optimal
12 percutaneous treatment of even the most challenging calcified coronary anatomy. Yet, this
13 remains one of the most difficult PCI procedures, and therefore rigorous training is warranted in
14 order to master all possible techniques, develop a superior knowledge of the technologies, and
15 acquire advanced skills in anticipating and treating potential complications.

16 Of particular prognostic impact is the adequate management of severely calcified lesions in
17 patients presenting with ACS and needing emergency PCI around the clock, a situation that
18 imposes an urgent need for adequate training of the entire interventional team, including younger
19 operators, nurses and technicians.

20 21 **11. Acknowledgments**

22 The authors wish to thank Dr. Kai Ninomiya for his assistance in the preparation of the algorithm
23 and flow charts.

24 25 ~~12. Data Availability Statement~~

26 ~~The data supporting the findings of this manuscript were derived from the previously published~~
27 ~~manuscripts which have been listed in the references.~~

28

1 **Figure legends**

2

3 **Graphical Abstract:** Summary of the main points of the consensus document. In the central
4 section of the figures is represented the indication for each tool according to the type of calcified
5 lesion.

6 Abbreviations: CCTA: coronary computed tomography angiography; ICA: invasive coronary
7 angiography; IVUS: intravascular ultrasound; OCT: optical coherence tomography; NC: non-
8 compliant; C/S: cutting/scoring; PCI: percutaneous coronary intervention; SHP: super high
9 pressure; IVL: Intravascular Lithotripsy

10

11 **Figure 1.** Detection of coronary calcification on invasive coronary angiography. Coronary
12 calcification is documented as radiopaque densities in the coronary artery wall. Moderate
13 calcification is defined as radiopaque densities noted only during cardiac motion and involving
14 only one side of the vascular wall, which is typically visible only in a single projection. Severe
15 calcification is defined as radiopaque densities noted without cardiac motion prior to contrast
16 injection and involving both sides of the arterial wall. At variance, in the assessment of the
17 Syntax score, severe calcification is defined as multiple persisting opacifications of the coronary
18 wall visible in multiple projections, surrounding the complete lumen of the coronary artery at the
19 site of the lesion.

20

21 **Figure 2.** Paired cross-sectional images of coronary angiography, intravascular ultrasound
22 (IVUS) (A-E) and optical coherence tomography (OCT) (A'-E') in severely calcified coronary
23 artery. Both IVUS and OCT disclose significant calcification that is heavily overlooked at the
24 baseline coronary angiogram (Pre-PCI). Due to the limited penetration of ultrasound into the
25 calcium, calcium on IVUS is depicted as a high-echogenic edge with acoustic shadow behind it
26 (A-E). In contrast, on OCT (A'-E'), light can penetrate calcium to enable measurement of
27 thickness, area and volume. Panel A and A' present nodular with large lumen area; Pane B and B'
28 demonstrate nodular eccentric with a small lumen area, Panel C and C' are the images of focal
29 superficial calcification. Panel D and D' shows concentric and superficial calcification with large
30 lumen area; Panel E and E' represent eccentric thick calcium (> 0.5 mm). Lower part of the

1 figure shows post-PCI angiographic, IVUS and OCT findings suggesting an adequate stent
2 expansion and apposition despite significant calcification.

3
4 **Figure 3.** Scoring systems of calcified lesion on intravascular ultrasound (IVUS) and optical
5 coherence tomography (OCT).

6
7 **Figure 4** Optimal interventional management of calcified lesion based on coronary angiography
8 or coronary computed tomography angiography (CCTA).

9
10 **Figure 5.** Optimal interventional management of calcified lesions based on intravascular
11 imaging.

12 13 References

- 14
- 15 1. Barbato E, Carrié D, Dardas P, Fajadet J, Gaul G, Haude M, *et al.* European expert
16 consensus on rotational atherectomy. *EuroIntervention* 2015;**11**:30-36. doi: 10.4244/eijv11i1a6
- 17 2. Barbato E, Noc M, Baumbach A, Dudek D, Bunc M, Skolidis E, *et al.* Mapping
18 interventional cardiology in Europe: the European Association of Percutaneous Cardiovascular
19 Interventions (EAPCI) Atlas Project. *Eur Heart J* 2020;**41**:2579-2588. doi:
20 10.1093/eurheartj/ehaa475
- 21 3. Kirtane AJ, Doshi D, Leon MB, Lasala JM, Ohman EM, O'Neill WW, *et al.* Treatment
22 of Higher-Risk Patients With an Indication for Revascularization. *Circulation* 2016;**134**:422-
23 431. doi: doi:10.1161/CIRCULATIONAHA.116.022061
- 24 4. Généreux P, Madhavan MV, Mintz GS, Maehara A, Palmerini T, Lasalle L, *et al.*
25 Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes.
26 Pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization
27 and Stents in Acute Myocardial Infarction) and ACUTY (Acute Catheterization and Urgent
28 Intervention Triage Strategy) TRIALS. *J Am Coll Cardiol* 2014;**63**:1845-1854. doi:
29 10.1016/j.jacc.2014.01.034
- 30 5. Généreux P, Redfors B, Witzenbichler B, Arsenault MP, Weisz G, Stuckey TD, *et al.*
31 Two-year outcomes after percutaneous coronary intervention of calcified lesions with drug-
32 eluting stents. *Int J Cardiol* 2017;**231**:61-67. doi: 10.1016/j.ijcard.2016.12.150
- 33 6. Madhavan MV, Tarigopula M, Mintz GS, Maehara A, Stone GW, Généreux P. Coronary
34 Artery Calcification. *Journal of the American College of Cardiology* 2014;**63**:1703-1714. doi:
35 doi:10.1016/j.jacc.2014.01.017
- 36 7. Akers EJ, Nicholls SJ, Di Bartolo BA. Plaque Calcification: Do Lipoproteins Have a
37 Role? *Arterioscler Thromb Vasc Biol* 2019;**39**:1902-1910. doi: 10.1161/ATVBAHA.119.311574
- 38 8. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am*
39 *Coll Cardiol* 2006;**47**:C13-18. doi: 10.1016/j.jacc.2005.10.065

