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MANAGEMENT OF MYOCARDIAL REVASCULARIZATION FAILURE: AN EXPERT CONSENSUS DOCUMENT OF THE EAPCI

Short title: EAPCI Consensus Document on the Management of Myocardial Revascularization Failure

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Keywords

Prior cardiovascular surgery; Prior PCI; In-stent restenosis; Saphenous vein graft; Stent thrombosis; Multidiscplinary Heart Team

Abbreviations

ACS= acute coronary syndrome

BID= bis in die

BMS= bare-metal stent

CABG= coronary artery bypass grafting

CAD= coronary artery disease

CI= confidence interval

DAPT= dual antiplatelet treatment

DCB= drug-coated balloons

DES= drug-eluting stent

ECG= electrocardiogram

FFR= fractional flow reserve

HR= hazard ratio

ISR= in-stent restenosis

IVUS= intravascular ultrasound

LAD= left anterior descending artery

LIMA= left internal mammary artery anastomosis

MI= myocardial infarction

OCT= optical coherence tomography

OR= odds ratio

PCI= percutaneous coronary interventions

PROSPECT= Prospective Natural History Study of Coronary Atherosclerosis

RR= risk ratio

TLR= target lesion revascularization

Abstract

Myocardial revascularization represents the most frequently performed therapeutic intervention worldwide. Current percutaneous and surgical revascularization techniques provide excellent short- and long-term clinical outcomes. However, despite the technological and procedural advances with the widespread use of drug-eluting stents and arterial bypass grafts in contemporary practice, a considerable proportion of patients require repeat revascularization procedures during long-term follow-up. The need for repeat revascularization has a major impact on patients quality of life and is associated with a significant economic burden. This Consensus Document summarizes the views on the management of myocardial revascularization failure of an expert panel of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). The present document provides a broad and pragmatic overview of the clinical management of myocardial revascularization failure with a focus on the three key underlying mechanisms leading to repeat revascularization: 1) failure of percutaneous coronary interventions, 2) failure of coronary artery bypass grafting and 3) progression of coronary artery disease in native coronary segments previously untreated. The scope of the present position document is to provide a patient-oriented approach for the management of myocardial revascularization failure.

1. Introduction

Myocardial revascularization represents the most frequently performed therapeutic intervention worldwide.[1,2] Current revascularization techniques provide excellent clinical outcomes during long-term follow-up.[1,3] Notwithstanding, approximately 20% of patients undergoing myocardial revascularization require a repeat revascularization procedure during the first 5 years of follow-up, with a higher risk after percutaneous coronary interventions (PCI) as compared with coronary artery bypass grafting (CABG).[4–7] The need for repeat revascularization has a significant impact on quality of life and health care resources, and exposes patients to risks intrinsically related to repeat hospitalizations and invasive procedures.[4,8,9] Moreover, patients requiring repeat revascularization are characterized by a high cardiac risk profile, due to comorbidities and anatomical features,[7][10] rendering their clinical management a relevant challenge in daily practice.

This document summarizes the views on the management of myocardial revascularization failure of an expert panel of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). The committee members were proposed by the document chair and co-chair, and approved by the EAPCI Scientific Documents and Initiatives Committee.

This document approaches the management of myocardial revascularization failure from a patient-oriented perspective, based on the underlying mechanisms leading to the clinical need for repeat revascularization: failure of PCI, failure of CABG, and progression of coronary artery disease (CAD) in native coronary segments previously untreated. The latter is not directly related to overt failure of a previous PCI or CABG. However, from a patient perspective, the need for a new revascularization

procedure represents a failure of the initial treatment strategy and should, therefore, be evaluated in the context of revascularization failure.

This document has three key objectives: 1) To outline the different mechanisms underlying myocardial revascularization failure; 2) To detail the specific challenges to short- and long-term success of repeat revascularization procedures; 3) To delineate systematic and informed strategies aiming to increase the safety and efficacy of these procedures.

2. Failure of percutaneous coronary interventions

The vast majority of PCI procedures include stent implantation. Stent thrombosis and restenosis are key mechanisms of stent failure requiring repeat revascularization.

2.1 Stent thrombosis

Early stent thrombosis

Early stent thrombosis is defined as stent thrombosis occurring within the first 30 days after stent implantation and is subclassified into acute (0-24 hours) and subacute (>24 hours–30 days) stent thrombosis.[11] Early stent thrombosis is a relatively infrequent occurrence in contemporary clinical practice (**Table 1**).[12] Most cases are related to mechanical or anatomical factors, in association with a thrombogenic milieu or an acute triggering event (**Table 2**).

Late and very late stent thrombosis

Late stent thrombosis is defined as stent thrombosis that occurs between 30 days and one year after stent implantation, while very late stent thrombosis is defined as stent thrombosis that occurs later than year after stent implantation.[13]

In contemporary large-scale drug-eluting stent (DES) trials, with broad inclusion criteria, stent thrombosis rates are low beyond 30 days after stent implantation (**Table 1**).

Risk factors and underlying mechanisms of late and very late stent thrombosis are summarized in **Table 2**.

Management of patients with stent thrombosis

Most patients with stent thrombosis present with acute myocardial infarction (MI), with or without ST-segment elevation.[14] Accordingly, the principles of management are those recommended in relevant clinical practice guidelines.[15–17] Usually patients with suspected ST should undergo urgent coronary angiography to confirm the diagnosis and treat the underlying cause.

Liberal use of intracoronary imaging [18] – with intravascular ultrasound or optical coherence tomography - is recommended by clinical practice guidelines, in order to detect and modify underlying mechanical factors, and to assess the contribution of concomitant restenosis or neoatherosclerosis to in-stent obstruction.[15]

In case of a completely occluded vessel, flow should be restored initially, and intravascular imaging should be performed afterwards. In addition to intracoronary imaging, radiological stent enhancement is a helpful method to diagnose loss of stent integrity or under-expansion.[19] Although routine thrombus aspiration is not recommended by current guidelines, it might be considered in selected cases of stent thrombosis with a large thrombus burden. Similarly, glycoprotein IIb/IIIa receptor antagonists should be considered in view of the elevated pro-thrombotic milieu. Cangrelor use may be considered in patients not treated with a P2Y12 inhibitor at the time of stent thrombosis.

Identified factors likely to have contributed to stent thrombosis should be corrected (**Figure 1**). Patients with deficits in mechanical stent integrity – such as stent gap, stent fracture or longitudinal deformation – as well as those with residual edge disease or dissection should generally be treated with repeat stenting. Stent crush or collapse is very rare but may be seen in heavily calcified lesions or at ostial locations and

also mandates repeat stenting. Significant stent under-expansion or malapposition should be corrected with non-compliant balloon dilation, including use of balloons with very high rated burst pressure as required. Intravascular lithotripsy may be considered for severe, otherwise non-dilatable stent under-expansion.[20] Following dilation of under-expanded stents, additional stent may be considered, although systematic repeat stenting in such cases should be avoided, especially if there are already multiple stent layers.

