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Review Article

Acute Coronary Syndrome Associated with Calcified Coronary Lesions-

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ABSTRACT

A large majority of acute coronary syndromes are triggered by plaque rupture, plaque erosion and a small number of cases resulting from a calcified nodule. The calcified nodule is defined as an eruptive accumulation of a nodular calcification within the coronary artery. Between 2% and 7% of life-threatening acute coronary thrombosis is provoked by calcified nodules. Coronary calcification cannot be assessed on coronary angiography alone and hence adjunctive intracoronary imaging devices are advocated to evaluate the severity and characterisation of the plaque morphology. Heavily calcified coronary lesions are incredibly difficult to dilate optimally by employing the conventional balloons and are usually associated with peri - procedural complications, stent under - expansion, delamination of drugs and polymers from stents, mal-apposition, and unfavourable clinical outcomes. Adequate calcium modification is pivotal to mandate better procedural success, and to enable optimal stent expansion and apposition, which subsequently may result in better long - term outcomes. We analyse the literature in a cohort of patients with calcified coronary lesions presenting with acute coronary syndrome along with the description of the various current calcium - modification techniques.

Key words: Acute coronary syndrome; ACS; Calcified coronary arteries; Coronary calcification; IVL; Intravascular lithotripsy; Calcium-modification techniques

INTRODUCTION

Acute Coronary Syndrome (ACS) refers to a clinical spectrum resulting from an atherosclerotic coronary artery disease that incorporates ST-Segment Elevation Myocardial Infarction (STEMI), non-ST Segment Elevation Myocardial Infarction (NSTEMI) and unstable angina.In STEMI, the ECG demonstrates persistent ST-segment elevation in two or more anatomically contiguous leads. Unstable angina and NSTEMI characterise a continuum of pathology, varying predominantly by the presence of elevated cardiac biomarkers in NSTEMI [1] (Figure 1). In the majority of the cases, the underlying mechanism is an obstruction of coronary artery blood flow by a thrombus that evolves on an erosion of an underlying atherosclerotic plaque. Other less common causes of ACS with unobstructed coronaries include Spontaneous Coronary Artery Dissection (SCAD), coronary artery spasm and coronary microvascular disease.

Post-mortem studies and in-vivo studies using intracoronary imaging suggests four different pathological pathways leading to ACS, which may coexist in some patients. These include plaque rupture associated with systematic inflammation, plaque rupture without systematic inflammation, plaque erosion and plaque without thrombus [2]. The published literature demonstrates that most acute coronary syndromes are triggered by either a plaque rupture (60%) or a plaque erosion (30%) and a small number of cases result from a calcified nodule [3,4]. A calcified nodule is defined as an eruptive accumulation of a nodular calcification within the coronary artery. Between 2% and 7% of life-threatening coronary thromboses are provoked by calcified nodules.[4,5] In pathological terms, calcified nodules are defined as lesions with acute thrombi demonstrating eruptive calcific nodules through disarrayed fibrous tissue with an associated underlying fibro-calcific plaque [4,5].

CALCIFIED NODULES

Calcified nodules manifest only in arteries that are significantly calcified. Calcified material disintegrates into several nodules that protrude into the lumen. Subsequent thrombus formation occurs over these calcified nodules and although the thrombus is usually