- 1 9. Lee T, Mintz GS, Matsumura M, Zhang W, Cao Y, Usui E, *et al.* Prevalence, Predictors,
2 and Clinical Presentation of a Calcified Nodule as Assessed by Optical Coherence Tomography.
3 *JACC Cardiovasc Imaging* 2017;**10**:883-891. doi: 10.1016/j.jcmg.2017.05.013
- 4 10. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, *et al.* In vivo diagnosis of plaque
5 erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical
6 coherence tomography. *J Am Coll Cardiol* 2013;**62**:1748-1758. doi: 10.1016/j.jacc.2013.05.071
- 7 11. Alfonso F, Macaya C, Goicolea J, Hernandez R, Segovia J, Zamorano J, *et al.*
8 Determinants of coronary compliance in patients with coronary artery disease: an intravascular
9 ultrasound study. *J Am Coll Cardiol* 1994;**23**:879-884. doi: 10.1016/0735-1097(94)90632-7
- 10 12. Knuuti J, Ballo H, Juarez-Orozco LE, Saraste A, Kolh P, Rutjes AWS, *et al.* The
11 performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in
12 patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J*
13 2018;**39**:3322-3330. doi: 10.1093/eurheartj/ehy267
- 14 13. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, *et al.* 2019
15 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*
16 2020;**41**:407-477. doi: 10.1093/eurheartj/ehz425
- 17 14. Collet C, Sonck J, Leipsic J, Monizzi G, Buytaert D, Kitslaar P, *et al.* Implementing
18 Coronary Computed Tomography Angiography in the Catheterization Laboratory. *JACC*
19 *Cardiovasc Imaging* 2021;**14**:1846-1855. doi: 10.1016/j.jcmg.2020.07.048
- 20 15. Monizzi G, Sonck J, Nagumo S, Buytaert D, Van Hoe L, Grancini L, *et al.* Quantification
21 of calcium burden by coronary CT angiography compared to optical coherence tomography. *Int J*
22 *Cardiovasc Imaging* 2020;**36**:2393-2402. doi: 10.1007/s10554-020-01839-z
- 23 16. Si-Mohamed SA, Boccalini S, Lacombe H, Diaw A, Varasteh M, Rodesch PA, *et al.*
24 Coronary CT Angiography with Photon-counting CT: First-In-Human Results. *Radiology*
25 2022;**303**:303-313. doi: 10.1148/radiol.211780
- 26 17. Fujino A, Mintz GS, Matsumura M, Lee T, Kim SY, Hoshino M, *et al.* A new optical
27 coherence tomography-based calcium scoring system to predict stent underexpansion.
28 *EuroIntervention* 2018;**13**:e2182-e2189. doi: 10.4244/EIJ-D-17-00962
- 29 18. Sekimoto T, Akutsu Y, Hamazaki Y, Sakai K, Kosaki R, Yokota H, *et al.* Regional
30 calcified plaque score evaluated by multidetector computed tomography for predicting the
31 addition of rotational atherectomy during percutaneous coronary intervention. *J Cardiovasc*
32 *Comput Tomogr* 2016;**10**:221-228. doi: 10.1016/j.jcct.2016.01.004
- 33 19. Bourantas CV, Zhang YJ, Garg S, Iqbal J, Valgimigli M, Windecker S, *et al.* Prognostic
34 implications of coronary calcification in patients with obstructive coronary artery disease treated
35 by percutaneous coronary intervention: a patient-level pooled analysis of 7 contemporary stent
36 trials. *Heart* 2014;**100**:1158-1164. doi: 10.1136/heartjnl-2013-305180
- 37 20. Onuma Y, Tanimoto S, Ruygrok P, Neuzner J, Piek JJ, Seth A, *et al.* Efficacy of
38 everolimus eluting stent implantation in patients with calcified coronary culprit lesions: two-year
39 angiographic and three-year clinical results from the SPIRIT II study. *Catheter Cardiovasc*
40 *Interv* 2010;**76**:634-642. doi: 10.1002/ccd.22541
- 41 21. Ali ZA, Nef H, Escaned J, Werner N, Banning AP, Hill JM, *et al.* Safety and
42 Effectiveness of Coronary Intravascular Lithotripsy for Treatment of Severely Calcified
43 Coronary Stenoses: The Disrupt CAD II Study. *Circ Cardiovasc Interv* 2019;**12**:e008434. doi:
44 10.1161/circinterventions.119.008434

- 1 22. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, *et al.*
2 Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009;**5**:50-56. doi:
3 10.4244/eijv5i1a9
- 4 23. Torii S, Jinnouchi H, Sakamoto A, Mori H, Park J, Amoa FC, *et al.* Vascular responses to
5 coronary calcification following implantation of newer-generation drug-eluting stents in humans:
6 impact on healing. *Eur Heart J* 2020;**41**:786-796. doi: 10.1093/eurheartj/ehz850
- 7 24. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Chuang YC, *et al.* Patterns of
8 calcification in coronary artery disease. A statistical analysis of intravascular ultrasound and
9 coronary angiography in 1155 lesions. *Circulation* 1995;**91**:1959-1965. doi:
10 10.1161/01.cir.91.7.1959
- 11 25. Nakazawa G, Finn AV, Vorpahl M, Ladich E, Kutys R, Balazs I, *et al.* Incidence and
12 predictors of drug-eluting stent fracture in human coronary artery a pathologic analysis. *J Am*
13 *Coll Cardiol* 2009;**54**:1924-1931. doi: 10.1016/j.jacc.2009.05.075
- 14 26. Wang X, Matsumura M, Mintz GS, Lee T, Zhang W, Cao Y, *et al.* In Vivo Calcium
15 Detection by Comparing Optical Coherence Tomography, Intravascular Ultrasound, and
16 Angiography. *JACC Cardiovasc Imaging* 2017;**10**:869-879. doi: 10.1016/j.jcmg.2017.05.014
- 17 27. Sharma SK, Vengrenyuk Y, Kini AS. IVUS, OCT, and Coronary Artery Calcification: Is
18 There a Bone of Contention? *JACC Cardiovasc Imaging* 2017;**10**:880-882. doi:
19 10.1016/j.jcmg.2017.06.008
- 20 28. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, *et al.* American
21 College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition,
22 Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the
23 American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am*
24 *Coll Cardiol* 2001;**37**:1478-1492. doi: 10.1016/s0735-1097(01)01175-5
- 25 29. Friedrich GJ, Moes NY, Muhlberger VA, Gabl C, Mikuz G, Hausmann D, *et al.*
26 Detection of intralumenal calcium by intracoronary ultrasound depends on the histologic pattern.
27 *Am Heart J* 1994;**128**:435-441. doi: 10.1016/0002-8703(94)90614-9
- 28 30. Kostamaa H, Donovan J, Kasaoka S, Tobis J, Fitzpatrick L. Calcified plaque cross-
29 sectional area in human arteries: correlation between intravascular ultrasound and undecalcified
30 histology. *Am Heart J* 1999;**137**:482-488. doi: 10.1016/s0002-8703(99)70496-5
- 31 31. Kobayashi Y, Okura H, Kume T, Yamada R, Kobayashi Y, Fukuhara K, *et al.* Impact of
32 target lesion coronary calcification on stent expansion. *Circ J* 2014;**78**:2209-2214. doi:
33 10.1253/circj.cj-14-0108
- 34 32. Raber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y, *et al.* Clinical use
35 of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert
36 consensus document of the European Association of Percutaneous Cardiovascular Interventions.
37 *Eur Heart J* 2018;**39**:3281-3300. doi: 10.1093/eurheartj/ehy285
- 38 33. Deftereos S, Giannopoulos G, Tousoulis D, Raisakis K, Kossyvakis C, Kaoukis A, *et al.*
39 Feasibility and safety of transulnar access for performing rotational atherectomy. *Int J Cardiol*
40 2011;**147**:285-286. doi: 10.1016/j.ijcard.2010.12.022
- 41 34. Redfors B, Maehara A, Witzenbichler B, Weisz G, Stuckey TD, Henry TD, *et al.*
42 Outcomes After Successful Percutaneous Coronary Intervention of Calcified Lesions Using
43 Rotational Atherectomy, Cutting-Balloon Angioplasty, or Balloon-Only Angioplasty Before
44 Drug-Eluting Stent Implantation. *J Invasive Cardiol* 2017;**29**:378-386. doi:

- 1 35. Fonseca A, Costa Jde R, Jr., Abizaid A, Feres F, Abizaid AS, Costa R, *et al.* Intravascular
2 ultrasound assessment of the novel AngioSculpt scoring balloon catheter for the treatment of
3 complex coronary lesions. *J Invasive Cardiol* 2008;**20**:21-27. doi:
- 4 36. Ashida K, Hayase T, Shinmura T. Efficacy of lacrosse NSE using the "leopard-crawl"
5 technique on severely calcified lesions. *J Invasive Cardiol* 2013;**25**:555-564. doi:
- 6 37. Song X, Adachi T, Kawase Y, Kimura T, Saito N. Efficacy of the Wolverine cutting
7 balloon on a circumferential calcified coronary lesion: Bench test using a three-dimensional
8 printer and computer simulation with the finite element method. *Cardiovasc Interv Ther*
9 2022;**37**:78-88. doi: 10.1007/s12928-020-00739-2
- 10 38. Rheude T, Rai H, Richardt G, Allali A, Abdel-Wahab M, Sulimov DS, *et al.* Super high-
11 pressure balloon versus scoring balloon to prepare severely calcified coronary lesions: the ISAR-
12 CALC randomised trial. *EuroIntervention* 2021;**17**:481-488. doi: 10.4244/EIJ-D-20-01000
- 13 39. Secco GG, Buettner A, Parisi R, Pistis G, Vercellino M, Audo A, *et al.* Clinical
14 Experience with Very High-Pressure Dilatation for Resistant Coronary Lesions. *Cardiovasc*
15 *Revasc Med* 2019;**20**:1083-1087. doi: 10.1016/j.carrev.2019.02.026
- 16 40. Hemetsberger R, Gori T, Toelg R, Byrne R, Allali A, El-Mawardy M, *et al.* Optical
17 Coherence Tomography Assessment in Patients Treated With Rotational Atherectomy Versus
18 Modified Balloons: PREPARE-CALC OCT. *Circ Cardiovasc Interv* 2021;**14**:e009819. doi:
19 10.1161/CIRCINTERVENTIONS.120.009819
- 20 41. Ritchie JL, Hansen DD, Intlekofer MJ, Hall M, Auth DC. Rotational approaches to
21 atherectomy and thrombectomy. *Z Kardiol* 1987;**76 Suppl 6**:59-65. doi:
- 22 42. Ayoub M, Tajti P, Ferenc M, Akin I, Behnes M, Neumann FJ, *et al.* Feasibility and
23 outcome of the Rotapro system in treating severely calcified coronary lesions: The Rotapro
24 study. *Cardiol J* 2021. doi: 10.5603/CJ.a2021.0128
- 25 43. Abdel-Wahab M, Richardt G, Joachim Büttner H, Toelg R, Geist V, Meinertz T, *et al.*
26 High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex
27 calcified coronary lesions: the randomized ROTAXUS (Rotational Atherectomy Prior to Taxus
28 Stent Treatment for Complex Native Coronary Artery Disease) trial. *JACC Cardiovasc Interv*
29 2013;**6**:10-19. doi: 10.1016/j.jcin.2012.07.017
- 30 44. Abdel-Wahab M, Toelg R, Byrne RA, Geist V, El-Mawardy M, Allali A, *et al.* High-
31 Speed Rotational Atherectomy Versus Modified Balloons Prior to Drug-Eluting Stent
32 Implantation in Severely Calcified Coronary Lesions. *Circ Cardiovasc Interv* 2018;**11**:e007415.
33 doi: 10.1161/CIRCINTERVENTIONS.118.007415
- 34 45. Mizutani K, Hara M, Nakao K, Yamaguchi T, Okai T, Nomoto Y, *et al.* Association
35 between debulking area of rotational atherectomy and platform revolution speed-Frequency
36 domain optical coherence tomography analysis. *Catheter Cardiovasc Interv* 2020;**95**:E1-e7. doi:
37 10.1002/ccd.28212
- 38 46. Allali A, Abdel-Wahab M, Sulimov DS, Jose J, Geist V, Kassner G, *et al.* Comparison of
39 Bailout and Planned Rotational Atherectomy for Heavily Calcified Coronary Lesions: A Single-
40 Center Experience. *J Interv Cardiol* 2017;**30**:124-133. doi: 10.1111/joic.12361
- 41 47. Fitzgerald S, Allali A, Toelg R, Sulimov DS, Geist V, Kastrati A, *et al.* Angiographic
42 predictors of unplanned rotational atherectomy in complex calcified coronary artery disease: a
43 pooled analysis from the randomised ROTAXUS and PREPARE-CALC trials. *EuroIntervention*
44 2021. doi: 10.4244/EIJ-D-21-00612

- 1 48. Bouisset F, Barbato E, Reczuch K, Dobrzycki S, Meyer-Gessner M, Bressollette E, *et al.*
2 Clinical outcomes of PCI with rotational atherectomy: the European multicentre Euro4C registry.
3 *EuroIntervention* 2020;**16**:e305-e312. doi: 10.4244/EIJ-D-19-01129
- 4 49. Chambers JW, Diage T. Evaluation of the Diamondback 360 Coronary Orbital
5 Atherectomy System for treating de novo, severely calcified lesions. *Expert Rev Med Devices*
6 2014;**11**:457-466. doi: 10.1586/17434440.2014.929493
- 7 50. Parikh K, Chandra P, Choksi N, Khanna P, Chambers J. Safety and feasibility of orbital
8 atherectomy for the treatment of calcified coronary lesions: the ORBIT I trial. *Catheter*
9 *Cardiovasc Interv* 2013;**81**:1134-1139. doi: 10.1002/ccd.24700
- 10 51. Kini AS, Vengrenyuk Y, Pena J, Motoyama S, Feig JE, Meelu OA, *et al.* Optical
11 coherence tomography assessment of the mechanistic effects of rotational and orbital
12 atherectomy in severely calcified coronary lesions. *Catheter Cardiovasc Interv* 2015;**86**:1024-
13 1032. doi: 10.1002/ccd.26000
- 14 52. Shlofmitz E, Jeremias A, Shlofmitz R, Ali ZA. Lesion Preparation with Orbital
15 Atherectomy. *Interv Cardiol* 2019;**14**:169-173. doi: 10.15420/icr.2019.20.R1
- 16 53. Chambers JW, Feldman RL, Himmelstein SI, Bhatheja R, Villa AE, Strickman NE, *et al.*
17 Pivotal trial to evaluate the safety and efficacy of the orbital atherectomy system in treating de
18 novo, severely calcified coronary lesions (ORBIT II). *JACC Cardiovasc Interv* 2014;**7**:510-518.
19 doi: 10.1016/j.jcin.2014.01.158
- 20 54. Lee M, Généreux P, Shlofmitz R, Phillipson D, Anose BM, Martinsen BJ, *et al.* Orbital
21 atherectomy for treating de novo, severely calcified coronary lesions: 3-year results of the pivotal
22 ORBIT II trial. *Cardiovasc Revasc Med* 2017;**18**:261-264. doi: 10.1016/j.carrev.2017.01.011
- 23 55. Lee MS, Shlofmitz E, Kong J, Srivastava PK, Al Yaseen S, Sosa FA, *et al.* Outcomes of
24 patients with severely calcified aorto-ostial coronary lesions who underwent orbital atherectomy.
25 *J Interv Cardiol* 2018;**31**:15-20. doi: 10.1111/joic.12432
- 26 56. Ambrosini V, Sorropago G, Laurenzano E, Golino L, Casafina A, Schiano V, *et al.* Early
27 outcome of high energy Laser (Excimer) facilitated coronary angioplasty ON hARD and
28 complex calcified and balloOn-resistant coronary lesions: LEONARDO Study. *Cardiovasc*
29 *Revasc Med* 2015;**16**:141-146. doi: 10.1016/j.carrev.2015.02.002
- 30 57. Protty MB, Gallagher S, Farooq V, Sharp ASP, Egred M, O'Kane P, *et al.* Combined use
31 of rotational and excimer LASER coronary atherectomy (RASER) during complex coronary
32 angioplasty-An analysis of cases (2006-2016) from the British Cardiovascular Intervention
33 Society database. *Catheter Cardiovasc Interv* 2021;**97**:E911-e918. doi: 10.1002/ccd.29377
- 34 58. Fernandez JP, Hobson AR, McKenzie D, Shah N, Sinha MK, Wells TA, *et al.* Beyond
35 the balloon: excimer coronary laser atherectomy used alone or in combination with rotational
36 atherectomy in the treatment of chronic total occlusions, non-crossable and non-expandible
37 coronary lesions. *EuroIntervention* 2013;**9**:243-250. doi: 10.4244/eijv9i2a40
- 38 59. Kereiakes DJ, Virmani R, Hokama JY, Illindala U, Mena-Hurtado C, Holden A, *et al.*
39 Principles of Intravascular Lithotripsy for Calcific Plaque Modification. *JACC Cardiovasc Interv*
40 2021;**14**:1275-1292. doi: 10.1016/j.jcin.2021.03.036
- 41 60. Brinton TJ, Ali ZA, Hill JM, Meredith IT, Maehara A, Illindala U, *et al.* Feasibility of
42 Shockwave Coronary Intravascular Lithotripsy for the Treatment of Calcified Coronary
43 Stenoses. *Circulation* 2019;**139**:834-836. doi: 10.1161/circulationaha.118.036531
- 44 61. Hill JM, Kereiakes DJ, Shlofmitz RA, Klein AJ, Riley RF, Price MJ, *et al.* Intravascular
45 Lithotripsy for Treatment of Severely Calcified Coronary Artery Disease. *J Am Coll Cardiol*
46 2020;**76**:2635-2646. doi: 10.1016/j.jacc.2020.09.603