Non-mechanical causes of stent thrombosis may predominate in some cases. These include insufficient platelet inhibition due to hyporesponsiveness, non-compliance to antiplatelet therapy, or interruption for unplanned or non-deferrable surgery. In the absence of clear identifiable mechanical causes of stent thrombosis, it may be sufficient to dilate the thrombosed stent to restore blood flow and administer antithrombotic agents (e.g. glycoprotein receptor inhibitors, intravenous $P2Y_{12}$ inhibitors). Subsequently, insufficient platelet inhibition must be evaluated. Use of point-of-care phenotypic and genetic testing have been suggested in patients with stent thrombosis without an evident underlying mechanical cause.[21,22] Assessment of dual antiplatelet treatment (DAPT) compliance is of paramount importance, especially within the first 30 days after PCI.[23] Prasugrel and ticagrelor are preferred over clopidogrel after an acute stent thrombosis.[15] Prolonged DAPT therapy beyond 12 months should be considered in patients after a stent thrombosis, weighting their increased thrombotic risk against their bleeding risk.[24–26]

Stent Thrombosis: What To Do
Intracoronary imaging with IVUS and/or OCT to identify factors likely to have contributed to stent thrombosis
PCI with DES in case of deficits in mechanical stent integrity (stent fracture or collapse)
PCI with DES in case of residual edge disease or dissection
High-pressure non-compliant balloon dilation in case of stent under-expansion or malapposition
Assess adherence to antiplatelet therapy
Assess platelet reactivity with point-of care assays in selected cases of acute stent thrombosis without a clearly identified mechanical cause
After PCI for stent thrombosis, dual antiplatelet therapy with aspirin 75-100mg daily and prasugrel 10mg daily or ticagrelor 90mg BID for 12 months

Stent Thrombosis: What NOT To Do
Systematic repeat stenting in cases of stent under-expansion, especially in the presence of multiple stent layers

2.2 In-stent restenosis

In-stent restenosis (ISR) is a response to vessel wall injury that results in excessive tissue formation (i.e., neointimal hyperplasia or neoatherosclerosis) in stented segment. ISR is an angiographic diagnosis, defined as a diameter stenosis >50% within the stented segment (i.e. the stent and a 5 mm border proximal or distal to the stent). Although DES were highly effective in reducing the risk of ISR compared with bare-metal stent (BMS), ISR remains the most frequent cause of stent failure and the most common indication for target lesion revascularization (TLR). Large-scale clinical trials of patients treated with contemporary DES with broad inclusion criteria report rates of clinical restenosis (i.e. clinically indicated TLR) of <3% at 1-year and 10% at 5 years (**Table 1**). Of note, ISR presents as an acute coronary syndrome in up to 20% of cases.[27]

Clinical and angiographic factors predisposing to ISR are summarized in **Table 2**.

Management of patients with in-stent restenosis

Treatment of ISR is challenging compared with treatment of *de novo* lesions, owing to relatively high recurrence rates.[28]

As the underlying substrate in ISR often overlaps with that of stent thrombosis, the principles of management are similar. However, while patients with thrombosis usually present with acute MI, patients with ISR may be asymptomatic and should only be treated in the presence of symptoms or objective evidence of ischemia. In stable settings, if revascularization is deemed necessary the strategy should be carefully planned. As is the case with native coronary artery stenoses, when ISR angiographic severity is unclear physiological guidance should be considered. If possible, the original lesion and the initial procedure (e.g., material used, maximum balloon pressures,

challenges encountered, etc.) should be reviewed to identify potential technical issues that may need to be addressed during the repeat intervention. Intracoronary imaging of restenotic lesions, with IVUS or OCT, may provide insights into the mechanisms underlying ISR (**Table 2**), by identifying contributing mechanical factors as well as characterizing the restenotic tissue type. Of note, in addition to intracoronary imaging, radiological stent enhancement is a helpful method to diagnose stent fracture or under-expansion in patients with ISR.[19]

There are a number of technical issues that should be considered in the treatment of patients with ISR. Treatment should generally be focused on the stenosed segment rather than on the full length of the stented segment.[28] To prevent recurrent ISR, it is important to optimize the results of repeat procedures. Careful lesion preparation is required and mechanical issues should be recognized and corrected. Aggressive dilation of the underlying stent might be required especially in under-expanded or collapsed stents, ideally using noncompliant balloons at high pressures (frequently >18 bar). Care should be taken to avoid geographic miss as this may lead to edge-related recurrence. Use of cutting balloons, or more flexible scoring balloons for lesion pre-dilation, reduces slippage of the balloon out of the stent (so called “water-melon seeding”), which may lead to stent edge dissections, with the potential for subsequent “candy wrapper” patterns of stent edge-restenosis. These devices also incise the surface of the neointimal tissue, which theoretically may facilitate the uptake of drug delivery with drug-coated balloons (DCB) angioplasty or repeat DES implantation. Indeed, the ISAR-DESIRE-4 trial, showed improved angiographic outcomes after lesions pre-dilation with a scoring balloon compared with plain balloon angioplasty prior to DCB-angioplasty.[29]

Occlusive ISR constitutes a challenging lesion subset for revascularization. While the use of a contemporary approach to chronic total occlusion recanalization is associated with improved procedural outcomes,[30] long-term results are worse than in de novo chronic total occlusion lesions, largely due to higher TLR rates.[31]

In the case of resistant stent under-expansion, very-high pressure (25 to 35 bar) balloons may be used. Modification of calcific plaques accounting for stent under-expansion can be performed with excimer laser atherectomy [32] or intravascular lithotripsy, the latter also being useful in ISR with calcified neoatherosclerosis.[33] [34] Rotational atherectomy (also termed "rotastenting") of undilatable under-expanded stents might be considered a second-line strategy and should be undertaken with caution due to the risk of serious complications.[35] Further study of the therapies discussed is required to confirm their potential benefits.