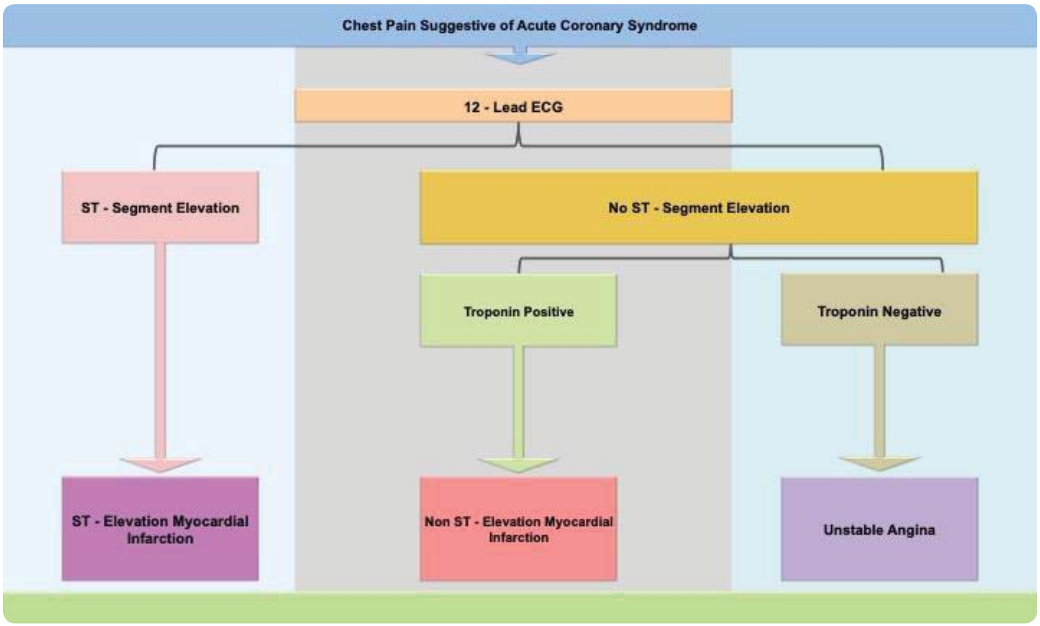

Figure 1: The Acute Coronary Syndrome algorithm.

non-occlusive. It can be difficult to identify these lesion on invasive coronary angiography but intracoronary imaging, e.g. Optical Coherence Tomography (OCT), has identified these in about 8% of the cases presenting with ACS [6].

Pathophysiology of coronary calcification

The death of the inflammatory and smooth muscle cells is considered to be the major factor in the genesis of calcification in the atheroma, while a role is also played by macrophage – driven matrix vesicles. The sub – endothelial cholesterol deposits ensue a significant inflammatory response leading to micro – calcification over areas extending between 0.5-15.0 mm [7]. The whole cascade is spurred by the merger of cell debris which results from the smooth muscle cells apoptosis, and this in turn caters as a core for the formation of calcium phosphate crystals [8]. In some cases, fibro - calcific plaques are exhibited by the presence of dense, calcific nodules that disrupt the luminal surface and protrude into the lumen [3]. Large plates of calcified matrix with adjacent areas of inflammation, fibrosis and neovascularization are often noted in significantly calcified vessels. These lesions are typically seen in elderly individuals with tortuous and significantly calcifiedcoronary arteries. The calcified nodule erodes into the vessel lumen, letting the calcium come in close contact with flowing blood, encouraging thrombus formation. In a minority of patients, plaque rupture might be associated with abrupt cholesterol crystallization within a rupture-prone plaque [9].

ACS and calcified coronary lesions

In patients with ACS, calcified lesions are incessantly seen in culprit vessels. Genereaus et al. [10] reported moderate calcification in 26.1% and severe calcification in 5.9% in this cohort. The authors reported that the presence of calcification in this group is a strong predictor of poor clinical outcomes, including stent thrombosis (ST) (HR 1.62 ; 95% CI [1.14 – 2.30]; p = 0.007) and target lesion revascularisation (TLR) (HR 1.44 ; 95% CI [1.17 – 1.78]; p <0.001) [10].

Genereaux et al. [10] in their pooled analysis from the HORIZONS – AMI (STEMI) and ACUITY (NSTEACS) trials, concluded that the culprit lesions in ACS often have significant calcification, as evaluated by the angiographic core laboratory. Performing coronary intervention in patients who had moderate or severely calcified target lesions was linked to suboptimal angiographic results and procedure - related complications, compared to those who had no or mild calcification. Furthermore, carrying out PCI on these calcified lesions was independently associated with definite stent thrombosis and repeat revascularisation within one year after intervention when compared to the patients who had no or minimally calcified target lesions.

