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STATE OF THE ART REVIEW
Ischaemic heart disease

Angina after percutaneous coronary interventions

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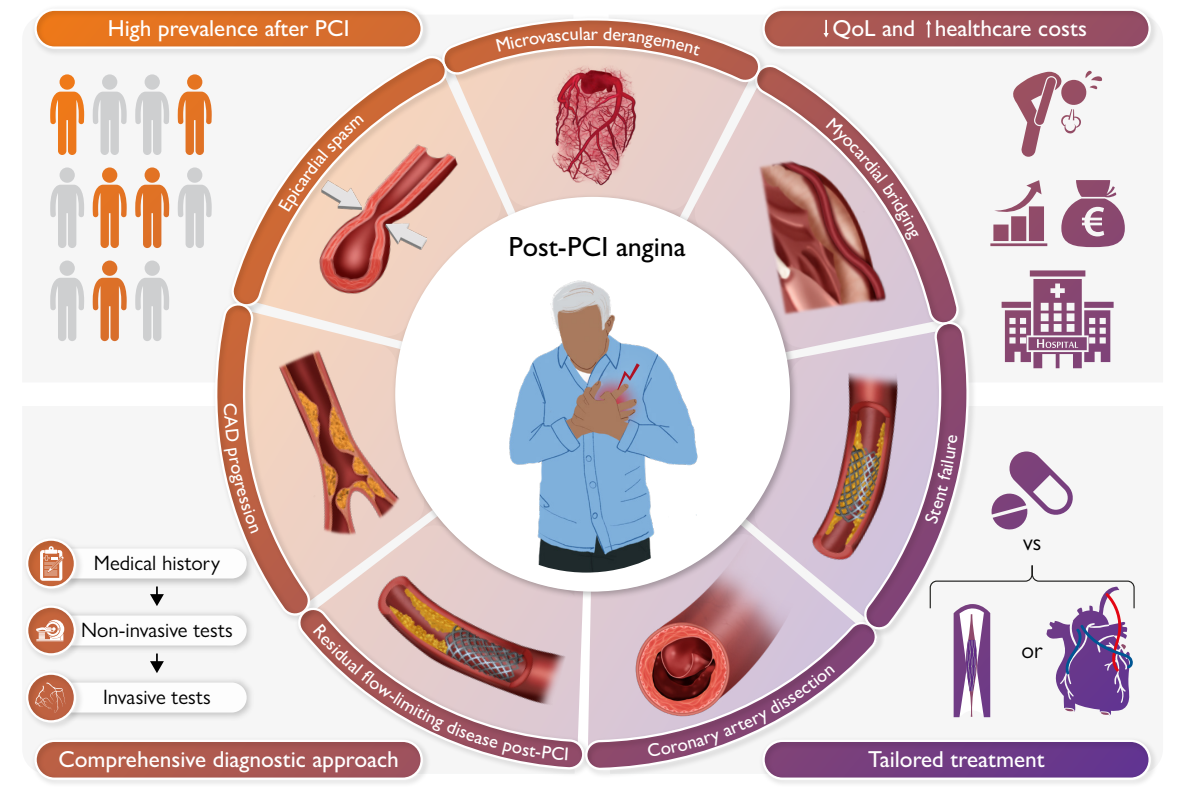
Graphical Abstract



Persistence or recurrence of angina after percutaneous coronary intervention (PCI) is a frequent clinical problem, associated with reduced quality of life and increased healthcare costs. Post-PCI angina is a multifaceted entity with multiple causes which should be taken into account in making a differential diagnosis and setting effective treatment

CAD, coronary artery disease; **PCI**, percutaneous coronary intervention; **QoL**, quality of life

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Abstract

Persistence or recurrence of angina after percutaneous coronary intervention (PCI) has gained recognition as an unfortunately common condition, which defeats the most frequent purpose of performing PCI in patients with stable coronary artery disease, the relief or reduction of anginal symptoms. Many aspects of this problem remain unknown and underexplored, with clinical practice guidelines providing limited information on guidance for its causative diagnosis, prevention and management. This review article aims to provide a contemporary perspective on the problem of post-PCI angina, leveraging recent advancements on the pathophysiological mechanisms that frequently underlie this condition, including sub-optimal functional results of PCI and non-obstructive causes of myocardial ischaemia. The opportunities provided by new functional coronary angiography tools are explored. A practical structured approach to the aetiological diagnosis and treatment of these patients is proposed.

Keywords Angina • Percutaneous coronary intervention • Intracoronary physiology • Intracoronary imaging • Functional coronary angiography • INOCA

Introduction

Percutaneous coronary intervention (PCI) is the predominant modality of myocardial revascularization worldwide. The introduction of drug-eluting stents (DESs) dramatically decreased the occurrence of target vessel failure.[1] Further technological developments, such as second-generation drug-eluting stent (DES) and advanced imaging or physiology techniques, have contributed to improve outcomes of PCI.[2,3] In patients with acute coronary syndromes (ACS), PCI improves outcomes,[2,3] while in patients with chronic coronary syndromes (CCS) without high risk anatomy, PCI improves quality of life and reduces angina, without a significant impact on prognosis compared to optimal medical therapy (OMT).[4–6] However, up to half of the patients continue to suffer from post-PCI angina, regardless of the clinical presentation, use of DES, and standard PCI practices.[7,8] Many aspects of this problem, including its aetiology, prevalence, and consequences for patient prognosis, quality of life, and healthcare economics, remain underexplored.

This article reviews the problem of post-PCI angina from a contemporary perspective, supported by updated clinical evidence. Overall, it gives rise to a multifaceted problem in which procedural and patient-specific characteristics contribute to the failure of PCI to control anginal symptoms in a substantial number of patients. In looking forward to decreasing the occurrence of post-PCI angina, a more careful diagnosis of the cause of angina, better selection of PCI candidates, and improved procedural planning and optimization appear as important actions. A structured practical approach to the aetiological diagnosis and stratified treatment of these patients is proposed as part of our review.

Frequency and implications of post-PCI angina

As an operative definition, post-PCI angina can be defined as chest pain with anginal characteristics with or without evidence of myocardial ischaemia, persisting after PCI or recurring after an angina-free period. It is worth noting that in clinical trials, the definition of post-PCI angina is not standardized, with studies using various assessment tools such as the Seattle Angina Questionnaire Angina Frequency (SAQ-AF), SAQ Summary Score (SAQ-SS), Canadian Cardiovascular Society class, or patient-reported measures through remote digital smart device.[9] The lack of standardization, combined with varying follow-up durations, results in a significant heterogeneity in the reported prevalence across different studies.