- 1 62. Kereiakes DJ, Di Mario C, Riley RF, Fajadet J, Shlofmitz RA, Saito S, *et al.*
2 Intravascular Lithotripsy for Treatment of Calcified Coronary Lesions: Patient-Level Pooled
3 Analysis of the Disrupt CAD Studies. *JACC Cardiovasc Interv* 2021;**14**:1337-1348. doi:
4 10.1016/j.jcin.2021.04.015
- 5 63. Gallinoro E, Monizzi G, Sonck J, Candraeva A, Mileva N, Nagumo S, *et al.* Physiological
6 and angiographic outcomes of PCI in calcified lesions after rotational atherectomy or
7 intravascular lithotripsy. *Int J Cardiol* 2022;**352**:27-32. doi: 10.1016/j.ijcard.2022.01.066
- 8 64. Mushtaq S, De Araujo Goncalves P, Garcia-Garcia HM, Pontone G, Bartorelli AL,
9 Bertella E, *et al.* Long-term prognostic effect of coronary atherosclerotic burden: validation of
10 the computed tomography-Leaman score. *Circ Cardiovasc Imaging* 2015;**8**:e002332. doi:
11 10.1161/CIRCIMAGING.114.002332
- 12 65. Andreini D, Pontone G, Mushtaq S, Gransar H, Conte E, Bartorelli AL, *et al.* Long-term
13 prognostic impact of CT-Leaman score in patients with non-obstructive CAD: Results from the
14 Coronary CT Angiography Evaluation For Clinical Outcomes International Multicenter
15 (CONFIRM) study. *Int J Cardiol* 2017;**231**:18-25. doi: 10.1016/j.ijcard.2016.12.137
- 16 66. Collet C, Onuma Y, Andreini D, Sonck J, Pompilio G, Mushtaq S, *et al.* Coronary
17 computed tomography angiography for heart team decision-making in multivessel coronary
18 artery disease. *Eur Heart J* 2018;**39**:3689-3698. doi: 10.1093/eurheartj/ehy581
- 19 67. Papadopoulou SL, Girasis C, Dharampal A, Farooq V, Onuma Y, Rossi A, *et al.* CT-
20 SYNTAX score: a feasibility and reproducibility Study. *JACC Cardiovasc Imaging* 2013;**6**:413-
21 415. doi: 10.1016/j.jcmg.2012.09.013
- 22 68. Kocka V, Theriault-Lauzier P, Xiong TY, Ben-Shoshan J, Petr R, Labos M, *et al.*
23 Optimal Fluoroscopic Projections of Coronary Ostia and Bifurcations Defined by Computed
24 Tomographic Coronary Angiography. *JACC Cardiovasc Interv* 2020;**13**:2560-2570. doi:
25 10.1016/j.jcin.2020.06.042
- 26 69. Ding D, Yu W, Tazuin H, De Maria GL, Wu P, Yang F, *et al.* Optical flow ratio for
27 assessing stenting result and physiological significance of residual disease. *EuroIntervention*
28 2021;**17**:e989-e998. doi: 10.4244/EIJ-D-21-00185
- 29 70. Hong SJ, Kim BK, Cho I, Kim HY, Rha SW, Lee SH, *et al.* Effect of Coronary CTA on
30 Chronic Total Occlusion Percutaneous Coronary Intervention: A Randomized Trial. *JACC*
31 *Cardiovasc Imaging* 2021;**14**:1993-2004. doi: 10.1016/j.jcmg.2021.04.013
- 32 71. Mintz GS, Guagliumi G. Intravascular imaging in coronary artery disease. *Lancet*
33 2017;**390**:793-809. doi: 10.1016/S0140-6736(17)31957-8
- 34 72. Fujimura T, Matsumura M, Witzenbichler B, Metzger DC, Rinaldi MJ, Duffy PL, *et al.*
35 Stent Expansion Indexes to Predict Clinical Outcomes: An IVUS Substudy From ADAPT-DES.
36 *JACC Cardiovasc Interv* 2021;**14**:1639-1650. doi: 10.1016/j.jcin.2021.05.019
- 37 73. Saito S, Yamazaki S, Takahashi A, Namiki A, Kawasaki T, Otsuji S, *et al.* Intravascular
38 Lithotripsy for Vessel Preparation in Severely Calcified Coronary Arteries Prior to Stent
39 Placement- Primary Outcomes From the Japanese Disrupt CAD IV Study. *Circ J* 2021;**85**:826-
40 833. doi: 10.1253/circj.CJ-20-1174
- 41 74. Amemiya K, Yamamoto MH, Maehara A, Oyama Y, Igawa W, Ono M, *et al.* Effect of
42 cutting balloon after rotational atherectomy in severely calcified coronary artery lesions as
43 assessed by optical coherence tomography. *Catheter Cardiovasc Interv* 2019;**94**:936-944. doi:
44 10.1002/ccd.28278

- 1 75. Sugiyama T, Yamamoto E, Fracassi F, Lee H, Yonetsu T, Kakuta T, *et al.* Calcified
2 Plaques in Patients With Acute Coronary Syndromes. *JACC Cardiovasc Interv* 2019;**12**:531-540.
3 doi: 10.1016/j.jcin.2018.12.013
- 4 76. Kim HO, Kim CJ, Cho JM, Soeda T, Kurihara O, Russo M, *et al.* Characteristics of non-
5 culprit plaques in acute coronary syndrome patients with calcified plaque at the culprit lesion.
6 *Catheter Cardiovasc Interv* 2021;**97**:E298-E305. doi: 10.1002/ccd.29005
- 7 77. Morino Y, Abe M, Morimoto T, Kimura T, Hayashi Y, Muramatsu T, *et al.* Predicting
8 successful guidewire crossing through chronic total occlusion of native coronary lesions within
9 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and
10 time assessment tool. *JACC Cardiovasc Interv* 2011;**4**:213-221. doi: 10.1016/j.jcin.2010.09.024
- 11 78. Sziggyarto Z, Rampat R, Werner GS, Ho C, Reifart N, Lefevre T, *et al.* Derivation and
12 Validation of a Chronic Total Coronary Occlusion Intervention Procedural Success Score From
13 the 20,000-Patient EuroCTO Registry: The EuroCTO (CASTLE) Score. *JACC Cardiovasc*
14 *Interv* 2019;**12**:335-342. doi: 10.1016/j.jcin.2018.11.020
- 15 79. Sakakura K, Nakano M, Otsuka F, Yahagi K, Kutys R, Ladich E, *et al.* Comparison of
16 pathology of chronic total occlusion with and without coronary artery bypass graft. *Eur Heart J*
17 2014;**35**:1683-1693. doi: 10.1093/eurheartj/ehd422
- 18 80. Vo MN, Karpaliotis D, Brilakis ES. "Move the cap" technique for ambiguous or
19 impenetrable proximal cap of coronary total occlusion. *Catheter Cardiovasc Interv* 2016;**87**:742-
20 748. doi: 10.1002/ccd.26079
- 21 81. Roy J, Hill J, Spratt JC. The "side-BASE technique": Combined side branch anchor
22 balloon and balloon assisted sub-intimal entry to resolve ambiguous proximal cap chronic total
23 occlusions. *Catheter Cardiovasc Interv* 2018;**92**:E15-E19. doi: 10.1002/ccd.27422
- 24 82. Ybarra LF, Rinfret S, Brilakis ES, Karpaliotis D, Azzalini L, Grantham JA, *et al.*
25 Definitions and Clinical Trial Design Principles for Coronary Artery Chronic Total Occlusion
26 Therapies: CTO-ARC Consensus Recommendations. *Circulation* 2021;**143**:479-500. doi:
27 10.1161/CIRCULATIONAHA.120.046754
- 28 83. Oksnes A, Cosgrove C, Walsh S, Loland KH, Laffan J, Biswas S, *et al.* Intravascular
29 Lithotripsy for Calcium Modification in Chronic Total Occlusion Percutaneous Coronary
30 Intervention. *J Interv Cardiol* 2021;**2021**:9958035. doi: 10.1155/2021/9958035
- 31 84. Karacsonyi J, Karpaliotis D, Alaswad K, Jaffer FA, Yeh RW, Patel M, *et al.*
32 Prevalence, indications and management of balloon uncrossable chronic total occlusions:
33 Insights from a contemporary multicenter US registry. *Catheter Cardiovasc Interv* 2017;**90**:12-
34 20. doi: 10.1002/ccd.26780
- 35 85. Latib A, Colombo A. Bifurcation disease: what do we know, what should we do? *JACC*
36 *Cardiovasc Interv* 2008;**1**:218-226. doi: 10.1016/j.jcin.2007.12.008
- 37 86. Kim MC, Ahn Y, Sim DS, Hong YJ, Kim JH, Jeong MH, *et al.* Impact of calcified
38 bifurcation lesions in patients undergoing percutaneous coronary intervention using drug-eluting
39 stents: results from the COronary BIfurcation Stent (COBIS) II registry. *EuroIntervention*
40 2017;**13**:338-344. doi: 10.4244/EIJ-D-16-00264
- 41 87. Murphy JL, Patel N, Vengrenyuk Y, Okamoto N, Barman N, Sweeny J, *et al.*
42 Cardiovascular outcomes after percutaneous coronary intervention on bifurcation lesions with
43 moderate to severe coronary calcium: A single-center registry study. *Catheter Cardiovasc Interv*
44 2021;**98**:35-42. doi: 10.1002/ccd.29069
- 45 88. Fujino Y, Attizzani GF, Tahara S, Takagi K, Naganuma T, Wang W, *et al.* Impact of
46 main-branch calcified plaque on side-branch stenosis in bifurcation stenting: an optical