In a study by [11]. Three different types of calcified plaques associated with culprit lesion were noted in patients presenting with ACS. They were categorised as: 1) eruptive calcified nodules; 2) superficial calcific sheet; and 3) calcified protrusion.

They documented the following findings: [11]

1) superficial calcific sheet is found to be the most prevalent type;
2) eruptive calcified nodules are invariably detected in the right coronary artery; on the other hand, superficial calcific sheet is often encountered in the left anterior descending artery;
3) the superficial calcific sheet cohort is found to have a poor initial TIMI flow and a very small vessel luminal diameter;
4) the eruptive calcified nodule cohort was noted to have the greatest burden of calcium;
5) red thrombus is found to be dominant in eruptive calcified nodules while white thrombus is often seen in superficial calcific sheet; and
6) myocardial damage following coronary intervention is predominantly seen in the superficial calcific sheet cohort.

Calcium score and prognosis

Coronary artery calcium score, which is calculated by CT, is an independent predictor of cardiac events in symptomatic as well as asymptomatic patients, as described in the Multi-Ethnic Study of Atherosclerosis (MESA) study by Budoff and his colleagues [12]. Furthermore, coronary artery calcification is considered to be a benchmark for advanced atherosclerosis and is coalesced with exceedingly complex coronary lesions which may include lengthy-lesion segments, chronic total occlusions (CTO) and complex bifurcation lesions.

Managing patients with coronary calcification

Statin and coronary calcification: High-dose statin therapy has been shown to be related to plaque regression by sequential intravascular ultrasound (IVUS) studies. [13-15] Puri and his colleagues [16]. evaluated serial changes in coronary calcification as well as coronary atheroma using intracoronary imaging in a cohort of patients who were treated with high –intensity statin therapy (atorvastatin 80 mg or rosuvastatin 40 mg), low – intensity statin therapy (atorvastatin, fluvastatin or simvastatin less than 40 mg, lovastatin or simvastatin less than 20 mg or pravastatin less than 80 mg) and no statin therapy [16]. They concluded that high – intensity statin therapy was associated with plaque regression from baseline (-0.6%), whereas both the other groups, low – intensity statin therapy and no-statin therapy, were linked to plaque progression (+0.8%, +1.0%), p <0.001 for all) [16].

Antiplatelet therapy in ACS: A key pathological feature of acute coronary syndrome is platelet activation, which results in thrombin generation, activation of the coagulation cascade and release of inflammatory mediators [17]. This dominance of platelet aggregation during intracoronary thrombus formation reflects the dramatic effects that antiplatelet therapies have on clinical outcomes. The benefit of dual antiplatelet therapy following an acute coronary syndrome was established by the CURE [18]. COMMIT/CCS-2 [19] and CLARITY-TIMI 28 [20] trials. Combined Aspirin and Clopidogrel therapy reduced the 1-year incidence of cardiovascular events by approximately 20% compared with aspirin alone. More potent and consistent P2Y12 receptor inhibition with either prasugrel or ticagrelor was superior to clopidogrel in the subsequent TRITON [21] and PLATO [22] trials. Such antiplatelet therapy confers greater antithrombotic efficacy but at the risk of increased bleeding.

Current guidelines recommend dual antiplatelet therapy for 1 year following ACS [23]. This was partly based on the risk of stent thrombosis with early generation drug eluting stents. However, there is now a move towards tailored antiplatelet therapy according to the clinical need and bleeding risk of the individual patient. With the introduction of new generation drug eluting stents, there

is emerging evidence for the safety of shortening dual antiplatelet therapy to as little as 1 month [24]. Therefore, selected patients with high cardiovascular risk or recurrent events may benefit from prolonged antiplatelet therapy beyond 1 year whereas those with lower cardiovascular risk and/or high bleeding risk may be treated with a shorter course of dual antiplatelet therapy

Intracoronary imaging: Coronary calcification cannot be properly assessed on coronary angiography alone and intravascular imaging, either an IVUS or OCT, is advocated in order to get an accurate assessment of the severity and characterisation of the plaque morphology [25]. Significant coronary artery calcification (CAC) increases the procedural complexity in patients undergoing percutaneous coronary intervention [10].