There is overwhelming evidence supporting the fact that the prevalence of post-PCI angina in the DES era is high. An analysis of 51 710 patients undergoing PCI showed that angina occurred in 28% within the first year and 40% within 3 years post-PCI.[10] In the Fractional Flow Reserve vs Angiography for Guidance of PCI in Patients with Multivessel Coronary Artery Disease (FAME) trial, the reported rate of post-PCI angina was 19% at 1 year in patients with DES and fractional flow reserve (FFR)-based ischaemia-driven revascularization.[11] In the FAME-2 trial, the proportion of patients with Canadian Cardiovascular Society angina class II, III, or IV was lower in patients in the PCI plus OMT group than those in the OMT group alone during the three first years of follow-up, but this difference was no longer significant at 5 years [7.4% vs 10.2%; relative risk, 0.72; 95% confidence intervals (CIs), 0.45–1.18].[12] The International Study for Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial reported that patients with a baseline SAQ-AF score of 50 (i.e. weekly angina) randomized to an invasive management strategy had a 40% probability of persistent or recurrent angina at 1 year compared to a 75% probability in those managed conservatively.[13] In the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects With de Novo Native Coronary Artery Lesions (ABSORB-IV) trial, which randomized patients with CCS or ACS to PCI with implantation of bioresorbable vascular scaffolds vs DES and, applied a very thorough methodology to measure patient's symptoms, angina recurred in 53% of patients treated with DES at 5 years after PCI.[14] Finally, in the recent ORBITA-2 (Objective Randomized Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina) study, a randomized placebo-controlled trial which included patients with stable angina who discontinued antianginal medications and with evidence of myocardial ischaemia, 59% of patients treated with PCI were still symptomatic at 3 months of follow-up.[5] In the ISCHEMIA trial, which enrolled a highly selected population with moderate-to-severe ischaemia, SAQ scores indicated that only a minority of patients experienced daily angina.[13] These findings suggest

that not all residual or recurrent symptoms warrant aggressive diagnostic or therapeutic pursuit, particularly when they are mild and do not significantly impair quality of life. Importantly, patients with typical and more severe angina are most likely to benefit from PCI in terms of symptom relief.[4,15,16] For example, a sub-analysis of the ORBITA-2 trial has shown that patients with Rose angina (i.e. exertional chest pain resolved with rest) and guideline-based 'typical' angina, are most likely to benefit from PCI for symptoms management.[16]

Post-PCI angina is associated with higher rates of anxiety, depression, lower physical functioning, and other psychological problems when compared with individuals without recurrent or persistent angina symptoms[17]—factors that may also interact in a complex, bidirectional manner with the perception and experience of angina. A relationship between post-PCI angina and increased mortality has been reported in one study.[18] Consistently, in the Physiologic Assessment of Coronary Stenosis Following PCI (DEFINE PCI) study a post-PCI instantaneous wave-free ratio (iFR) < 0.95 was linked to less improvement in anginal symptoms and higher rates of adverse cardiovascular events.[19] Additionally, patients with post-PCI angina consume considerable health care resources, causing an estimated costs excess of $14 524 at 1 year and $19 977 at 3 years after PCI.[10]

In summary, contemporary data suggest that post-PCI angina occurs frequently, has a major impact on quality of life and prognosis, and constitutes an important burden for healthcare systems.

Table 1 Distinct pathophysiological mechanisms of persistent vs recurrent post-PCI angina

Persistent angina	Recurrent angina
Incomplete revascularization (intended incomplete revascularization, geographic miss, disease not amenable to PCI)	Stent failure (e.g. restenosis, stent thrombosis)
Residual ischaemia (low physiological gain or suboptimal post-PCI physiological result)	CAD progression in previously non-obstructed segments (e.g. due to inadequate secondary prevention)
Pre-existing CMD or vasomotor disorder	Delayed-onset vasomotor disorder (e.g. stent-induced endothelial dysfunction or spasm)
Procedure related complications (e.g. untreated dissections, side-branch compromise, pericarditis, procedural myonecrosis, stretch pain)	Non-cardiac causes (e.g. psychogenic, gastrointestinal or musculoskeletal)

CAD, coronary artery disease; CMD, coronary microvascular dysfunction; PCI, percutaneous coronary intervention.

Pathophysiological mechanism of post-PCI angina

The pathophysiologic mechanisms of post-PCI angina are multifactorial and may differ depending on the timing of symptom recurrence. It is clinically useful to distinguish between angina that persists immediately after PCI (persistent angina) and that which recurs following an initial angina-free period (recurrent angina). While both may share some overlapping features, their predominant causes often differ, as summarized in *Table 1*.

Epicardial flow obstruction (obstructive causes)

Incomplete revascularization and disease progression

Complete revascularization, defined as successful treatment of all flow-limiting coronary stenoses, is a theoretical objective of PCI. In practice, this objective is frequently not achieved, due to either conscious or unconscious reasons. Incomplete coronary revascularization may be the result of a conscious decision, like following a culprit-only PCI strategy in patients with ACS and multivessel disease or in not addressing chronic total occlusions (CTOs).[3,20,21] Else, it may be the result of incomplete treatment of lesions or from not having addressed the functional impact of angiographically mild stenoses or diffuse disease.[3,20,21]

Importantly, reliance on angiographic guidance alone often creates an illusion of revascularization completeness, while leaving ischaemia-generating lesions unaddressed.[22] Studies based on longitudinal vessel interrogation with pressure guidewires or functional coronary angiography, identified residual flow-limiting disease immediately after PCI in up to a quarter of DES-treated vessels.[21,23] The DEFINE PCI study showed that a residual post-PCI iFR < 0.95 was significantly associated with a higher angina burden at 1-year follow-up.[19] The Angio-Based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation (HAWKEYE) study further demonstrated that in most cases, flow limitation after PCI was caused by focal or diffuse patterns of disease located out of the stented segment (32% and 34%, respectively).[23] The stented site alone accounted for residual flow limitation in only 13% of cases, potentially linked to suboptimal stent implantation.[23] The use of intracoronary imaging for PCI guidance may improve the completeness and quality of revascularization, particularly in complex lesion subsets, and is now supported by a Class IA recommendation in current guidelines.[7]

Residual flow limitation can also be caused by side-branch stent jailing after PCI, although the overall contribution to post-PCI angina is unclear. At follow-up, occurrence of side branch ostial diameter stenosis >50% after a provisional stenting strategy is not rare (39%); yet, only a minority (8%) present ischaemic FFR values in the pinched side-branch.[24] As these values are derived from trial data, it is unclear whether a similar prevalence of side-branch compromise after bifurcation PCI occurs in real world practice.

Finally, progression of obstructive coronary artery disease (CAD) may occur after the index PCI as part of the natural history of atherosclerosis, particularly in cases of suboptimal secondary cardiovascular prevention.[25]

Stent failure

Another important cause of post-PCI angina is stent failure, which encompasses several mechanisms leading to tissue ingrowth (in-stent restenosis), stent under expansion, fracture, or thrombosis, causing luminal loss in the segment treated with PCI. Neointimal fibrous hyperplasia, the primary mechanism of bare metal stent restenosis, typically develops within the first 6 months as a response to PCI-associated injury.[26] In-stent neoatherosclerosis involves not only smooth muscle cells but also macrophages, lipid deposits, and even calcification.[27,28] While neoatherosclerosis typically occur also years after bare metal