- 1 coherence tomography study. *Int J Cardiol* 2014;**176**:1056-1060. doi:
2 10.1016/j.ijcard.2014.07.143
- 3 89. Allali A, Abdel-Wahab M, Traboulsi H, Hemetsberger R, Mankerious N, Byrne R, *et al.*
4 Impact of Lesion Preparation Technique on Side Branch Compromise in Calcified Coronary
5 Bifurcations: A Subgroup Analysis of the PREPARE-CALC Trial. *J Interv Cardiol*
6 2020;**2020**:9740938. doi: 10.1155/2020/9740938
- 7 90. Sturm R, Armstrong EJ, Benhuri B, Okamoto N, Vengrenyuk Y, Shlofmitz E, *et al.*
8 Orbital Atherectomy for Treatment of Severely Calcified Coronary Artery Bifurcation Lesions:
9 A Multicenter Analysis. *Cardiovasc Revasc Med* 2021;**26**:34-38. doi:
10 10.1016/j.carrev.2020.10.023
- 11 91. Patel NJ, Okamoto N, Murphy J, Vengrenyuk Y, Sharma SK, Kini AS. Management of
12 calcified coronary artery bifurcation lesions. *Catheter Cardiovasc Interv* 2021;**97**:1407-1416.
13 doi: 10.1002/ccd.29148
- 14 92. Stefanini GG, Stortecky S, Wenaweser P, Windecker S. Coronary artery disease in
15 patients undergoing TAVI: why, what, when and how to treat. *EuroIntervention* 2014;**10 Suppl**
16 **U**:U69-75. doi: 10.4244/EIJV10SUA10
- 17 93. Faroux L, Guimaraes L, Wintzer-Wehekind J, Junquera L, Ferreira-Neto AN, Del Val D,
18 *et al.* Coronary Artery Disease and Transcatheter Aortic Valve Replacement: JACC State-of-the-
19 Art Review. *J Am Coll Cardiol* 2019;**74**:362-372. doi: 10.1016/j.jacc.2019.06.012
- 20 94. Lunardi M, Pighi M, Venturi G, Del Sole PA, Pesarini G, Mainardi A, *et al.* Short-and-
21 Long-Term Outcomes after Coronary Rotational Atherectomy in Patients Treated with Trans-
22 Catheter Aortic Valve Implantation. *J Clin Med* 2020;**10**. doi: 10.3390/jcm10010112
- 23 95. Myat A, Patel N, Tehrani S, Banning AP, Redwood SR, Bhatt DL. Percutaneous
24 circulatory assist devices for high-risk coronary intervention. *JACC Cardiovasc Interv*
25 2015;**8**:229-244. doi: 10.1016/j.jcin.2014.07.030
- 26 96. Chieffo A, Burzotta F, Pappalardo F, Briguori C, Garbo R, Masiero G, *et al.* Clinical
27 expert consensus document on the use of percutaneous left ventricular assist support devices
28 during complex high-risk indicated PCI: Italian Society of Interventional Cardiology Working
29 Group Endorsed by Spanish and Portuguese Interventional Cardiology Societies. *Int J Cardiol*
30 2019;**293**:84-90. doi: 10.1016/j.ijcard.2019.05.065
- 31 97. Kini A, Reich D, Marmur JD, Mitre CA, Sharma SK. Reduction in periprocedural
32 enzyme elevation by abciximab after rotational atherectomy of type B2 lesions: Results of the
33 Rota ReoPro randomized trial. *Am Heart J* 2001;**142**:965-969. doi: 10.1067/mhj.2001.119382
- 34 98. Mehilli J, Baquet M, Hochholzer W, Mayer K, Tesche C, Aradi D, *et al.* Randomized
35 Comparison of Intensified and Standard P2Y12-Receptor-Inhibition Before Elective
36 Percutaneous Coronary Intervention: The SASSICAIA Trial. *Circ Cardiovasc Interv*
37 2020;**13**:e008649. doi: 10.1161/CIRCINTERVENTIONS.119.008649
- 38 99. Silvain J, Lattuca B, Beygui F, Range G, Motovska Z, Dillinger JG, *et al.* Ticagrelor
39 versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised,
40 open-label, phase 3b trial. *Lancet* 2020;**396**:1737-1744. doi: 10.1016/S0140-6736(20)32236-4
- 41 100. Lhermusier T, Motreff P, Bataille V, Cayla G, Farah B, Roncalli J, *et al.* Ticagrelor in
42 Rotational Atherectomy to Reduce TROPonin Enhancement: The TIRATROP Study, A
43 Randomized Controlled Trial. *J Clin Med* 2023;**12**. doi: 10.3390/jcm12041445
- 44 101. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, *et al.* 2017
45 ESC Guidelines for the management of acute myocardial infarction in patients presenting with
46 ST-segment elevation: The Task Force for the management of acute myocardial infarction in

1 patients presenting with ST-segment elevation of the European Society of Cardiology (ESC).
 2 *Eur Heart J* 2018;**39**:119-177. doi: 10.1093/eurheartj/ehx393
 3 102. Kinnaird T, Gallagher S, Sharp A, Proddy M, Salim T, Ludman P, *et al.* Operator
 4 Volumes and In-Hospital Outcomes: An Analysis of 7,740 Rotational Atherectomy Procedures
 5 From the BCIS National Database. *JACC Cardiovasc Interv* 2021;**14**:1423-1430. doi:
 6 10.1016/j.jcin.2021.04.034
 7

8 **Table 1.** Comparison of clinically available coronary imaging tools

	Non-invasive imaging prior to catheterization laboratory			Intravascular imaging in catheterization laboratory	
	CCTA	CS	CAG	OCT	IVUS
Spatial resolution	0.2-0.5 mm	1.25 mm	0.5-0.6 mm	15-20 μ	50-200 μ
Contrast needed	Yes	No	Yes	Yes	No
Time of data acquisition	1-5 min	1 min	15 min*	< 5-10 s	2-4 min
Availability	+++	+++	+++	+	++
Additional cost	+	+	+	+++	+++
Tissue penetration (non-calcified)	+++	+++	+++	+	++
Global assessment of calcification	+++	+++	+	-	-
Calcium volume quantification	+	-	-	++	-
Calcium arc	++	-	-	+++	+++
Calcium thickness	+	-	-	+++	-
Longitudinal calcium length	+	-	-	+++	+++

9 CCTA: coronary computed tomography angiography; CS: calcium scoring; CAG: coronary
 10 angiography; OCT: optical coherence tomography; IVUS: intravascular ultrasound.

11 *Per procedure ⁹⁸
 12

13 **Table 2.** Challenges related to vascular access in patients with heavily calcific vessels
 14 undergoing percutaneous coronary intervention.