Heavily calcified coronary lesions may be difficult to dilate optimally by employing the conventional balloons and are often associated with peri-procedural complications, stent under-expansion, delamination of drugs and polymers from stents, mal-apposition, and unfavourable clinical outcomes [26]. Balloon failure is seen more often these days due to the aging population and growing intricacy of the cases. Severe coronary calcification, chronic total occlusions and undilatable lesions incessantly entail strategies other than conventional balloon angioplasty with the aim to achieve optimal stent apposition and better clinical outcomes. Satisfactory calcium modification is pivotal to mandate better procedural success, and to achieve optimal stent expansion and apposition, which subsequently may lower the risk of stent thrombosis [27].

Current calcium modification techniques: The use of conventional balloon dilatation results in disruption and dissection of the plaque, which, in majority of the cases, will ascertain optimal vessel preparation before stenting. However, in severely calcified lesions, high-pressure inflations on semi-compliant balloons may be unproductive and associated with higher risk of complications. On the other hand, conventional non-compliant balloon often represents the first step in treating heavily calcific coronary lesions. The significant concern is that high-pressure inflations may cause balloon rupture which could result in coronary perforation.

The current calcium modification techniques are divided into two groups which are determined by the type of device used: 1) techniques using balloon-based plaque rupture; 2) techniques without balloon or atherectomy techniques.

The procedures with devices based on techniques with balloon include Cutting Balloon (CB), super high - pressure Non-Compliant (NC) balloon and Intravascular Lithotripsy (IVL) [28,29]. Atherectomy techniques include Rotational Atherectomy (RA), Orbital Atherectomy (OA) and Excimer Laser Coronary Atherectomy (ELCA) [28,29].

CUTTING BALLOONS

Cutting Balloon (CB) dilatation device is an NC balloon catheter which is longitudinally equipped with three or four parallel sharp atherotomes (microsurgical blades). It causes fractures along the calcific plaques.

Indications

CB is indicated in treating in-stent restenosis, resistant fibrotic lesions, ostial lesions, bifurcation lesions and in mild to moderate calcified lesions with minimal tortuosity to favourably alter vessel compliance.With CB, the increase in the vessel lumen diameter is achieved in a more controlled fashion and with a lower balloon inflation pressure compared to conventional angioplasty balloons, which in turn could reduce the extent of vessel wall injury and the incidence of in-stent rest enosis. The use of CB is recommended on lesions with mild to moderate CAC with a relatively short (< 20 mm) lesion length.

Risks and complications

CB has a higher crossing profile, which ranges from 0.041 to 0.046". The most dreaded complications are blade entrapment and coronary perforation, which are seen more often compared to conventional balloon angioplasty alone [30].

The Global randomised trial [31], compared the use of CB with conventional balloon angioplasty. The authors demonstrated that the controlled dilatation with CB did not lower the rate of restenosis when paralleled with the conventional angioplasty (31.4% vs 30.4%; $p = 0.03$). In terms of complications, CB group were noted to have five coronary perforations (0.8% *vs* 0%; $p = 0.03$).

OPN NC - SUPER HIGH - PRESSURE BALLOON

The OPN NC super high-pressure angioplasty balloon is a double-layered balloon permitting very high pressure dilation >30 atmospheres (atm). It is a rapid exchange balloon catheter which is compatible with 0.014" coronary wires and 5 French (Fr) guiding catheters.The recent reports shows that OPN can be inflated safely up to 50 atmbut this would require two indeflators [32].

Indications

This is a dedicated device for the treatment of in-stent restenosis, heavily calcified coronary lesions and other resistant or undilatable lesions.

Risks and complications

The major limitation of OPN is its high crossing profile (0.028" for the 2.0 mm balloon size) due to its greater rigidity and double – layer technology which may cause problems in crossing heavily calcified lesions [33] and it is difficult to recross or reuse after inflation.

The published literature exhibits data limited to the case reports and observational studies but demonstrates acceptable device efficacy and safety [25].