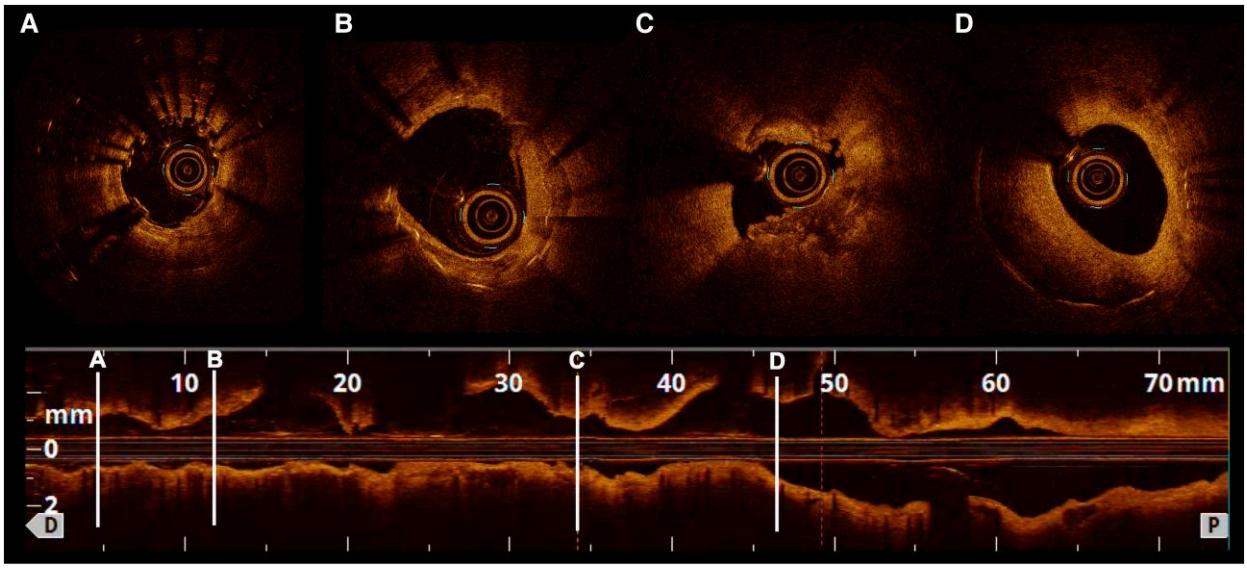

Figure 1 Optical coherence tomography illustrating different patterns of in-stent restenosis and progressive coronary artery disease in an individual patient with recurrent post–percutaneous coronary intervention angina, previously treated with two not overlapped drug-eluting stent in the right coronary artery. Description: (*A*) severe distal stent underexpansion; (*B*) calcified neo-atherosclerosis; (*C*) distal edge plaque progression with nodular calcification; (*D*) layered in-stent neointimal growth. DES, drug eluting stent; OCT, optical coherence tomography; PCI, percutaneous coronary intervention

stent implantation, pathological studies have demonstrated its presence in early phases of the healing process after first-generation DES implantation,[29] and it may also affect to a lesser degree second-generation DES.[27] Of note, different pathological mechanisms may contribute to the development of in-stent restenosis in the individual patient (*Figure 1*).

Finally, stent thrombosis typically presents as ACS, but occasionally may debut with subacute symptoms, probably as a result of episodic changes in luminal morphology caused by thrombus or associated vasospasm.[30]

Coronary artery dissection

Untreated coronary dissections generated during PCI may potentially be flow-limiting and account for persisting symptoms after PCI.[31] Residual dissections are more likely to occur in native vessel segments treated with drug coated balloon (DCB) alone, although its contribution to post-PCI angina remains unknown.

Epicardial vasomotion disorders and microvascular domain (non-obstructive causes)

Non-obstructive causes of myocardial ischaemia (INOCA) involved in post-PCI angina are frequently overlooked.[32] Anginal symptoms in patients in whom PCI is indicated on clinical grounds are not necessarily the result of epicardial flow-limiting obstructions. In the ORBITA-STAR (Symptomatic trial of Angina Assessment Before Revascularization), a significant number of patients did not experience angina while epicardial vessel obstruction was caused by balloon inflation.[33] Of note, PCI was less effective in relieving angina in patients in whom PCI failed in triggering similar anginal symptoms to those justifying the intervention, while patients developing similar anginal symptoms were more likely to obtain symptomatic relief at follow-up. Two important lessons derived from these observations are the following: (i) non-obstructive cause of ischaemia may coexist with epicardial stenosis, justifying persistence of symptoms after successful PCI and (ii) patients in whom PCI is performed on grounds of pressure-wire values may still have post-PCI angina after the intervention. The Advanced Invasive Diagnosis for Patients with Chronic Coronary Syndromes Undergoing Coronary ANGIOgraphy (AID-ANGIO) study has shown that 51% of patients with epicardial intermediate stenosis have an FFR > 0.80 with a subtended microvascular or vasomotor abnormalities accounting for patients' symptoms.[34] Patients with recurrent angina post-PCI have been found to have higher index of microcirculatory resistance (IMR) and lower coronary flow reserve (CFR) 6–12 months after the index procedure than control subjects who remained asymptomatic after PCI.[35]

The reasons why INOCA may coexist with the presence of epicardial stenosis are multiple. Chronic exposure to pressure overload or persistent vasodilation in the setting of hypertension, left ventricular hypertrophy and even epicardial stenosis may lead to structural remodelling of the coronary microvasculature—such as arteriolar medial hypertrophy and perivascular fibrosis.[36] These maladaptive remodelling responses increase baseline microvascular resistance,[37] favour chronic hyper-reactivity and limit vasodilatory reserve,[38] all contributing factors to myocardial ischaemia, particularly during stress. These abnormalities may be pre-existing to PCI, and there is no definite evidence suggesting that they resolve once epicardial stenosis are tackled with stenting or after setting cardiovascular risk factors treatment. In this complex context, myocardial resistance reserve (MRR) has emerged as a promising index to characterize microvascular function independently of epicardial disease severity.[39] It remains unknown whether this phenomenon can be triggered also by DES implantation, in a similar fashion as described below for DES-induced endothelial dysfunction. Capillary

rarefaction may also be pre-existing to PCI, causing impaired microcirculatory conductance and myocardial ischaemia.[37] Collapse of compressible elements of the coronary circulation (capillaries and venules) and, consequently, reduction in myocardial blood volume may occur as a consequence of extravascular compression caused by intra-myocardial haemorrhage or raised left ventricular filling pressures.[40]

Vasomotor disorders may affect both the epicardial vessels and the microcirculation, and may be pre-existing or secondary to PCI. Vasodilatory dysregulation may be pre-existing to PCI and cause paradoxical vasoconstriction of arterioles in response to increased myocardial oxygen demands.[41] Persistent endothelial dysfunction has been documented after PCI in the myocardial territory subtended to CTO.[42] Coronary spasm in major epicardial vessels may occur as a consequence of endothelial dysfunction related to atherosclerotic disease or as a separate vasomotor disorder. Pre-existing coronary spasm may lead to stenting of epicardial lesions while missing the dominant cause of angina and explain the cause of post-PCI angina with an electrocardiographic (ECG) expression of coronary spasm triggered by stimuli like cold exposure or exercise.[43] PCI-induced coronary spasm has also been proposed as a mechanism of angina after DES implantation.[44] Vasomotor disorders in coronary segments adjacent to the site of DES implantation have been disclosed using pacing, exercise, or acetylcholine challenge, both with first- and second-generation DES.[45,46] Proposed mechanisms include defective endothelial DES coverage, persistent inflammation, hypersensitivity reaction to eluting polymer or downstream drug elution. Finally, it is important to remember that individuals affected with heart failure with preserved ejection fraction (HFpEF) frequently describe symptoms resembling angina,[47] even in the absence of coronary stenoses. Various studies have demonstrated that coronary microvascular dysfunction is present in up to 80% of the patients with HFpEF,[48,49] which may justify the existence of ischaemia of non-obstructive origin in this condition. This fact has to be kept in mind when considering PCI to treat coronary stenoses in patients with HFpEF.