Following lesion preparation, a proportion of patients will require repeat stenting to correct loss of mechanical integrity of the underlying stent (e.g. due to fracture or gap or in rare cases, with demonstrated stent collapse). In the remaining patients, after dilatation and correction of any stent under-expansion, a number of treatment options are available, but there is general consensus that additional treatment beyond mechanical dilatation is required as outcomes after plain balloon angioplasty alone are poor.[36] The two most effective options are DCB-angioplasty or repeat stenting with DES.[37,38] European clinical practice guidelines recommend the use of DES or DCB as first-line therapy in patients with ISR (class I recommendation and level of evidence A for both).[15] Repeat stenting with DES seems to be marginally more effective in terms of angiographic recurrences and need for TLR as compared with DCB, particularly in patients with ISR of DES.[38,39] However, DCB avoids multiple metallic

layers on the vessel wall, which may be of particular concern in patients with recurrent ISR. Accordingly, selection between the two strategies may be considered based on the individual characteristics of the patient and lesion to be treated. For instance, DCB may be preferred over DES in ISR of BMS, multiple metal layers, or large side branches. Conversely, DES may be preferred over DCB in lesions with stent fracture, diffuse ISR extending beyond the stent edges, or in case of significant residual dissection or impaired flow after a balloon-only approach (**Figure 2**). Some operators prefer repeat stenting in the case of ISR at the stent edge though studies suggest that DCB appear to be equally effective for ISR confined to the body of the stent as for those mainly involving its edges.[40,41]

Antiplatelet treatment for patients undergoing PCI for ISR should not differ from that in patients with a de novo lesion. When ISR clinically presents as chronic coronary syndrome, switching antiplatelet therapy is not recommended unless neoatherosclerosis with plaque rupture or erosion is identified by intracoronary imaging.[42]

In-Stent Restenosis: What To Do

Intracoronary imaging with IVUS and/or OCT to detect stent-related mechanical problems leading to ISR
Aggressive pre-dilation of the underlying stent with non-compliant balloons at high pressure, especially in under-expanded or collapsed stents
Lesion preparation with cutting balloons or scoring balloons in order to reduce balloon slippage outside the stent
Very-high pressure balloons, intravascular lithotripsy, excimer laser or rotational atherectomy in case of resistant stent under-expansion
After adequate lesion preparation, PCI with DES or DCB
DES preferred for suboptimal predilation results (residual stenosis >50%, large* or flow-limiting dissections), diffuse ISR, loss of mechanical integrity, and failed DCB-strategy
DCB preferred for focal ISR, first ISR episode, ISR of BMS, and multiple metal layers
CABG or a conservative strategy instead of a new PCI attempt in patients with recurrent episodes of diffuse ISR, after a Heart Team discussion
After PCI for ACS due to underlying ISR, dual antiplatelet therapy with aspirin 75-100mg daily and prasugrel 10mg daily or ticagrelor 90mg BID for 12 months

In-Stent Restenosis: What NOT To Do

Treatment of the full length of the initial stent instead of focusing on the stenosed segment
Plain balloon angioplasty-only strategy

* Large dissection defined if: longitudinal extension >2mm, lateral extension >60^{o} and involvement of medial or adventitia layers.[43]

▪ 2.3. Acute functional failure after PCI

Failing to identify hemodynamically significant coronary stenoses is one of the most common reasons portending to revascularization failure. Complementing coronary angiography with invasive functional assessment has received the highest level of recommendation by current guidelines to evaluate the hemodynamic relevance of intermediate-grade stenosis, when non-invasive evidence of ischemia is not available.[15] Myocardial revascularization aims to eliminate ischemia and is, therefore, expected to normalize findings of invasive functional assessment.

While angiography is considered to be of limited ability to assess the hemodynamic relevance of coronary lesions, the adequacy of acute results after PCI is still mainly assessed based on angiographic visual estimation only. However, early evidence with fractional flow reserve (FFR) suggested that suboptimal FFR after stenting is an independent predictor of adverse clinical outcomes at 6 months.[44] More recently, a prospective observational study including 574 consecutive patients (664 lesions) with FFR pre- and post-PCI evaluated clinical outcomes during a mean follow-up of 31±16 months. Despite adequate angiographic result, 143 lesions (21%) had post-PCI FFR values within the ischemic range (FFR ≤0.80).[45]

A meta-analysis that synthesized evidence of 59 observational (prospective and retrospective) studies evaluating the relationship between post-PCI FFR and clinical outcomes found a normal distribution of post-PCI FFR values, with a mean of 0.90±0.04, and indicated that post-PCI FFR values appear to be related to the risk of repeat revascularization (OR 0.43, 95% CI 0.34-0.56) and major adverse cardiac events (0.71, 95% CI 0.59-0.85) during follow-up.[46] A threshold of final FFR <0.90 has been proposed to define a suboptimal result after stenting.[47]

Several investigations showed that additional interventions may optimise the acute result in patients with suboptimal post-PCI FFR.[45,47,48] A recent prospective small-scale study suggested that intracoronary imaging with optical coherence tomography may reveal potentially treatable causes (i.e., stent underexpansion, incomplete lesion coverage, stent malaposition, edge dissection, or tissue protrusion), allowing optimisation of the post-PCI functional result.[47] However, whether additional interventions based on post-PCI functional assessment have a significant impact on clinical outcomes has not been clearly determined.[49]

Acute Functional Failure: What To Do

Repeat invasive functional assessment after stenting when already used to assess the hemodynamic relevance of the treated lesion
Attempt to identify reasons for suboptimal (i.e., FFR <0.90) invasive functional assessment post-PCI, possibly with the use of intracoronary imaging

3. Failure of coronary artery bypass grafting

Surgical graft failure is frequently observed with increasing time after CABG. Graft failure after use of saphenous vein grafts is as high as 50% at 10 years with vein graft occlusion rates of up to 27% within the first year after CABG.[50–52] Within the first month after surgery, the causes of graft failure are mostly related to the surgical technique and flow-pattern related thrombotic complications, while graft failure thereafter is characterized by neointimal hyperplasia and accelerated progression of CAD.[53–55]

3.1 Acute graft failure (<1 month after surgery)

Acute graft failure can be due to graft dissection, kinking or twisting, anastomotic technical errors, impaired vessel run-off into the native coronary artery, competitive flow from the native coronary artery, or graft thrombosis. In a study of 366 patients with routine post-CABG angiography, 12.2% of the grafts were found to have relevant angiographic defects requiring a minor adjustment of the graft in 2.8%, an anastomosis revision in 3.4%, and intraoperative open-chest PCI in 6.0%.[53] Because of the logistic issues associated with routine direct postoperative angiography, intraoperative transit-time flow measurements and high-frequency epicardial ultrasound have been used to detect causes of graft failure before chest closure and allow the opportunity for revision before myocardial ischemia occurs or progresses.