ROTATIONAL ATHERECTOMY

The Rotational Atherectomy (RA) device consists of an elliptical diamond crystal-coated olive-shaped burr rotating at high speed and performing differential cutting as it moves forward. RA has been in use for over 30 years and was initially developed to aid atherosclerotic plaque debulking but has subsequently vanished in view of significant procedure-related complications and restenosis [34].

After the introduction of drug-eluting stents, interventionists started using RA again not for plaque debulking but for lesion preparation to facilitate balloon expansion and optimal stent apposition in cases of severe coronary calcification.

The European Expert consensus document describes the contemporary RA technique and endorses the usage of smaller burrs (burr-to-artery ratio <0.7) at lower rotational speed (135,000 to 180,000 rpm) and with shorter burr runtimes (10s-20s) than in the traditional debulking technique [35].

By using this technique, RA can be conveniently implemented without disarraying the standard PCI settings. The procedure can be performed either via femoral or radial approach, without up-sizing the guiding catheter size in majority of the cases and temporary pacing is required very infrequently.

Indications

The primary indication for RA is for the treatment of heavily calcified coronary lesions that are non-dilatable through conventional methods by modifying the plaque, which facilitates the proper stent expansion and apposition.

Risks and complications

Severe vessel dissection abutting acute closure, slow or no re-flow, periprocedural myocardial infarction, complex dissection, athero embolism and transient profound hypotension are the most frequently encountered risks associated with RA. Vessel perforation and entrapment of rotablator burr are less frequently noted complications.

In the ROTAXUS trial, 240 patients with significant coronary calcification were randomised to RA followed by stenting or stenting alone. The authors reported more significant procedural success rate in the RA cohort (92.5% *vs* 83.3%; $p = 0.03$) and better acute luminal gain. However, the authors also reported a higher incidence ofluminal loss at nine months but with no impact on restenosis [36].

A recent, PREPARE CALC trial randomised 200 patients with significant coronary calcification either to RA or scoring/cutting balloon. The authors reported an excellent procedural success rate in RA group (98% *vs* 81%; $p = 0.0001$) and this was not linked to a significant luminal loss at ninemonths. The complication rate was comparable between the two groups [37].

ORBITAL ATHERECTOMY

OA is an endovascular procedure to modify atherosclerotic plaque by using a diamond - coated crown whose mechanism of action consists of the antegrade and retrograde modification of the plaque. Orbital Atherectomy (OA) is an adjunctive technique which intends to prepare the heavily calcified lesion prior to stenting.

Indications

The main indication of OA is for the management of calcified lesions non-dilatable using conventional methods to modify the plaque, increase vessel distensibility, and facilitate the proper stent expansion.

Risks and complications

The most commonly reported complications associated with OA include dissections, slow or no-reflow, and perforations.

Genereux, et al. [38] in ORBIT II trial, studied 443 patient with significant coronary calcification who underwent OA. They reported an excellent device success rate of 98.6% with residual stenosis of less than 50%. A 2-year follow-up demonstrated major adverse cardiovascular events of 19.4% with TLR rate of 6.2% [38]. The most frequent complications associated with this technique include coronary dissection, slow-flow/no-reflow and coronary perforation.

EXCIMER LASER CORONARY ATHERECTOMY

Excimer Laser Coronary Atherectomy (ELCA) was introduced a couple of decades ago as an adjunctive to conventional balloon angioplasty and is aimed to treat atherosclerostic plaque by photoablation. It exerts photochemical, photothermal and photomechanical effects. Despite the fact that a high procedural success rate of 93% has been reported, it is not commonly used as an initial strategy but may be useful in cases where a microcatheteror a guide – wire from an atherectmy device fails to cross the calcified stenosis [39].

Indications

ELCA is indicated in patients with acute myocardial infarction given its potential for effective thrombus removal, non-crossable or non-expandable lesions, chronic occlusions and stent under-expansion.

Risks and complications

The most common complications associated with this technique are coronary dissection (particularly with superficial calcium), coronary perforation and in-stent restenosis.