Challenge	Potential solutions
Frequent high bleeding risk patient profile	<ul style="list-style-type: none"> • Radial approach preferred • Ultrasound-guided arterial puncture • Reduce DAPT duration based on the bleeding risk according to guideline recommendations
Calcification in femoral arteries	<ul style="list-style-type: none"> • Review CT-angio whenever available • Ultrasound-guided arterial puncture
Need for 7 F	<ul style="list-style-type: none"> • 7 F slender sheaths for transradial access • Balloon tracking or Railway inner dilator if extreme radial/brachial tortuosity • Sheathless GC for transradial access

1 CT: computed tomography; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; GC:
2 guiding catheter.
3

4 **Table 3.** Complications potentially occurring during PCI of calcified lesions with related
5 management
6

	Prevention	Management
Coronary		
Rupture	<ul style="list-style-type: none"> • Proper contemporary RA or OA technique¹ • Avoid excessive high-pressure dilation with large balloons 	<ul style="list-style-type: none"> • Covered stent implantation • Immediate pericardial drainage in case of tamponade • Surgical stand-by
Perforation	<ul style="list-style-type: none"> • Proper contemporary RA or OA technique¹ • Avoid excessive high-pressure dilation with large balloons (especially in eccentric calcified lesions) 	<ul style="list-style-type: none"> • Prolonged balloon inflation • Covered stent implantation • Coils in case of distal vessel perforation
Late pericardial tamponade	<ul style="list-style-type: none"> • Limit the use of temporary pacemaker: e.g. by administering IV atropine boluses during the procedure, or use pacing on the wire technique. Prefer balloon-tipped temporary pacemakers 	<ul style="list-style-type: none"> • Consider clinical follow-up and/or transthoracic echocardiography 2 hours after the procedure • Pericardial drainage in case of tamponade
Peri-procedural myocardial infarction	<ul style="list-style-type: none"> • Proper contemporary RA or OA technique¹ • Prefer low speed OA • Procedural anti-thrombotic 	<ul style="list-style-type: none"> • According to guidelines⁹⁹

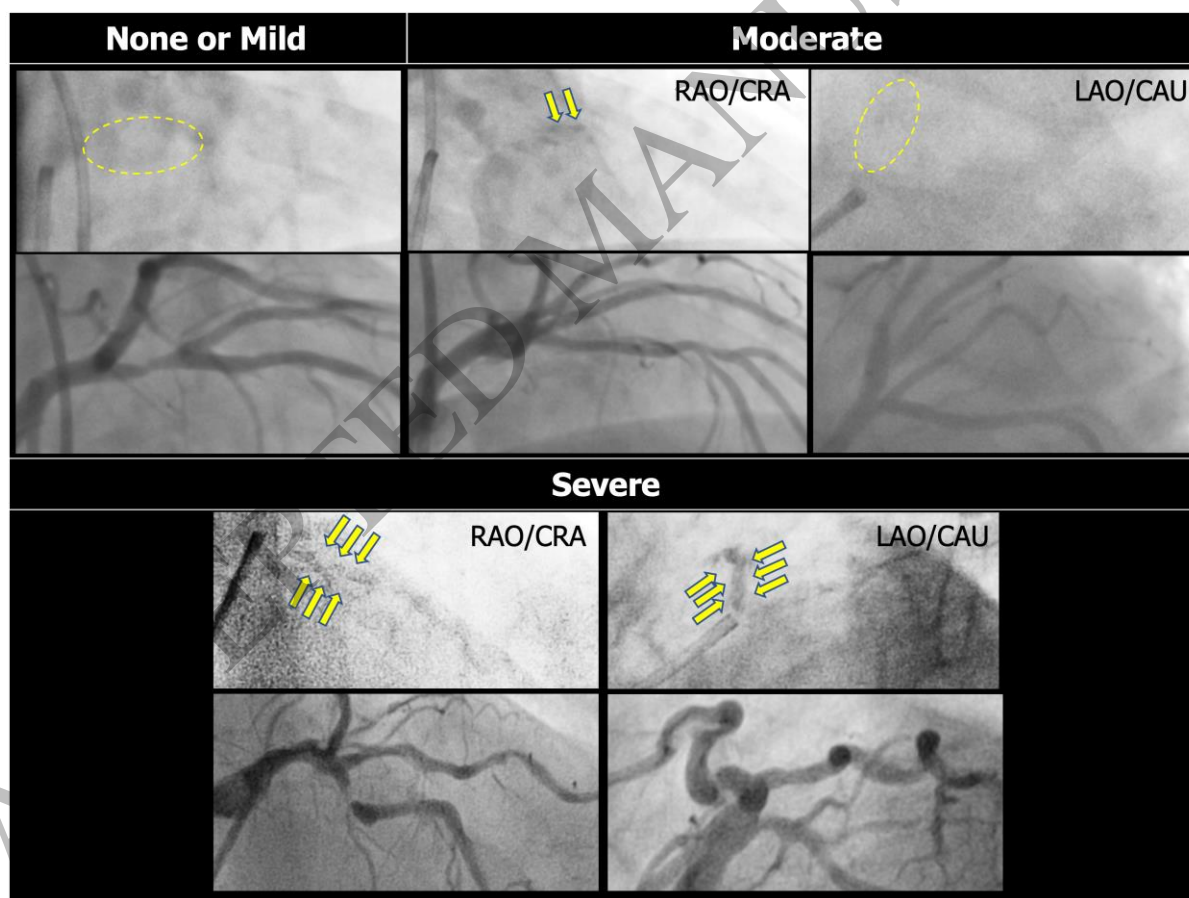
	therapy according to the coronary syndrome	
No/Slow Flow	<ul style="list-style-type: none"> • Prophylactic IC dilators +/- RA saline infusion plus heparin and nitrates • Short RA runs • Start with small burr size • Avoid high speeds • ACT > 250 s 	<ul style="list-style-type: none"> • Adenosine IC • Nitroprusside IC • Nicardipine IC • Verapamil
AV block	<ul style="list-style-type: none"> • More frequent in case of RA or OA of RCA and dominant LCX • Small burrs • Lower speed • Preventive placement of temporary pacemaker • IVL-induced ventricular captures might be associated with drop in systemic blood pressure and seldom with non-sustained tachyarrhythmias 	<ul style="list-style-type: none"> • Physical manoeuvres (i.e. coughing) if patient is stable • Atropine • Temporary pacemaker
Vascular and hemodynamic		
Major bleeding	<ul style="list-style-type: none"> • Favour radial access • Consider DUS-guided femoral puncture • Consider patient blood management before elective procedure (e.g. pre-PCI IV iron, etc.) in patients with iron deficiency chronic anemia 	<ul style="list-style-type: none"> • Consider patient blood management after the procedure (e.g. follow-up with hemoglobin check at discharge and 7-10 days after discharge, etc.) • In case of hematoma at the puncture site perform DUS
Renal		
Contrast-induced nephropathy	<ul style="list-style-type: none"> • Assess for the risk of contrast-induced nephropathy • Adequate hydration • Use of low-osmolar or iso-osmolar contrast media • In patients with moderate/severe CKD perform pre- and post-hydration with isotonic saline or, alternatively, tailored hydration regimens • Minimize the contrast media 	<ul style="list-style-type: none"> • Check GFR before discharge and 24-48 hours post-procedure in all patients; then repeat GFR control 7-10 days after discharge in selected patients • Liberal hydration • Consider hemodialysis or renal ultrafiltration in case of severe contrast-induced nephropathy