Related to both obstructive and non-obstructive causes (mixed)

Myocardial bridge

The presence of myocardial bridges (MB) should also be considered at the time of assessing post-PCI angina as they may trigger ischaemia by impairing diastolic conductance[50] and constitute a frequent seat of vasomotor disorders.[51] Myocardial bridge is associated with endothelial dysfunction that predisposes to paradoxical vasoconstriction during stress, particularly within the intramyocardial segment, where impaired nitric oxide bioavailability and heightened vasoreactivity may coexist.[51] The presence of MB distal to the site of stent implantation has been associated with worse long-term outcomes,[52] that may be associated to (i) low wall shear stress proximal to the MB segment may promote atherosclerotic plaque formation and progression; (ii) the Venturi effect, resulting from dynamic compression within the MB, may lower pressure in the proximal vessel, adversely affecting stent haemodynamics; and (iii) during stress or exercise, coronary steal from side branches proximal to the MB, further contributing to myocardial ischaemia.[53]

Non-anginal chest pain

Chest pain post-PCI is not always anginal in origin. Cardiac causes such as post-procedural pericarditis, procedural myonecrosis, and stent overstretch can present with chest discomfort indistinguishable from ischaemia.[7] These are frequently under-recognized sources of post-PCI symptoms that can lead to unnecessary repeat procedures if misinterpreted. In particular, stent overstretch or adventitial irritation from oversized stents or aggressive post-dilation can produce prolonged, non-ischaemic chest pain despite optimal PCI results.[54]

Additionally, numerous non-cardiac pathologies that cause chest pain, including respiratory, musculoskeletal, gastrointestinal and psychological causes, may influence the decision to perform PCI in patients with coronary stenoses. Psychogenic chest pain after PCI has been related to higher baseline depression scores obtained before PCI.[55]

PCI-related factors contributing to anginal symptom relief

It is also worth considering how coronary physiology assessment may be used to identify patients who are more, or less, likely to achieve symptomatic improvement following PCI. In the post-PCI angina substudy of the Trial of Angiography vs pressure-Ratio-Guided Enhancement Techniques—Fractional Flow Reserve (TARGET-FFR) trial, delta FFR emerged as the sole independent predictor of post-PCI angina at 3-month follow-up. Those with more severe physiological stenosis (lower baseline FFR) achieved greater FFR gains and were less likely to have residual angina. In this study, post-PCI IMR and CFR did not differ between those with or without residual symptoms, indicating the symptoms in those with persistent/recurrent post-PCI angina were not driven by a higher incidence of microvascular dysfunction.[56] Similarly, in the ORBITA-2 trial, a greater depth of physiological abnormality (i.e. lower FFR/iFR) was associated with greater symptom improvement following PCI. Notably, this relationship was independent of baseline symptoms severity.[57] Additionally, residual angina post-PCI was almost twice less common in patients with a high pullback pressure gradient, indicative of focal disease.[58]

Diagnosis of post-PCI angina

All the above outlines the diagnostic conundrum of post-PCI angina, which may result from multiple causes. A diagnostic workflow for patients with suspected post-PCI angina is proposed in *Figure 2*.

The 2024 European Society of Cardiology (ESC) Guidelines for CCS emphasize the need to move away from the 'typical vs atypical' classification of angina symptoms and instead encourage a thorough, descriptive assessment of chest pain characteristics, including precipitating factors (e.g. exertion, emotional stress), relieving factors (e.g. nitrates), and associated symptoms.[7] This approach is particularly important to differentiate post-PCI angina from non-cardiac chest pain, identify underlying mechanisms and potential predictors of residual symptoms.[7] For instance, patients with a history of atrial fibrillation, prior myocardial infarction or PCI, active smoking, and higher body mass index have been associated with an increased risk of residual symptoms after PCI.[56] The characteristics of chest pain (persistent vs recurrent) may point towards different pathophysiological mechanisms of post-PCI angina. The presence of an angina-free period of <1 year between the index PCI and the reappearance of anginal symptoms similar to the pre-existing ones may raise the suspicion of restenosis or CAD progression. The likelihood of post-PCI angina caused by progression of obstructive disease, either in PCI target or non-target vessels, increases with time.[59] Conversely, persistent symptoms in the early post-PCI period may suggest unrecognized INOCA at the time of the index procedure. Compliance to medical treatment after PCI should be carefully assessed, as discontinuation might facilitate stent failure, progression of obstructive disease and persistence of symptoms.[60] Optimal control of cardiovascular risk factors, such as diabetes,