INTRAVASCULAR LITHOTRIPSY

Shockwave Intravascular Lithotripsy (IVL) is an innovative technique, based on well-established technology for treating ureteral and renal calculi since 1980s. IVL for coronary calcification has been assessed in the pre-market Disrupt CAD I trial [40] and led to Conformite Europeenne (CE) approval for treating significantly calcified coronaries in Europe.

It is a single-use, disposable balloon-based system that has two emitters, 6 mm apart, which convert electrical energy into acoustic circumferential pulses resulting in disruption of both superficial and deep calcium within the arteries. The IVL catheter is attached to a generator with the help of a cable and is pre-programmed to deliver a series of 10 pulses (1 cycle) at a rate of 1 pulse per second. Each individual catheter is programmed to deliver a maximum number of 80 pulses or eight cycles.The balloon is available in diameters of 2.5-4 mm and in only 12 mm length [41-43]. The IVL balloon must be sized according to the reference vessel diameter in a 1:1 ratio and intracoronary imaging is usually suggested for optimal lesion preparation.

Indications

IVL is considered to be most effective with circumferential calcium with the recommendation that it be used with arcs > 180° on intracoronary imaging [44]. It is also deemed to be more proficient on the deepest calcium compared to other plaque – modification techniques.

Risks and complications

The complications associated with IVL include coronary dissection, coronary perforation and ventricular ectopy or "shocktopics" and asynchronous cardiac pacing.

The Disrupt CAD I was the primary trial for the introduction of IVL into coronary intervention [40,45]. It was a prospective, multi-centre, single–arm study which enrolled 60 patients and used Shockwave IVL to pre-dilate heavily calcified coronary lesions. By using intracoronary imaging, the authors demonstrated enhanced circumferential calcium fracture and acute gain in the lumen, with device success in 98.3% and stent delivery in 100% of the cases. The authors reported 95% freedom from MACE at 30-day and 92% at 6 months (included two cardiac deaths which were deemed unlikely to be related to the use of IVL) [33].

The Disrupt CAD II [46], a multicentre, prospective, single-arm, post – approval study, recruited 120 patients, and aimed to evaluate the efficacy and safety of IVL in calcified lesions. Using OCT, calcium fracture was identified in 78.7% of lesions. The primary end point of in-hospital MACE [defined as cardiac death, myocardial infarction or target vessel revascularisation], was reported in 5.8% of patients with 7 patients developing non - Q-wave myocardial infarctions. The IVL was safely accomplished in 92.4% of the cases.

The Disrupt CAD III [47] was a multicentre, prospective, single-arm trial which intended to get a regulatory endorsation of the use of coronary IVL. The trial recruited 431 patients at 47 sites in 4 countries. The IVL use resulted in calcium fractures in 67.4% of the lesions which were detected on OCT. The primary safety endpoint of freedom from 30-day MACE (defined as composite of cardiac death, myocardial infarction, or target vessel revascularization) was recognised in 92.2% of the cases, whereas the procedural success (successful stent delivery with residual stenosis of less than 50% and without in – hospital MACE) was reported in 92.4%.

Despite the fact that there is not yet persuasive evidence which would advocate the use of IVL in patients presenting with STEMI, nascent experience has demonstrated promising outcomes [48,49]. Figure 2 illustrates our proposed algorithm for treating significant coronary calcification in patients presenting with ACS.

CONCLUSIONS

The issue of significant coronary calcification will escalate in the times to come due to an aging population as well as rising number of patients with diabetes and chronic kidney disease. Culprit lesions in