When clinically relevant, acute graft failure may result in MI with a subsequent risk of mortality. The suspicion of early graft failure should arise in the presence of sudden clinical deterioration as indicated by ECG signs of ischemia, ventricular arrhythmias, biomarker changes, new wall motion abnormalities, or haemodynamic

instability. Due to the low specificity of ECG changes and echocardiographic wall motion abnormalities during the postoperative course and the delay in appearance of biomarker changes, careful assessment of all variables will influence the decision making for angiographic evaluation.[15]

Despite arterial grafting is recommended by current guidelines on myocardial revascularization [15], vein grafts continue to be used in larger numbers than arterial grafts, despite having lower long-term patency rates.[56] Arterial grafts tend to be reserved for the prognostically most important areas of myocardium (e.g., the left internal mammary artery anastomosis [LIMA] to the left anterior descending artery [LAD]). Acute arterial graft failure, therefore, typically has a more severe clinical presentation than vein graft failure, while the latter more often occurs subclinically. An observational study showed that acute graft failure of the LIMA-to-LAD anastomosis warranted reintervention in 80% of patients, while acute vein graft failure was treated conservatively in approximately 50% of patients.[57]

Management of acute graft failure

Angiographic assessment is recommended if there is a suspicion of acute graft failure early postoperatively, and is performed in about 1-5% of patients.[58–61] In a recent meta-analysis of 9 studies and 1,104 patients with suspected perioperative MI after CABG, acute graft failure was diagnosed in 62.1% of patients.[62] Incomplete revascularization was the cause of the MI in 6.1% of patients, and 3.5% of patients had a native coronary artery culprit. Remarkably, in 31.6% of patients no cause of perioperative MI could be identified. In this context, it is important to underscore that

haziness at the anastomosis in this acute period may be difficult to interpret and may not be related to the clinical problem.

The treatment strategy for acute graft failure should be made in an ad hoc Heart Team meeting. As summarized in **Figure 3**, a number of parameters should be considered in the decision-making process such as technical reason for acute failure (i.e., problems related with the suture), age and risk profile of the patient, the patient's clinical condition (e.g., haemodynamic status and inotropic support), pre-CABG native vessel CAD and coronary anatomy, extent and timing of ischemia, graft configuration, and extent of myocardium at risk.

In the setting of acute graft failure, emergency PCI may limit the extent of infarction. Current clinical guidelines advocate that PCI should be the preferred strategy in cases of acute graft failure where the anatomy is suitable.[15] In such cases, the target for PCI should be the native vessel or the internal mammary artery (IMA) graft, while an acutely occluded vein graft and any anastomotic site should be avoided, if possible, due to concerns regarding fragility of the new anastomosis as well as the risk of embolisation and perforation. The impact of in-hospital PCI following CABG was investigated in a retrospective study in which patients with acute coronary ischemia requiring PCI after CABG (N=14,323) were compared with those who did not undergo PCI (N=540,664). Post-CABG PCI was associated with an increased risk of unadjusted in-hospital mortality (5.1% vs. 2.7%; $p < 0.001$), higher rates of stroke (2.1% vs. 1.6%; $p < 0.001$), acute kidney injury (16% vs. 12.3%; $p < 0.001$), and a 50% cost increase.[63]

Redo CABG should be preferred when the anatomy is unsuitable for PCI, when an anastomotic error is evident, or when several important grafts are occluded.[15] Conservative treatment should be considered in cases where diagnosis has been

delayed and viability is expected to be limited. In asymptomatic patients, repeat revascularisation should be considered if the failed graft supplies a large territory of myocardium.

Acute Graft Failure: What To Do

Coronary angiography after CABG in patients with sudden clinical deterioration indicated by: - symptoms of ischemia and/or abnormal biomarkers suggestive of perioperative MI - ischemic ECG changes indicating large area of myocardium at risk - new significant wall motion abnormalities - haemodynamic instability.
Emergency redo-CABG or PCI decided upon by ad-hoc consultation in the Heart Team, based on the feasibility of revascularization, area at risk, comorbidities, and clinical status
PCI of the native vessel rather than PCI of the graft
Conservative treatment in graft failure cases where diagnosis has been delayed and viability is expected to be limited
In asymptomatic patients, repeat revascularisation if the failed graft supplies a large territory of myocardium

Acute Graft Failure: What NOT To Do

PCI in case of unsuitable anatomy, anastomotic error of the LIMA to LAD or at the Y-anastomosis of a composite arterial graft

3.2 Late graft failure (>1 month after CABG)

As the time from surgery increases, vein grafts become prone to a process of aggressive and accelerated atherosclerosis. This results in mostly diffuse soft lipid-rich atherosclerotic plaques with extensive necrotic cores with or without intraplaque haemorrhage prone to rupture and downstream embolization.[54][64]

Clinically relevant late graft failure presents mostly in form of stable or unstable angina pectoris.[65–68]

Management of late graft failure

A number of critical issues should be considered when treating patients with degenerated grafts, including whether to perform redo CABG or PCI, whether to treat native arteries or degenerated grafts, and the risk of distal embolization in case of graft intervention.

PCI is considered treatment of choice in case of late graft failure. Randomized comparisons between redo CABG and PCI, however, are lacking partly due to patients' unwillingness to be allocated to redo CABG.[69] In a subgroup analysis of patients with late graft failure from the AWESOME trial and registry, redo CABG surgery was associated with higher peri-procedural mortality as compared with PCI.[69] Therefore, redo CABG surgery is recommended only in case of extensive native CAD with multiple graft occlusion, particularly in the absence of patent arterial grafts.[15]

PCI of vein grafts is considered a high-risk intervention due to an increased risk of slow/no-reflow related to distal embolization of the friable atheroma, depending on the degree of graft degeneration.[70,71] Embolic protection devices have been proposed to prevent distal embolization.[72,73] A randomized trial performed in early 2000 showed a significant benefit of embolic protection devices in PCI of vein grafts [72] and a similar trend was seen in a subsequent randomized trial that was underpowered due to premature termination [73]. However, a meta-analysis of 52.893 patients enrolled in these randomized trials and in more recent observational studies did not suggest a benefit of routine use of embolic protection devices in PCI of vein grafts.[74]

Several randomized trials have compared DES with BMS in vein graft lesions.[68] In a meta-analysis of randomized evidence, no differences between DES and BMS was

observed in terms of all-cause death (RR 1.06, 95% CI 0.76-1.48), MI (RR 0.81, 95% CI 0.50-1.29), target vessel revascularization (RR 0.73, 95% CI 0.48-1.11) and target lesion revascularization (RR 1.05, 95% CI 0.76-1.43) at longest follow-up.[68] In the ISAR-CABG trial, DES use was associated with a significantly lower risk of target-lesion revascularization during the first year of follow-up (HR 0.49, 95%CI 0.28-0.86) which was offset by a higher risk between 1 and 5 years (HR 2.10, 95% CI 1.37-3.22) as compared to BMS, with a significant interaction between treatment effect and time ($p_{interaction}$ <0.001) .[66,67]

PCI of vein grafts is associated with a higher risk of adverse events as compared to PCI of native coronary arteries among patients with late graft failure.[75] In a registry of 11,118 veterans, PCI of vein grafts was associated with significantly higher risk of mortality (adjusted hazard ratio 1.30, 95% CI 1.18-1.42), MI (adjusted HR 1.61, 95% CI 1.43-1.82) and repeat revascularization (adjusted HR 1.69, 95% CI 1.50-1.71) as compared to PCI of native arteries during a median follow-up of 3 years.[75]

Although available evidence clearly supports PCI of the native artery in case of late graft failure, anatomical complexities – such as multiple chronic total occlusions of native arteries – might limit the success of such strategy, forcing interventionalists to treat degenerated grafts instead. Despite improvements in recanalization techniques and available dedicated tools, previous CABG surgery remains one of the most important predictors of PCI failure in chronic total occlusions.[76] Therefore, the decision to treat native artery lesions or surgical grafts depends on CAD anatomical complexity and the interventionalists expertise in complex PCI, seeking the most complete revascularization. The decision should be made on an individual patient basis, giving priority to PCI of native arteries.