volume

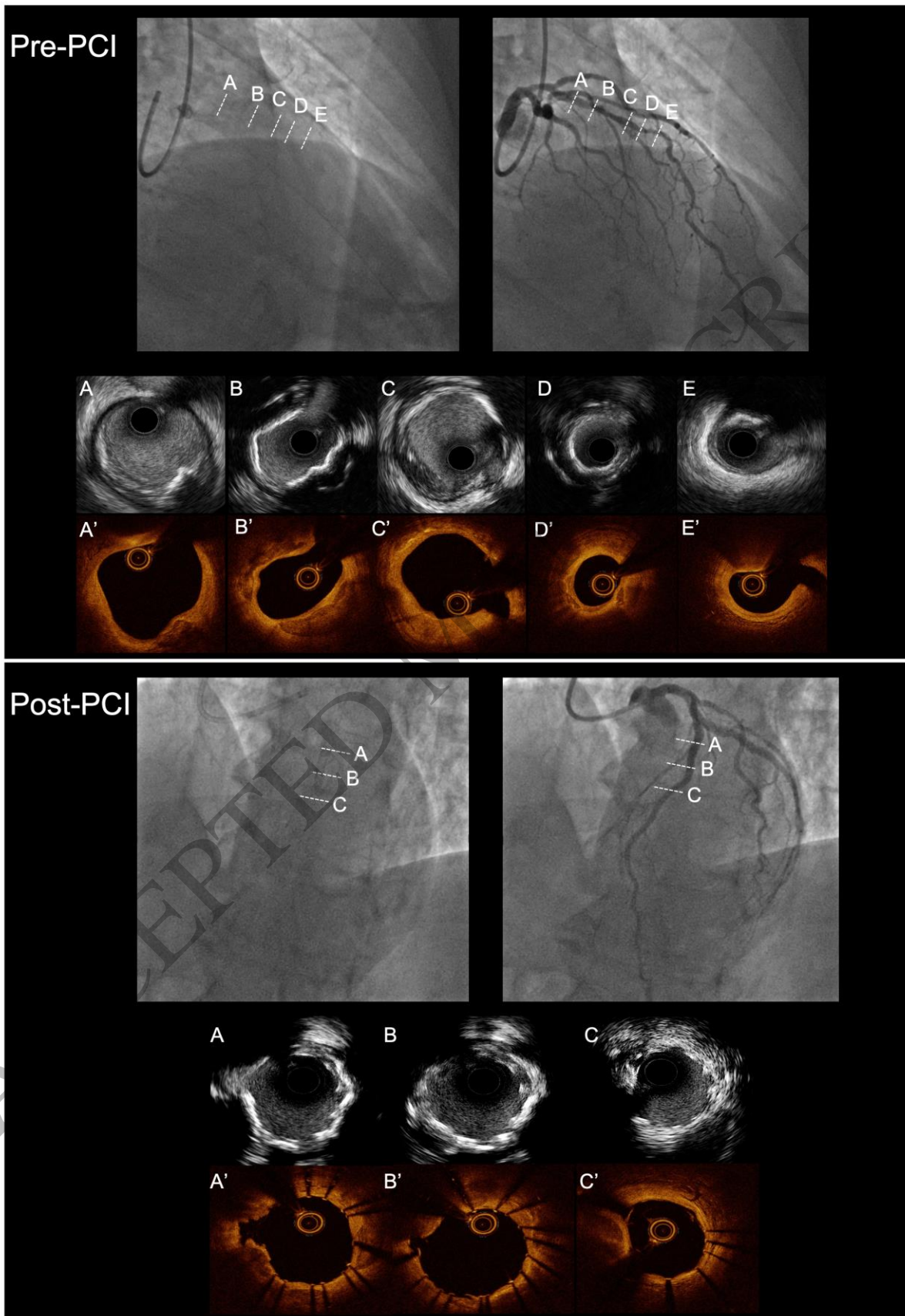
- Consider IVUS to reduce angiographic incidences with associated contrast volume
- Prefer IVUS to OCT as intravascular imaging to avoid additional contrast medium

1 RA: rotational atherectomy; IV: intravenous; IC: intracoronary; DUS: Doppler ultrasound; CKD:
 2 chronic kidney disease; GFR: glomerular filtration rate; OCT: optical coherence tomography;
 3 PCI: percutaneous coronary intervention; OA: orbital atherectomy; RCA: right coronary artery;
 4 LCX: left circumflex artery; ACT: activated clotting time; AV: atrio-ventricular; IVL:
 5 intravascular lithotripsy; IVUS: intravascular ultrasound.
 6