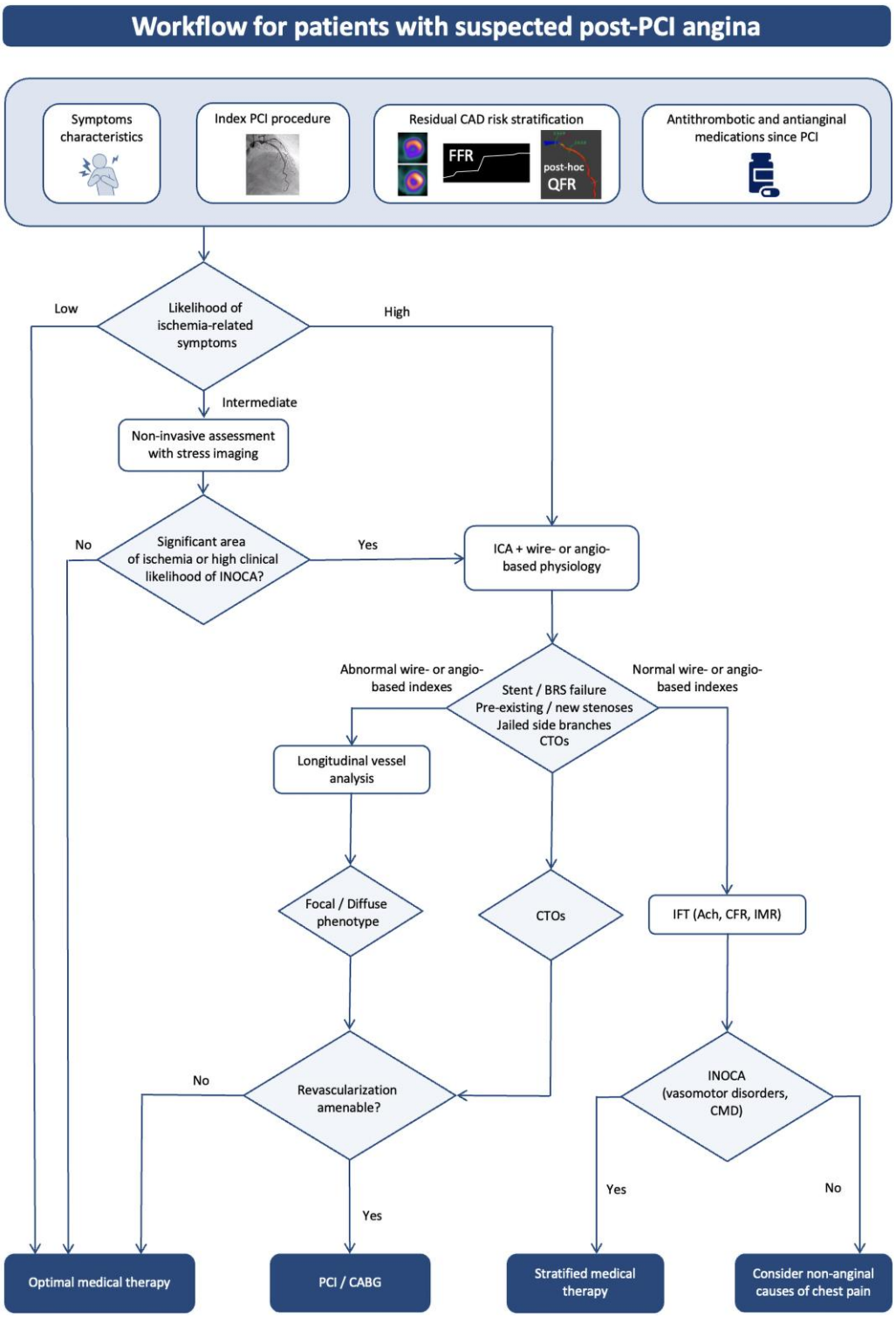

Figure 2 Workflow for patients with suspected post–percutaneous coronary intervention angina. Ach, acetylcholine; BVS, bioresorbable vascular scaffold; CABG, coronary artery by-pass grafting; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CTO, chronic total occlusion; FFR, fractional flow reserve; ICA, invasive coronary angiography; IFT, invasive functional tests; IMR, index of microvascular resistance; INOCA, myocardial ischaemia with no obstructive coronary arteries; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio

is critical due to their role in both obstructive and non-obstructive causes of post-PCI angina.[7] Nevertheless, antianginal therapy and OMT remain markedly underutilized. In the ISCHEMIA trial, only 25% of patients achieved all guideline-directed medical therapy goals,[61] while registry data revealed a low mean number of antianginal drugs (1.4) among post-PCI patients.[62]

High risk of thrombosis and/or restenosis related to the index PCI should also be identified, including multiple stents or use of bioresorbable vascular scaffold, left main or proximal left anterior stent, multivessel PCI, long lesion lengths, and complex lesions.[63]

Relief in angina in patients with multivessel disease undergoing PCI relies on the degree of revascularization completeness. Analysis of the index PCI should include the calculation of the residual SYNTAX score to quantify incomplete revascularization.[64] Non-treated CTO are a frequent cause of incomplete revascularization[65] not seldom due the assumption of absence of myocardial viability due to regional hypo- or akinesia. Yet, recent studies suggest that, when based on the presence of myocardial ischaemia shown by positron emission tomography, CTO revascularization is associated with a significant improvement in myocardial perfusion.[66,67] This evidence may challenge the value of more conservative indices of myocardial viability and provide indirect support to trials demonstrating the superiority of PCI over medical treatment in terms of angina control in patients with CTO.[68] Physiology-based studies have also shown a time-dependent increase in myocardial blood flow once the CTO has been successfully opened.[69]

Angiographic examination of the result of PCI should include assessment of side branches jailed or occluded by the implanted stent. In provisional stenting techniques, the need for side branch rescue can be safely guided by FFR or iFR assessment of the jailed branch.[24,70,71]

Whenever available, FFR or iFR data on non-treated stenosis should be integrated in assessing the residual ischaemic burden. Angiography-based functional assessment of the result of the index PCI using quantitative flow ratio or similar functional angiography indices may identify the existence of residual flow-limiting disease, providing insights on the potential of correction with repeat PCI based on diffuse or focal haemodynamic phenotypes (*Figure 3*). In this regard, the HAWKEYE study showed that lower values of quantitative flow ratio ($\leq$0.89) after PCI was a predictor of subsequent adverse events.[23]

Most patients with post-PCI angina present as a CCS. In patients with equivocal symptoms stress, echocardiogram is recommended, while exercise treadmill test may be used only as an alternative if the former is not available.[7,72] Radionuclide studies and stress cardiac magnetic resonance imaging can be particularly useful for more complex cases, such as those with prior myocardial infarctions, complex revascularization, left ventricular dysfunction, or suspected coronary microvascular dysfunction.[7] By providing accurate measurements of coronary flow reserve, positron emission tomography may provide information on both obstructive and non-obstructive causes of post-PCI angina. However, their widespread use is limited by cost and availability. While coronary computed tomography (CT) angiography is growingly used as the first test to diagnose epicardial coronary disease, its use in post-PCI angina is limited by the presence of stents and more extensive atheromatosis with frequent calcifications, all hampering image interpretation.[73,74] New CT modalities including photon counting and CT-FFR may contribute to a wider use of this method in patients with previous interventions.[75]

Direct referral for coronary angiography may be considered for patients with severe angina, provided that physiological assessment of haemodynamic stenosis significance and assessment of microvascular function/coronary spasm is available in the catheterization laboratory.[7,72] Since up to a third of post-PCI patients exhibit residual flow-limiting disease on longitudinal physiology analysis,[21,56] pressure guidewire interrogation of major coronary arteries should be considered at the time of repeat angiography. Intracoronary pressure mapping with hyperaemic or non-hyperaemic indices may outline which coronary segments contribute to impaired vessel conductance, avoiding the occurrence of anatomical-physiological mismatch should a new PCI procedure be considered.[7] Intracoronary imaging, particularly optical coherence tomography, may provide valuable clues on the substrate of stent failure.[26]

Since post-PCI angina may result from a variety of overlapping mechanisms, selecting the appropriate tool requires a full understanding of the underlying pathophysiology as each test interrogates different vascular domains. Pre-existing or PCI-induced abnormal vasomotor responses can be explored with the intracoronary acetylcholine (Ach) test, which assesses endothelium dependent coronary function allowing a diagnosis of either epicardial or microvascular spasm on the grounds of anginal symptoms, ECG ischaemic changes and/or changes in epicardial vessel diameter (*Figure 4*).[34,44] Current clinical practice guidelines recommend also endothelium independent coronary function testing using CFR guidewire-based and/or microcirculatory resistance measurements in patient with persistent angina despite therapy since a microvascular origin of angina is possible.[7] This may reflect either functional abnormalities (e.g. impaired vasodilation, CFR < 2.0) and/or structural alterations (e.g. capillary rarefaction or microcirculatory remodelling, IMR > 25 unit).