Late Graft Failure: What To Do
PCI as first choice over redo-CABG for late graft failure
PCI of the native vessel rather than PCI of the graft
PCI strategy based on operator experience in complex PCI
Distal protection devices for PCI of vein graft lesions with diffused degeneration
IMA for redo-CABG in patients in whom the IMA was not used previously
Redo-CABG in patients without a patent IMA graft to the LAD, after checking its patency
Redo-CABG in case of extensive native CAD, anatomically unsuitable for PCI, in absence of patent grafts (especially arterial)

Late Graft Failure: What NOT To Do
Routine use of embolic protection devices for PCI of vein grafts
Plain balloon-only for PCI of the graft

4. Repeat revascularization due to progression of CAD

CAD progression in native coronary segments previously untreated is the primary cause of repeat procedures after myocardial revascularization.

Native CAD progression after PCI

Disease progression is responsible for a relevant proportion of repeat revascularization procedures after PCI,[6] although the incidence varies based on the clinical and anatomic characteristics of the population studied. The Prospective Natural History Study of Coronary Atherosclerosis (PROSPECT) study studied the relative contribution of events related to the initially treated lesion (culprit lesion) and events related to CAD progression in non-culprit sites among 697 patients with ACS undergoing PCI.[77] The cumulative rate of major adverse cardiac events – a composite of cardiac death, arrest, MI, and hospitalization for angina – was 20.4% at 3 years, with 12.9% events related to the culprit lesion and 11.6% events due to CAD progression at non-culprit sites. Overall, 65% of all events occurred within 1 year after PCI, with a relatively equal distribution between events related to the culprit lesion and those related to CAD progression. The overall repeat revascularization rate was 17.1% at 3 years, with an equal contribution of events related to the culprit lesion and those related to CAD progression.

Predictors of CAD progression in previously untreated native coronary segments include clinical and angiographic factors that are largely overlapping with predictors of PCI and CABG failure, such as age, diabetes mellitus, complex coronary anatomy, extent of CAD, small vessel CAD, and previous PCI of vein grafts or ostial lesions.[6][78]

Native CAD progression after CABG

Current recommendations for CABG inherently select patients at higher risk for native CAD progression. These include patients with multi-vessel CAD, high anatomical complexity and extent of CAD, and coexistence of multiple comorbidities including diabetes mellitus, reduced left ventricular ejection fraction, and chronic kidney disease. Historical evidence indicates that accelerated CAD progression occurs up to 10-fold more frequently in non-obstructive atherosclerotic lesions in bypassed coronary arteries compared with similar lesions in non-bypassed vessels at 3 years after CABG.[79] In another study, the risk of CAD progression was twice as high in arteries with patent grafts as compared to those with closed grafts, with the majority of grafted arteries with CAD progression being completely occluded. A more recent analysis of contemporary surgical techniques showed similar results, with development of a new chronic total occlusion in a native coronary artery in >40% of patients within 1 year after CABG, strongly predicted by a severe (>90%) proximal stenosis in the same vessel.[80]

General principles for management of CAD progression

In case of CAD progression in previously untreated native coronary segments following revascularization, treatment recommendations should be based on symptoms and evidence of myocardial ischemia. In this context, optimal medical therapy plays a pivotal role not only to reduce the risk of CAD progression but also for an initial management of patients with evidence of CAD progression. We refer to relevant clinical practice guidelines for a comprehensive assessment on recommendations for optimal medical management, which represents the cornerstone for prevention and treatment

of CAD progression.[15,81,82] The interventional management of CAD progression differs according to the initial revascularization modality.

Management of CAD progression after PCI

In contemporary large-scale PCI trials, up to one-third of patients enrolled were previously treated with PCI.[83–85] Percutaneous treatment of CAD progression after a previous PCI is generally reasonable. A surgical revascularization strategy may be appropriate in case of CAD progression involving proximal segments of major coronary arteries or multivessel disease involving the left main or proximal LAD. A large registry that evaluated outcomes of patients with previous PCI undergoing CABG showed that early mortality and adverse ischemic events did not significantly increase in patients with single or multiple previous PCI procedures.[86] Therefore, a strategy based on clinical and anatomical factors similar to patients with a first diagnosis of CAD is recommended in patients with CAD progression after PCI (**Figure 4**).

Management of CAD progression after CABG

Repeat revascularization procedures after CABG are typically performed in older patients with more comorbidities and more complex coronary anatomy as compared to patients with a first diagnosis of CAD. Furthermore, in these patients arterial conduits tend to be less frequently available, having already been used.[87] Therefore, re-do CABG is associated with increased procedural risks and worse clinical outcomes compared with a first CABG. Recent evidence indicates a trend towards a decreased risk of adverse events in patients treated with PCI coupled with an increase in PCI use in this setting.[70][88] In view of the paucity of available comparative effectiveness evidence,

in these patients the selection of the repeat revascularization strategy should be based on the assessment of clinical and anatomical risk profiles on an individual patient basis in discussion within the Heart Team (**Figure 3**, **Figure 4**).[89][69]

CAD Progression: What To Do
Repeat revascularization in patients with evidence of CAD progression and with a large area of ischemia or severe symptoms despite medical therapy
Base the selection of the repeat revascularization strategy on the assessment of clinical and anatomical risk profiles on an individual basis in the context of the Heart Team
If considered safe, PCI with DES as first choice over CABG
IMA for redo-CABG in patients in whom the IMA was not used previously
Redo-CABG in patients without a patent IMA graft to the LAD

CAD Progression: What NOT To Do
Routine Invasive angiography tests in asymptomatic patients with prior revascularization
Routine ad-hoc PCI in patients with progression of CAD after CABG

Conclusions

Current percutaneous and surgical revascularization techniques are associated with excellent procedural and long-term clinical outcomes. However, a considerable proportion of patients require repeat revascularization procedures during long-term follow-up due to failure of the initial revascularization – either PCI or CABG – or progression of disease in previously untreated coronary segments. This document provides an evidence-based guidance for the management of myocardial revascularization failure based on the underlying mechanism, the timing and the clinical and angiographic characteristics of individual patients.