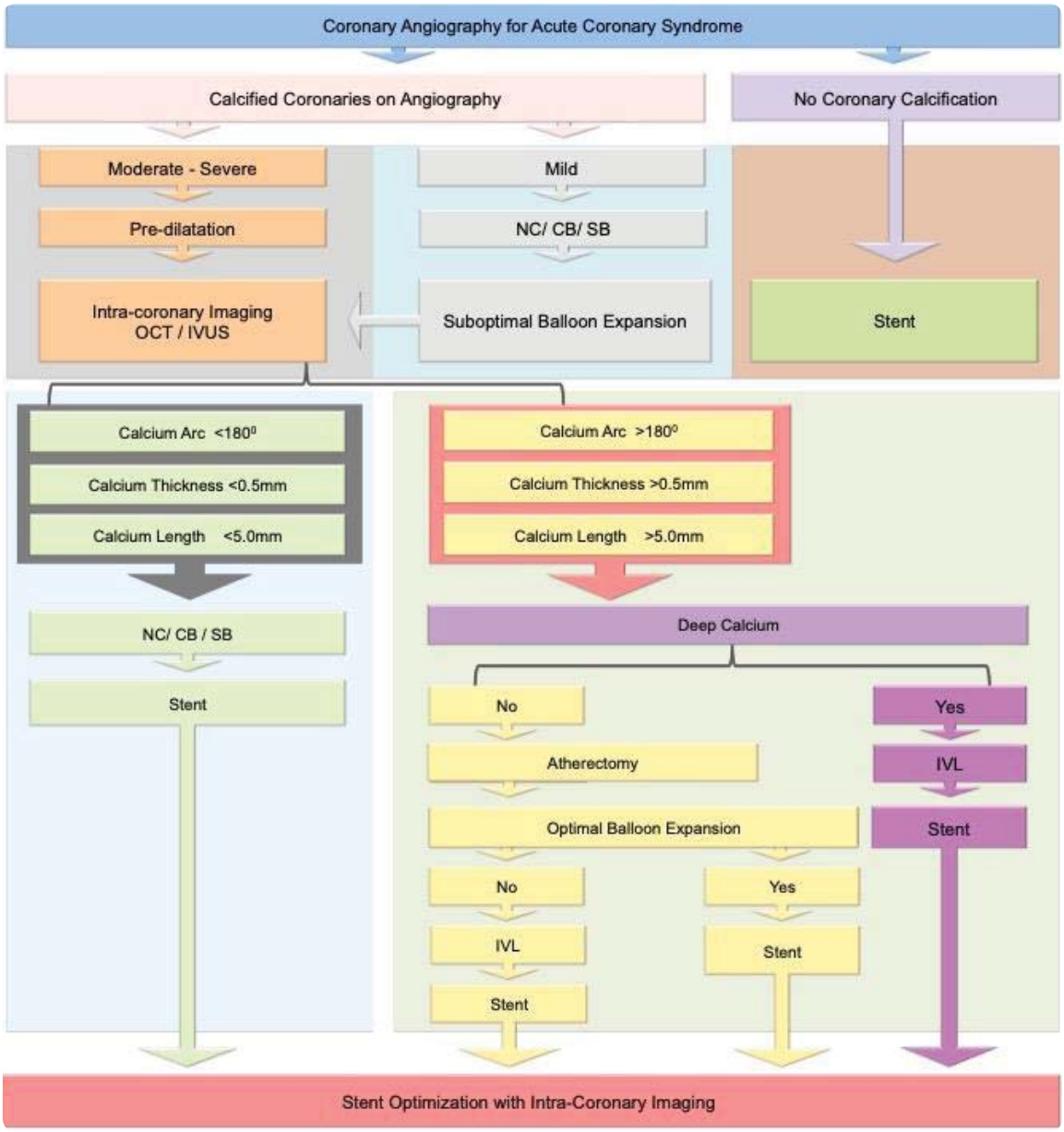

Figure 2: Our proposed algorithm for the treatment of calcified lesions in patients presenting with ACS. OCT optical coherence tomography; IVUS intravascular ultrasound; NC non – compliant balloon; CB cutting balloon; SB scoring balloon; IVL intravascular lithotripsy.

patients with ACS are often found to have significant calcification, and performing coronary intervention on these lesions is independently predictive of poor outcomes, including stent thrombosis and target lesion revascularisation in the intermediate terms, when matched with treatment of lesions with no or minimal calcification. Further data on the modernistic technologies are crucially desired to enhance the outcomes of high-risk individuals with ACS associated with significant coronary calcification undergoing percutaneous coronary intervention.

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