MB may generate myocardial ischaemia through obstructive and vasomotor mechanisms. The former can be assessed non-invasively with dobutamine echocardiography,[76] or invasively with diastolic FFR, resting flow ratio, iFR measurements during inotropic simulation with dobutamine. However, dobutamine primarily increases inotropism and heart rate, and may not fully replicate exercise-induced vasomotor dysfunction. To better evaluate the vasomotor component, Ach test can be used.[51,77,78]

Table 2 summarizes the pathophysiological mechanisms and diagnostic methods outlined in the previous paragraphs.

Angina post-PCI: secondary prevention and treatment

From all the above discussed, it follows that the first step in preventing post-PCI angina is to improve the planning of coronary interventions. *Figure 5* summarizes key aspects of such approach.

Structured anamnesis and angina assessment, along with adequate review of previous PCI and non-invasive tests, are essential in preventing post-PCI angina.

Lifestyle modification, control of CAD risk factors, evidence-based pharmacological therapy patient education, and revascularization are key in controlling symptoms and reducing the occurrence of cardiovascular events of patients with CCS. In accordance with current guidelines recommendations, PCI should be considered either to manage angina, particularly when medical treatment proved non-effective, or to improve patient prognosis in specific scenarios including left main stem or proximal left anterior descending artery disease, multi-vessel disease with impaired left ventricular dysfunction, last patent coronary artery stenosis, or high ischaemic burden.[3]

Recent findings from the ORBITA-2 trial highlight the importance of establishing a clear causal relationship between epicardial stenosis, myocardial ischaemia, and symptoms prior to revascularization.[79] If symptoms and ischaemia are disconnected, the risk of persistent symptoms after PCI increases significantly. This underscores the importance of integrating functional assessment into pre-PCI planning, especially when symptom burden is disproportionate to angiographic findings. Additionally, planning of PCI with image- or wire-based physiology

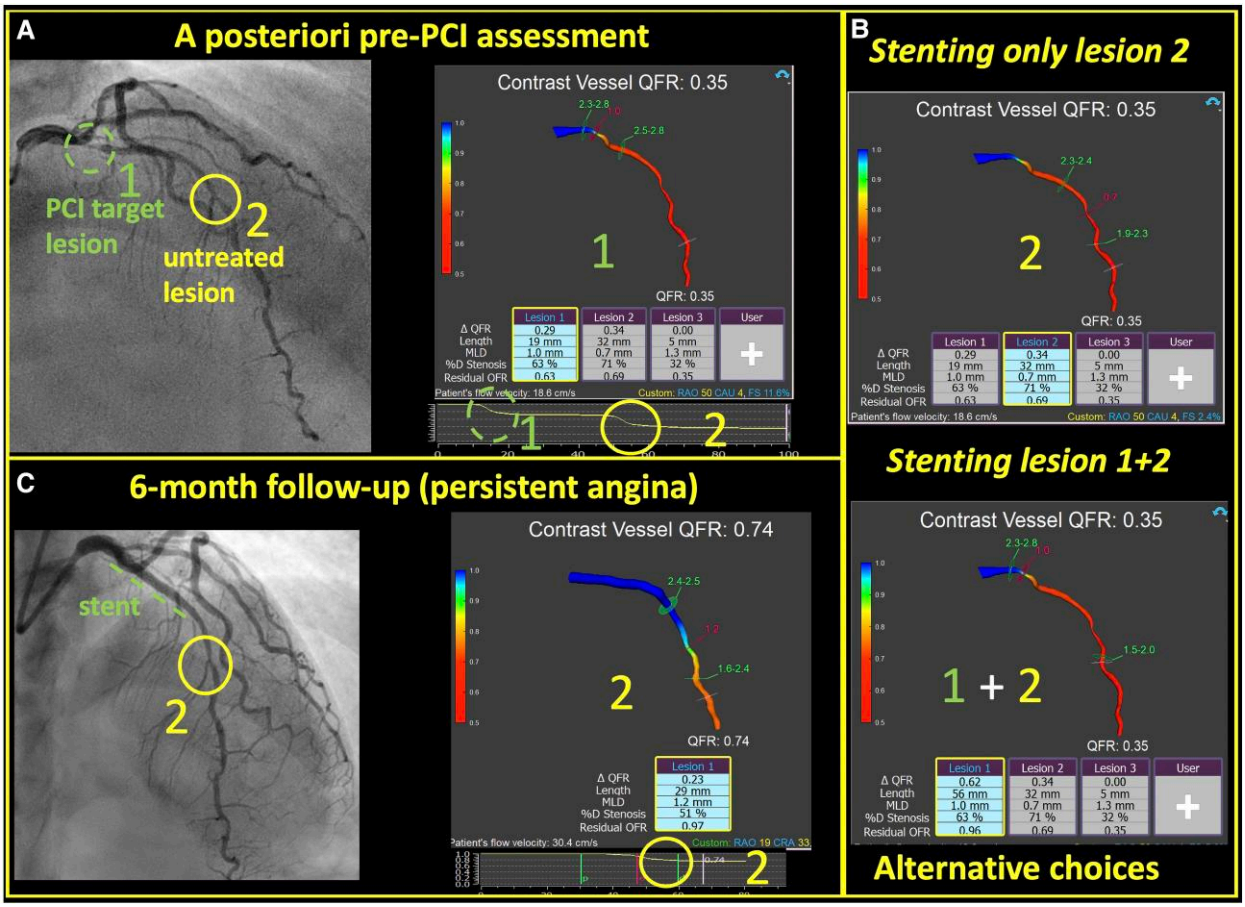

Figure 3 Assessment of a patient with persistent angina with functional coronary angiography. Case description: A 67-year-old-woman with persistent post–percutaneous coronary intervention angina unrelated to efforts was admitted to the cardiology department because of worsening of symptoms 6 months after the index procedure. The patient had been treated with a drug eluting stent implanted in the proximal left anterior descending artery segment based on visual inspection of the coronary angiogram. As a first step in investigating the potential causes of persisting angina, a review of the angiograms obtained over the index percutaneous coronary intervention (*a posteriori* assessment) was performed using 3D quantitative flow ratio (*A*). The overall quantitative flow ratio was haemodynamically significant (0.35) (*A*, lesions 1 and 2), thus confirming the existence of flow-limiting disease prior to percutaneous coronary intervention. Yet, longitudinal physiological assessment revealed the presence of two functionally significant stenoses in the left anterior descending artery accounting for the abnormal quantitative flow ratio value: (i) a proximal left anterior descending artery stenosis (*A*, lesion 1), which was the lesion treated with percutaneous coronary intervention and (ii) a mid–left anterior descending artery stenosis (*A*, lesion 2), which was left untreated. Then, the functional impact of the prior percutaneous coronary intervention was simulated with a dedicated quantitative flow ratio tool. According to the simulation performed on pre–percutaneous coronary intervention angiograms, stenting only the proximal left anterior descending artery lesion would not be enough to restore epicardial conductance to non-ischaemic levels (residual quantitative flow ratio 0.63, *A*, lesion 1) due to the significant haemodynamic effect of the mid left anterior descending artery stenosis. Treatment of both lesions would have been required to achieve optimal post–percutaneous coronary intervention functional results (residual quantitative flow ratio 0.96, *B*, lesions 1 + 2). Based on the findings of the quantitative flow ratio analysis described above, a new invasive study was scheduled (*C*). Coronary angiography ruled out restenosis as a cause of the persistent anginal symptoms. Functional assessment of the residual mid–left anterior descending artery stenosis confirmed that it was flow limiting (quantitative flow ratio 0.74) (*C*, lesion 2). Quantitative flow ratio based percutaneous coronary intervention simulation predicted a good functional result associated to stenting of the mid left anterior descending artery stenosis (residual quantitative flow ratio 0.97). Implantation of a new drug eluting stent in that lesion was performed uneventfully and was associated with relief of the anginal symptoms at 3 months follow-up. LAD, left anterior descending artery; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio

tools allow simulation of the impact of planned PCI on coronary haemodynamics.[80] By doing so, the effectiveness of PCI to normalize coronary haemodynamics can be tested before embarking in the procedure, with re-consideration of PCI in those cases in which the pattern of CAD is judged not amenable for PCI, for example in cases with diffuse disease. Optimization of device implantation with intracoronary imaging or digital enhancement of stent images should be considered whenever possible.[81,82] Final interrogation of the treated vessel to assess haemodynamic result may be helpful in understanding the functional result of the intervention, as the post-stent implantation FFR/iFR values convey prognostic information.[21,83] Treatment of stent failure should include, whenever possible, guidance with intracoronary

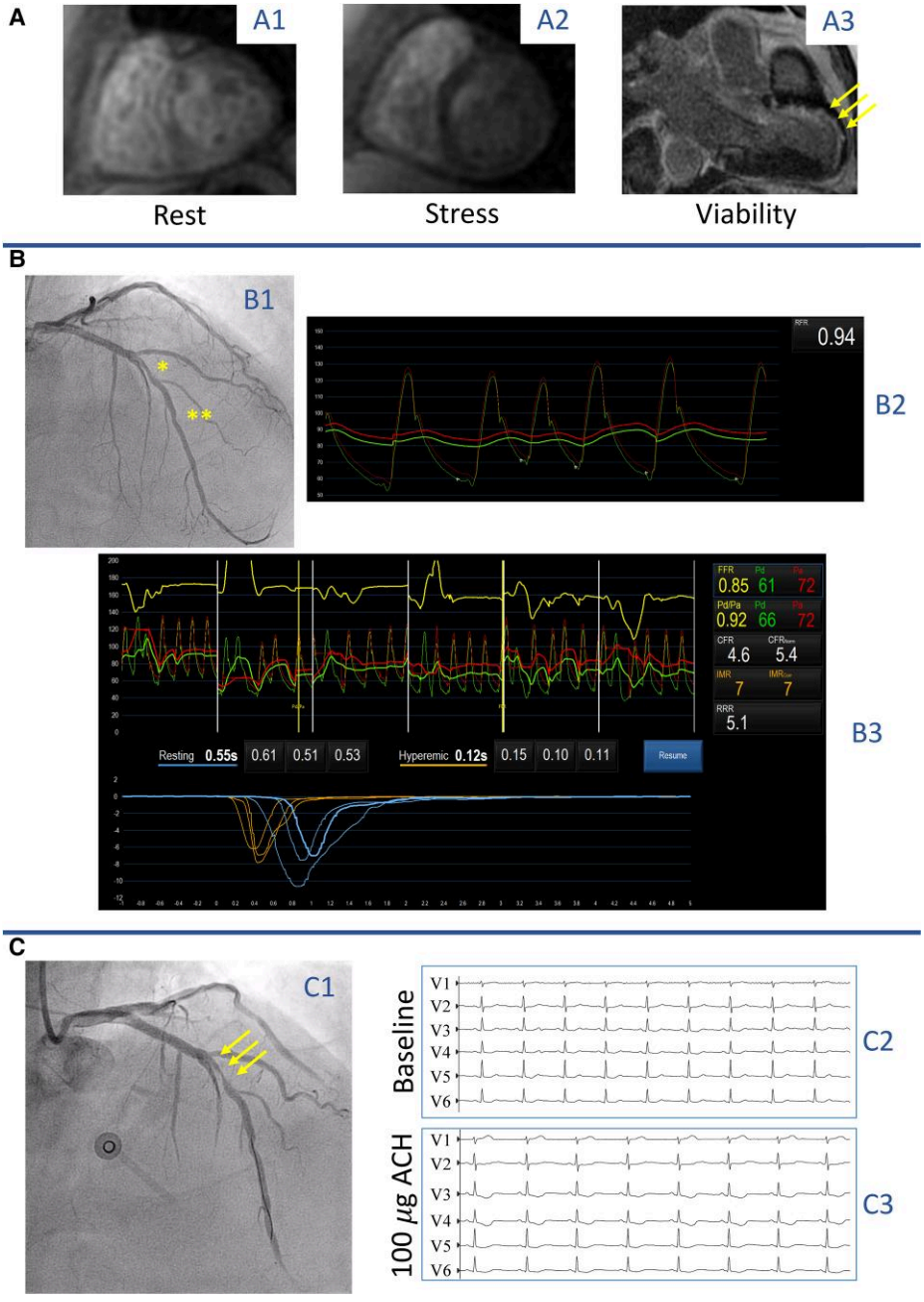

Figure 4 Assessment of non-obstructive mechanisms of myocardial ischaemia in a patient with persistent angina after percutaneous coronary intervention. Case description: A 72-year-old male with a history of episodes of resting angina underwent stent implantation on proximal left anterior descending artery. Due to symptoms persisting 2 years after percutaneous coronary intervention, he underwent a stress-magnetic resonance imaging; (*A*) that revealed anterior and anteroseptal hypokinesia and perfusion defects with stress (A2), not present at rest (A1). About <50% subendocardial late gadolinium enhancement in the anterior wall, suggesting myocardial viability of these segments (A3). Subsequently, he underwent coronary angiography, observing two 50% diameter stenosis in the mid-proximal and in the mid-distal segments of the left anterior descending artery, respectively (B1). Functional significance of epicardial stenoses was invasively ruled out by a resting full-cycle ratio of 0.94 (B2) and fractional flow reserve 0.85 (B3). Interrogation with intracoronary thermodilution revealed a normal endothelium-independent microvascular function (coronary flow reserve >2, index of microcirculatory resistance <25) (B3). Intracoronary administration of acetylcholine (*C*) elicited a focal spasm in the mid left anterior descending artery segment (C1) associated to ischaemic electrocardiographic changes in the anterior ECG leads (C3) and anginal symptoms similar to those persisting after percutaneous coronary intervention. Coronary spasm, ECG alterations and anginal symptoms were relieved by the administration of 200 μg of intracoronary nitrates. Based on these findings, stratified treatment for coronary vasomotor disorders was initiated. Ach, acetylcholine; CFR, coronary flow reserve; IMR, index of microcirculatory resistance; LAD, left anterior descending artery; LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; RFR, resting full-cycle ratio

Table 2 Management of the potential pathophysiological mechanisms of post-PCI angina