5. References

References available in the online supplementary material.

Figure legends

Figure 1. Algorithm for the management of stent thrombosis.

PCI=percutaneous coronary interventions, DES=drug-eluting stent. *Avoiding stent implantation should be considered in cases with severe under-expansion or malapposition without further underlying mechanisms. In patients with stent thrombosis due to severe neointimal hyperplasia or neoatherosclerosis PCI with DEB might be considered. Images were kindly provided by Drs Nicolas Amabile, Fernando Alfonso and Gennaro Sardella.

Figure 2. Algorithm for the management of in-stent restenosis

BMS=bare-metal stent; DCB=drug-coated balloon. DES=drug-eluting stent; ISR=in-stent restenosis; NC=non-compliant; PCI=percutaneous coronary intervention. *In patients with edge dissection or acute recoil after lesion predilation, PCI with DES should be considered. Images were kindly provided by Drs Nicolas Amabile, Fernando Alfonso and Gennaro Sardella.

Figure 3. Algorithm for the management of patients with surgical graft failure.

CTO= chronic total occlusion; DAPT= dual antiplatelet therapy; LAD= left anterior descending artery; LIMA= left internal mammary artery; PCI= percutaneous coronary intervention; SGF=surgical graft failure

Figure 4. Factors that may guide revascularization strategy for CAD progression.

CAD= coronary artery disease; COPD= chronic obstructive pulmonary disease; DAPT= dual antiplatelet therapy; STS = Society of Thoracic Surgery Risk Score

Table 1. Rates of stent thrombosis and TLR in selected contemporary large-scale all-comer clinical trials[90,91,100–107,92–99]

	RESOLUTE All comers		DUTCH PEERS		CENTURY II		BIOSCIENCE		BIO-RESORT			SORT OUT VII		BIONICS		BIONYX		SORT OUT VIII	
	Resolute	Xience	Resolute	Promus	Ultimaster	Xience	Orsiro	Xience	Synergy	Resolute	Orsiro	Orsiro	Nobiro	BioNIR	Resolute	Resolute	Orsiro	BioMatrix	Synergy
Definite ST																			
30 days							0.3%	0.2%										0.4%	0.7%
1 year	1.2%	0.3%	0.3%	0.6%	0.9%*	0.9%*	0.9%	0.4%	0.3%	0.2%	0.3%	0.4%	1.2%	0.4%	0.5%	0.1%	0.5%	0.9%	0.7%
2 years			0.8%	0.9%			1.0%	0.7%	0.6%	0.5%	0.4%	0.8%	1.4%						
3 years									0.7%	0.5%	0.7%								
5 years	1.6%	0.8%	1.1%	1.1%	1.3%	1.1%	1.5%	1.5%											
Definite or Probable ST																			
30 days	1.1%	0.5%					1.8%	2.2%											
1 year	1.7%	0.7%	0.5%	0.8%			2.8%	3.4%	0.4%	0.5%	0.4%	0.9%	1.6%	0.4%	0.6%	0.1%	0.7%	1.4%	1.1%
2 years	1.9%	0.9%	1.1%	1.1%			3.7%	4.7%	0.9%	0.7%	0.6%	1.3%	1.8%						
3 years									1.0%	0.8%	1.0%								
5 years	2.4%	1.7%	1.5%	1.3%	1.3%	1.3%	5.8%	7.2%											
TLR																			
30 days																			
1 year			2.2%	2.2%	2.2%*	1.6%*	4.0%	3.1%	1.4%	1.4%	1.5%	2.0%	2.9%	3.2%	2.3%	2.5%	1.9%	2.5%	2.3%
2 years	5.7%	5.1%	3.8%	3.5%			5.5%	4.8%	2.3%	2.9%	2.1%	3.6%	4.5%						
3 years									3.1%	3.6%	2.8%								
5 years	10.2%	8.9%			9.4%	8.2%	10.3%	10.0%											

ST=stent thrombosis, TLR=target lesion revascularization. *9 months follow-up.

Table 2. Risk factors and underlying mechanism of stent thrombosis and in-stent restenosis

	Stent Thrombosis[12,14,18,108–113]			**In-Stent Restenosis**[111,114–117]
	Early	**Late**	**Very late**	
Risk factors				
Patient-related	- Acute clinical presentation - Poor response to antiplatelet treatment - High on-treatment platelet reactivity - Current smoking - Genetic variants* - Diabetes mellitus - LVEF <40%	- Current smoking - Multivessel disease - Younger age - LVEF <40% - eGFR<30 ml/(min·m^2)	- Current smoking - Multivessel disease - Younger age	- Diabetes mellitus - Prior bypass surgery
Lesion-related	- LMCA or LAD lesion - Residual dissection - TIMI flow grade <3 - Bifurcation lesion - Type C lesions - Severe calcified lesions	- LAD lesion - Bypass graft lesion - Presence of thrombus - Bifurcation lesion - Severe calcified lesions	- LAD lesion - Bypass graft lesion - Presence of thrombus	- Small vessel size - Complex morphology - Previous diffuse ISR - Bifurcation lesion
Stent-related	- Under-sizing - Overlapping stents	- Long stent length - Overlapping stents	- Long stent length - Overlapping stents	- Long stent length
Underlying mechanisms	- Uncovered struts - Stent under-expansion - Malapposition	- Uncovered struts - Malapposition	- Neoatherosclerosis - Uncovered struts - Malapposition	- Neointimal hyperplasia - Neoatherosclerosis - Stent under-expansion - Loss of mechanical integrity

eGFR= estimated glomerular filtration rate, ISR=in-stent restenosis, LAD=left anterior descending artery, LMCA= left main coronary artery, LVEF= left ventricular ejection fraction, TIMI=Thrombolysis in Myo