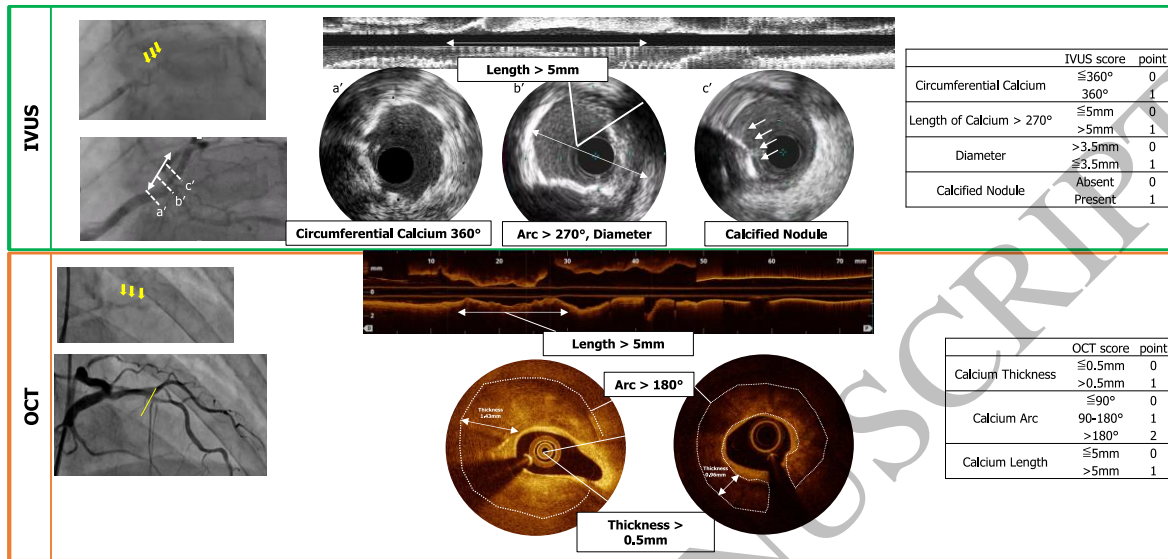
7 **Figure 1.**
 8



9
 10
 11
 12 **Figure 2.**



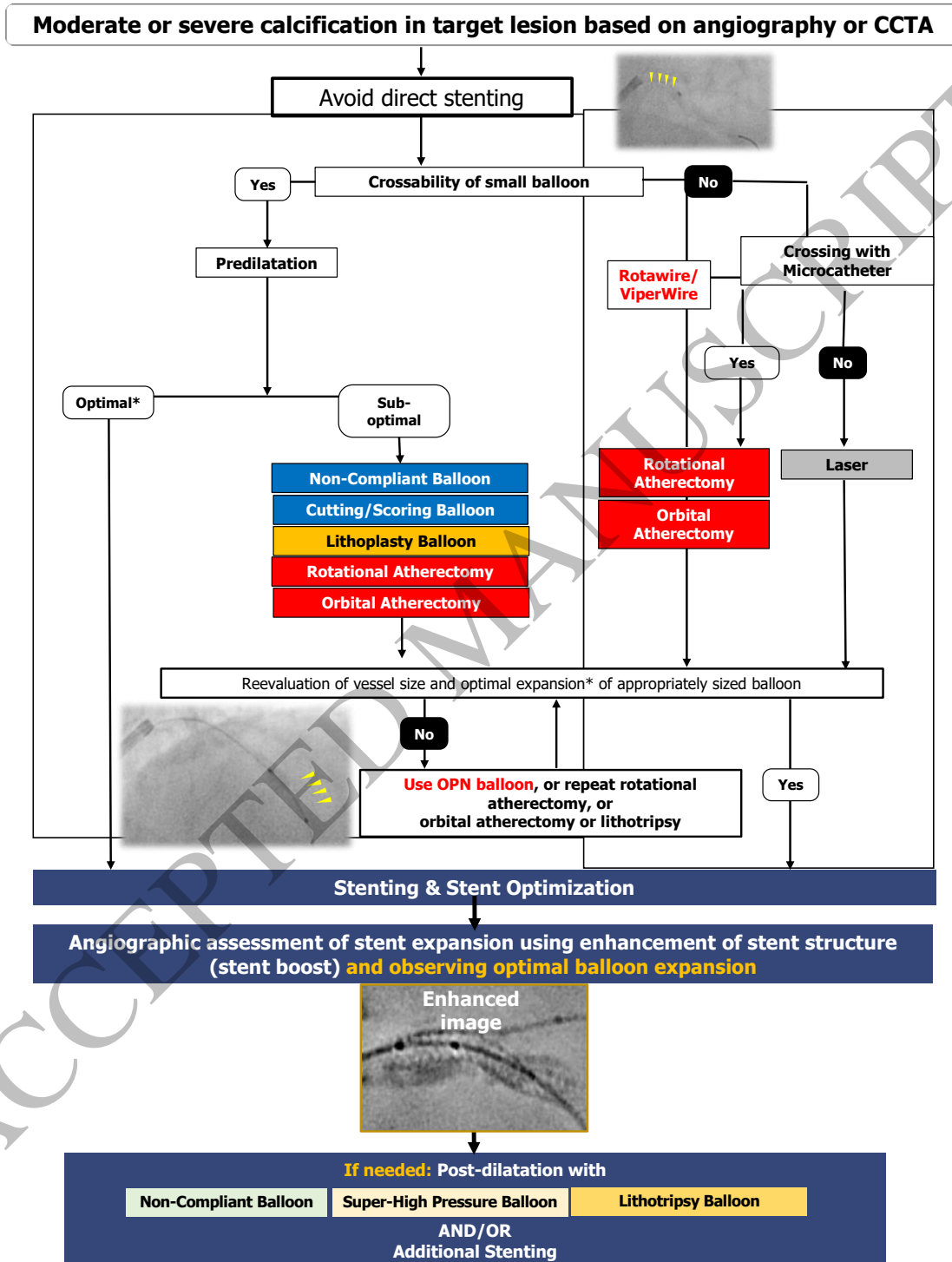
1 **Figure 3.**



2
3
4

ACCEPTED MANUSCRIPT

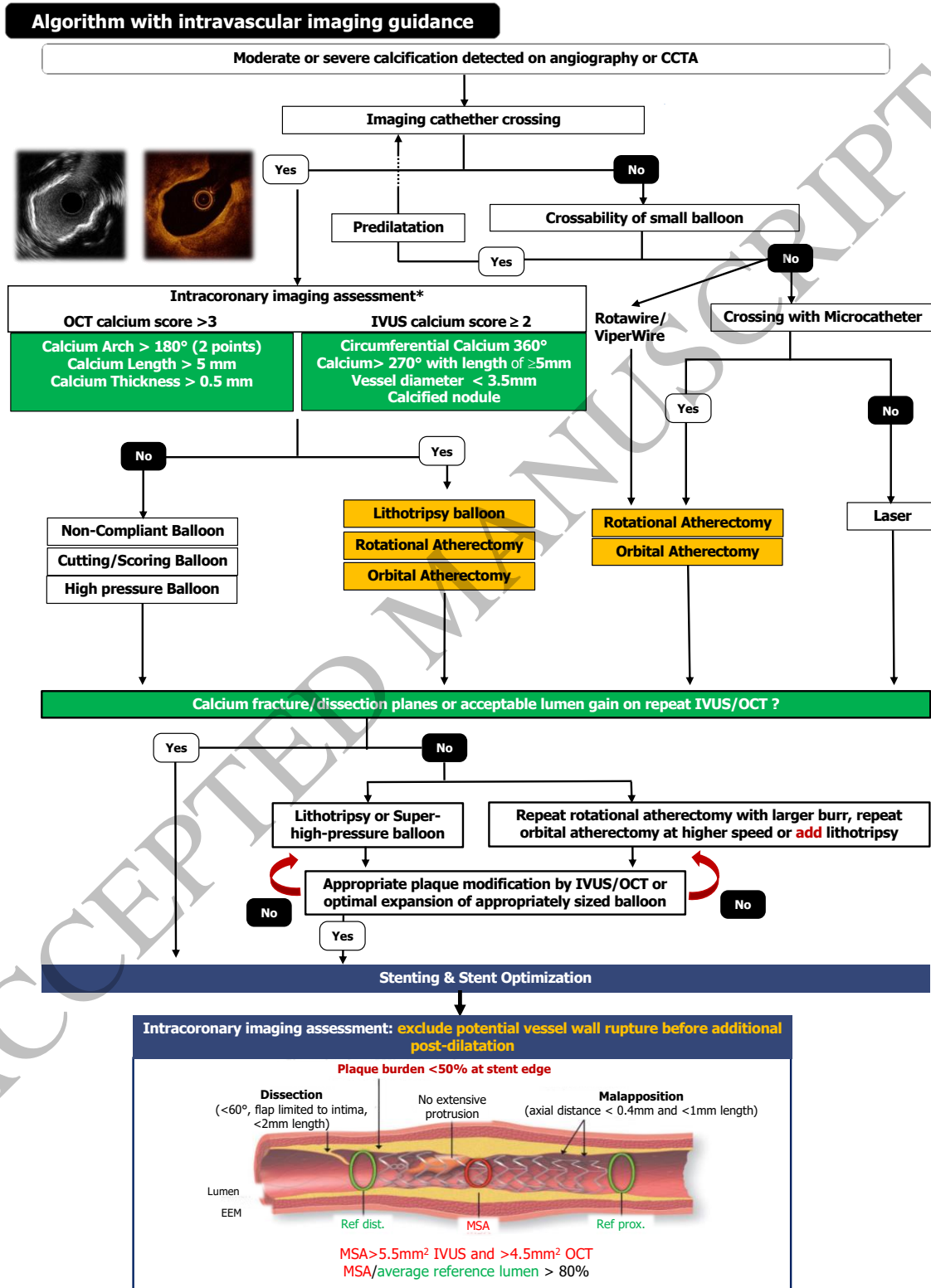
- 1 **Figure 4** Optimal interventional management of calcified lesion based on coronary angiography
- 2 or coronary computed tomography angiography (CCTA).



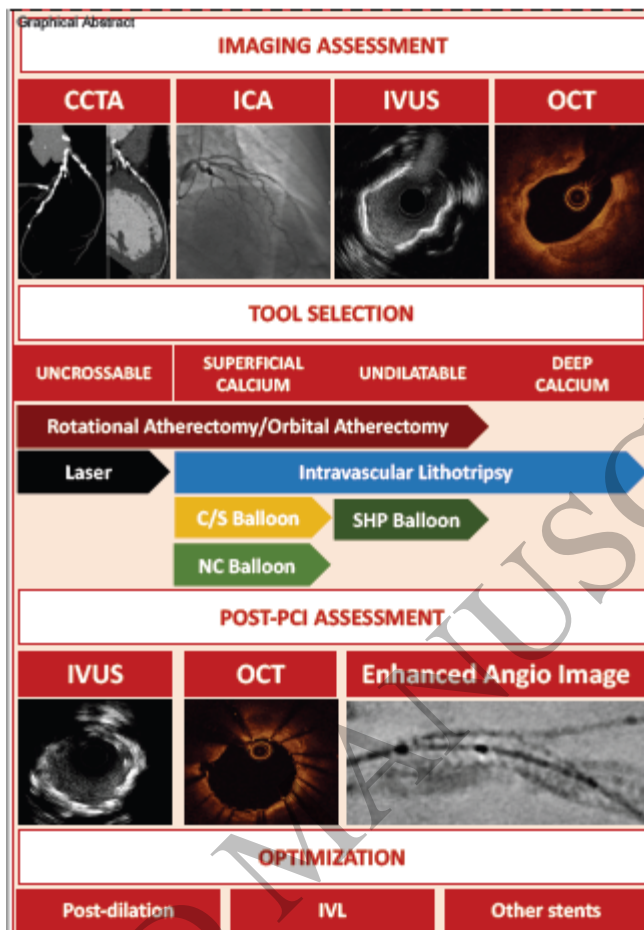
*Optimal expansion is defined as follows: i) during balloon inflation, homogeneous full balloon expansion is achieved throughout the entire balloon length, as assessed visually in two orthogonal views, and ii) on angiography after dilatation there is no luminal constriction observed at the site of visible calcification

3
4

1 **Figure 5.** Optimal interventional management of calcified lesions based on intravascular
 2 imaging.



3 * Automatic assessment of MLA might be used to guide size selection of plaque modification devices (e.g. size of burrs, cutting/scoring balloons, etc.)



Graphical Abstract
86x123 mm (x DPI)

1
2
3