Figure 1

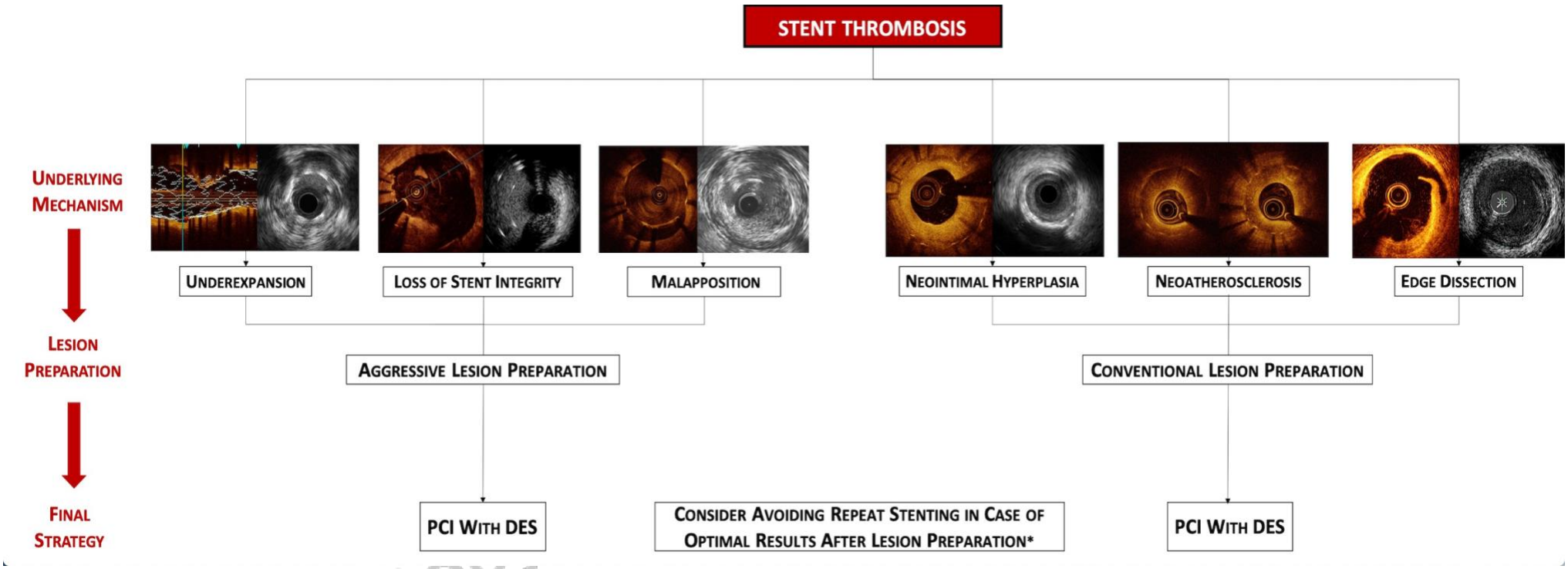


Figure 2

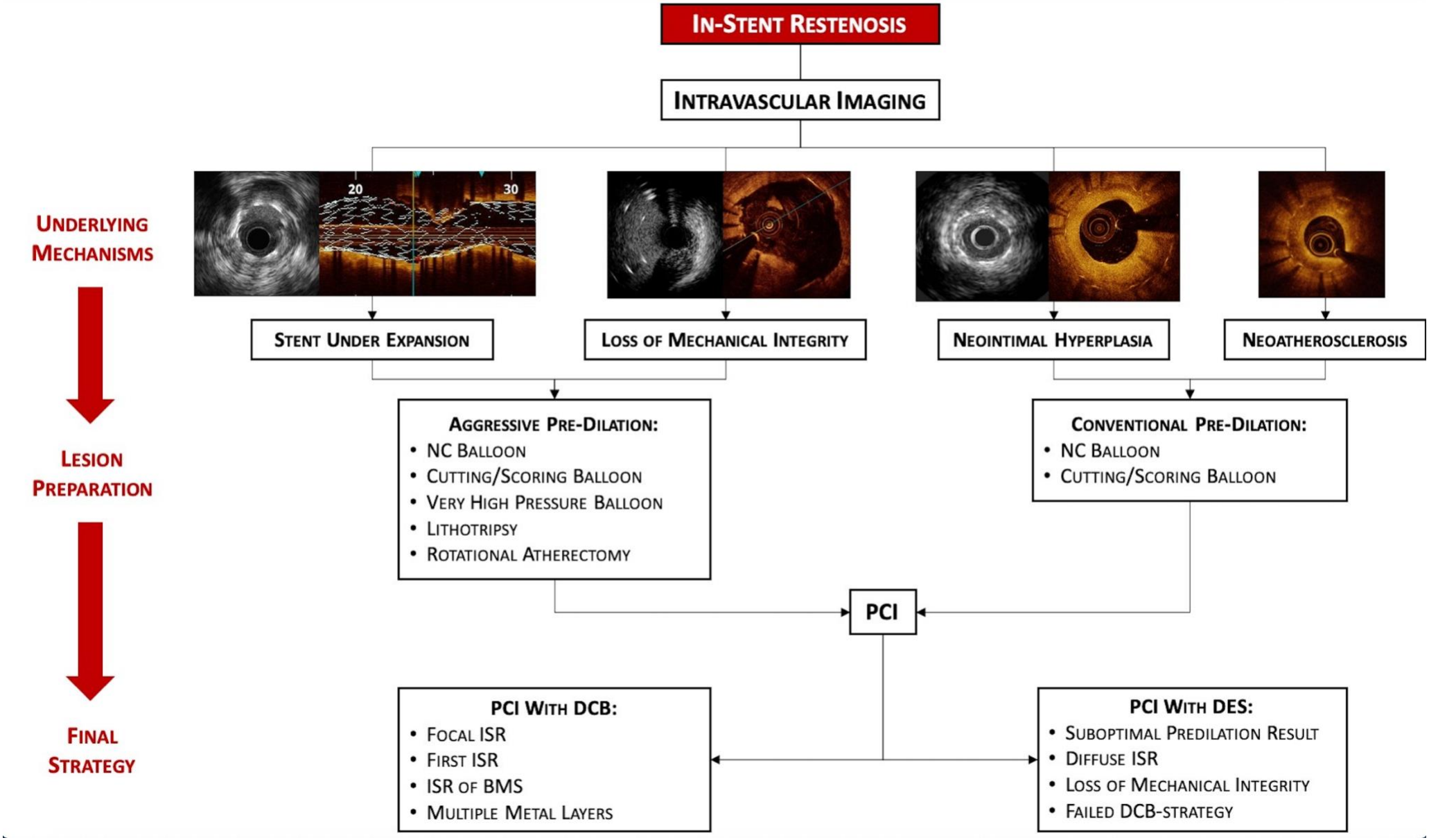


Figure 3

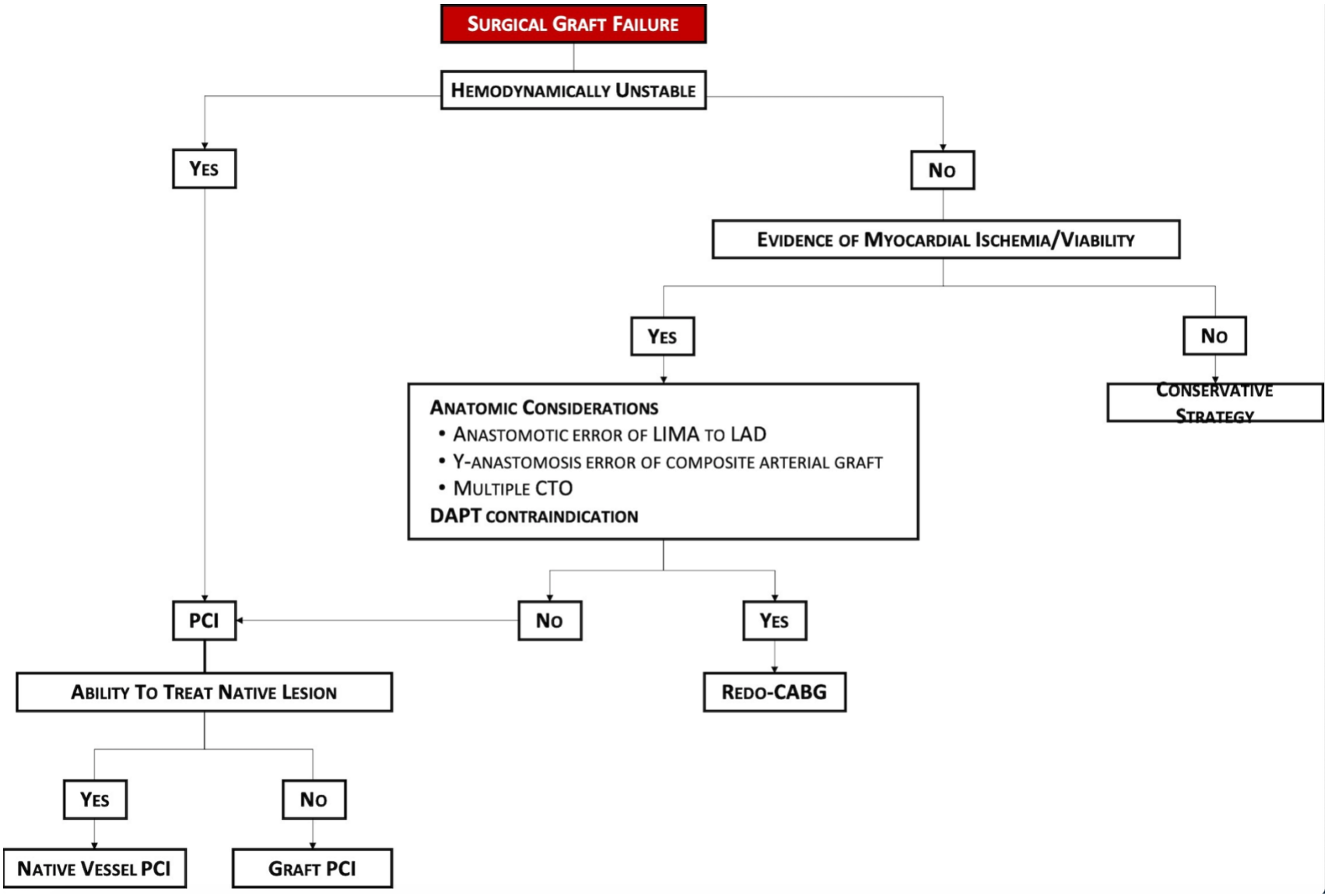
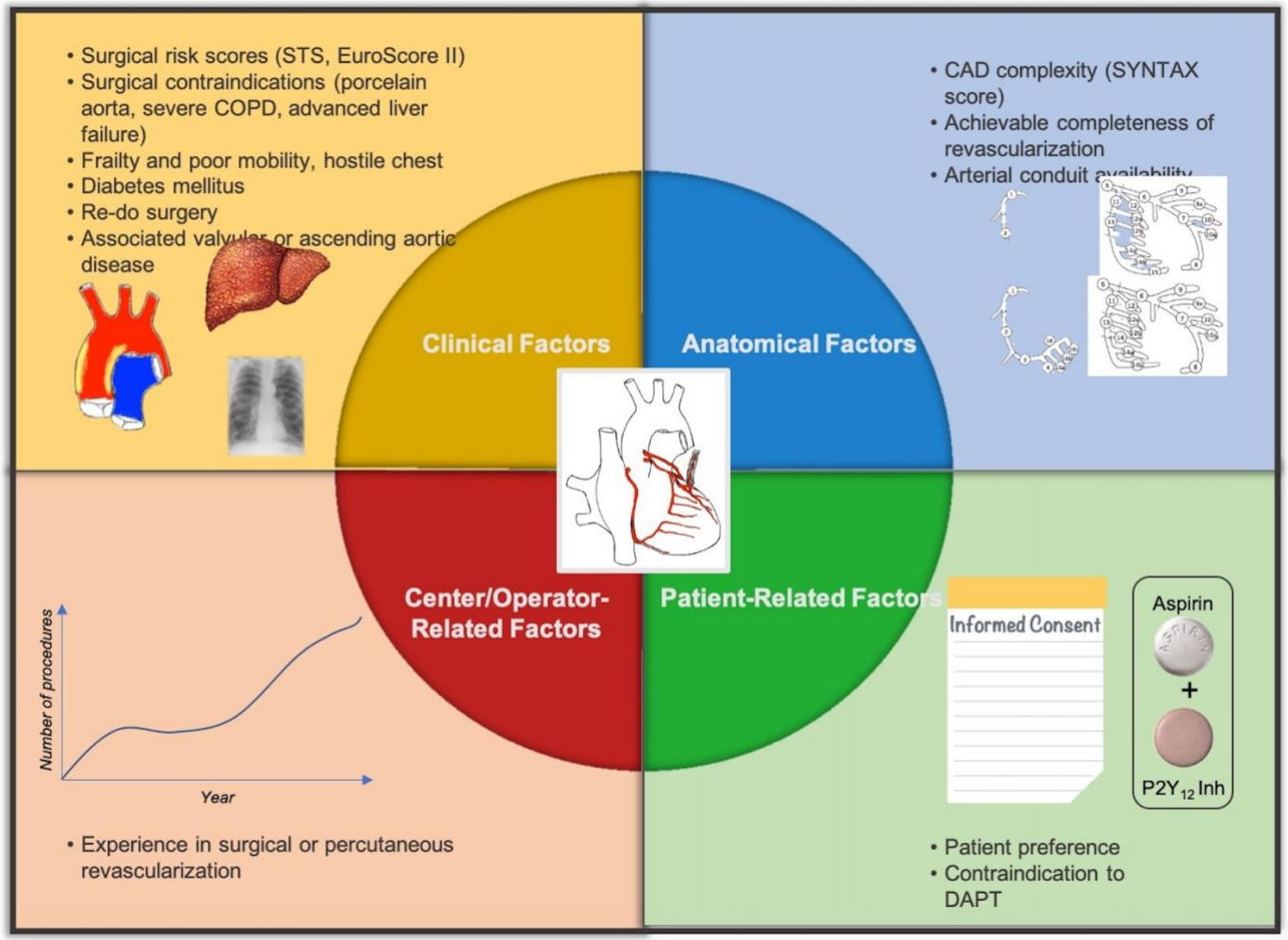


Figure 4



Supplementary Material

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