Pathophysiological mechanism	Diagnosis	Treatment plan
Epicardial flow obstruction domain (obstructive causes)		
Incomplete revascularization	• Review of previous coronary angiography or CCTA with functional coronary angiography (e.g. QFR or CT-FFR) to rule out residual/untreated obstructive disease. • Coronary angiography with invasive intracoronary imaging or physiology, included longitudinal physiological vessel analysis to differentiate focal vs diffuse disease.	Coronary revascularization (PCI or CABG) if amenable (focal disease) or optimal medical therapy (diffuse disease).
Progression of native coronary artery disease	• Review of previous coronary angiography/CCTA assessing the progression of native CAD in segments different from those treated with index PCI. • Invasive or non-invasive coronary physiology for intermediate lesions (50–90%).	Coronary revascularization (PCI or CABG) and/or optimal medical therapy.
Stent failure: in-stent restenosis	• Coronary angiography: luminal narrowing ≥70% in the stented portion of the artery and within 5 mm of stent edges. • Invasive or non-invasive coronary physiology for luminal narrowing ≥50%. • Intracoronary imaging (IVUS/OCT) should be used to assess the underlying mechanism of in-stent restenosis.	Optimization of previous stent implantation via intracoronary imaging, PCI (drug eluting balloon angioplasty or repeated stenting) or CABG.
Stent failure: stent thrombosis	• Coronary angiography: presence of intracoronary thrombus within 5 mm of the stent edges and typical clinical presentation as an ACS. • Intracoronary imaging (IVUS/OCT) should be used to assess the underlying mechanism of in stent thrombosis.	PCI and/or thrombus aspiration, optimization of previous stent implantation via intracoronary imaging and antiplatelet therapy adjustment (+/- glycoprotein IIb/IIIa inhibitors).
Coronary artery dissection (previously untreated or spontaneous)	• Review of previous coronary angiography or CCTA. Coronary artery dissection is defined as a disruption of the coronary artery wall, resulting in separation of the inner intimal lining from the outer vessel wall. • Coronary angiography and/or intracoronary imaging (IVUS preferred to avoid hydraulic propagation of dissection).	Preferentially optimal medical therapy. In case of proximal vessel involvement, haemodynamic instability, or refractory chest pain, consider coronary revascularization (PCI or CABG).
Epicardial vasomotion disorders and microvascular domain (non-obstructive causes)		
Microvascular derangements	• Coronary angiography and functional evaluation of the microcirculatory domain (bolus/continuous thermodilution or Doppler wire): o Reduction of coronary flow reserve (CFR < 2) in the absence of obstructive epicardial stenosis, or increase in the index of microvascular resistance (IMR > 25 units) or the hyperaemic myocardial resistance (HMR > 2.5 mmHg/cm/s).	Optimal medical therapy including beta-blockers as first line. Management of concomitant cardiovascular risk factors.
Epicardial or microvascular spasm	• Coronary angiography with provocative test (typically acetylcholine): reproduction of symptoms with accompanying ischaemic ECG changes with (epicardial spasm) or without (microvascular spasm) transient total or subtotal vessel occlusion in response to acetylcholine.	Optimal medical therapy, including calcium channel blockers and long-acting nitrates as first-line. Management of concomitant cardiovascular risk factors.
Obstructive and non-obstructive causes (mixed)		
Myocardial Bridging	• CCTA or coronary angiography: systolic narrowing or 'milking' of the vessel with complete/partial decompression in diastole. • Intracoronary imaging: half-moon sign on IVUS or a fusiform, signal-poor border with systolic compression on OCT.	Optimal medical therapy (first-line beta-blockers, unless vasomotor disorders). In selected cases: PCI/CABG or myotomy.

Continued

Table 2 *Continued*

Pathophysiological mechanism	Diagnosis	Treatment plan
	• Functional evaluation: o Non-invasive imaging (e.g. dobutamine stress echocardiography or MRI) with segmental perfusion defect. o Invasive diastolic FFR, or non-hyperaemic diastolic indices during inotropic stimulation (e.g. dobutamine): dFFR ≤ 0.76 or iFR ≤ 0.85. • Acetylcholine test to rule out vasomotor disorders in the intramyocardial coronary segment.	
Non-anginal chest pain (cardiac causes)		
Post-PCI pericarditis	• Clinical presentation: sharp or stabbing chest pain that worsens with breathing and changes with position, pericardial friction rub may be present. • ECG: PR depression, diffuse ST-segment elevation. • Elevated inflammatory biomarkers. • Transthoracic echocardiography may reveal a pericardial effusion.	Anti-inflammatory therapy (e.g. NSAIDs, or colchicine).
Procedural myonecrosis	• Mild-moderate post-PCI increasing of troponin without clinical signs of ischaemia (atypical chest pain that typically persists after PCI) or ECG changes. • Often associated with periprocedural complications such as side branch occlusion or distal embolization.	Supportive care.
Stretch pain	• Deep vessel wall injury during high-pressure stent implantation or use of large stent diameters may stimulate coronary adventitial nerve endings. • Diagnosis often clinical, sometimes supported by intracoronary imaging.	Supportive care.
Non-anginal chest pain (non-cardiac causes)		
Gastrointestinal	• Chest pain related to the meal or lying down, associated with acid reflux symptoms, may response to PPI trial. • Upper endoscopy if indicated.	PPI trial, dietary modifications, antacids.
Musculoskeletal	• Local tenderness on palpation, pain reproducible with movement or pressure.	NSAIDs, physical therapy and reassurance.
Respiratory	• Pleuritic chest pain related to breathing or dyspnoea. • Chest X-rays, D-dimer and/or CT scan based on suspicion.	Targeted therapy.
Psychogenic	• Psychological evaluation after excluding all the aforementioned possible causes.	Cognitive behavioral therapy, stress management, anxiolytics (if indicated).

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CCTA, coronary computed tomography angiography; CFR, coronary flow reserve; %DS, percentage diameter stenosis; ECG, electrocardiogram; iFR, instantaneous wave free ratio; FFR, fractional flow reserve; FFR-CT, fractional flow reserve-computed tomography; dFFR, diastolic fractional flow reserve; HMR, hyperaemic myocardial resistance; IMR, index of microcirculatory resistance; IVUS, intravascular ultrasound; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; OCT, optical coherence tomography; PPI, proton pump inhibitor; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio.

imaging. Correction of under-expansion of the previously implanted stent is mandatory as part of the treatment of stent restenosis. Potentially, features such as the presence of stent fracture might lead to treatment with DES, whereas situations such as the presence of jailed side branches or a fibromuscular neointima might be treated with DCB.[26]

The aims of the pharmacological management of CCS patients are also to obtain relief of symptoms and to prevent cardiovascular events. The latest ESC guidelines have also emphasized that there is no evidence of superiority amongst the anti-angina classes.[7] Regardless of whether the classification into two different level of therapy, they confirmed the need for a tailored approach, and advocated the early use of the so called 'second line drugs' along with the 'first line drugs', to ensure the appropriate treatment according to the patient's characteristics.[7]

In cases with ischaemia caused by obstructive disease, guidelines recommend a tailored therapy based on the patients´ phenotype. In general, beta-blockers are accepted as the first-line anti-ischaemic therapy and calcium channel blockers are recommended if beta-blockers are not tolerated or do no provide sufficient symptomatic control.

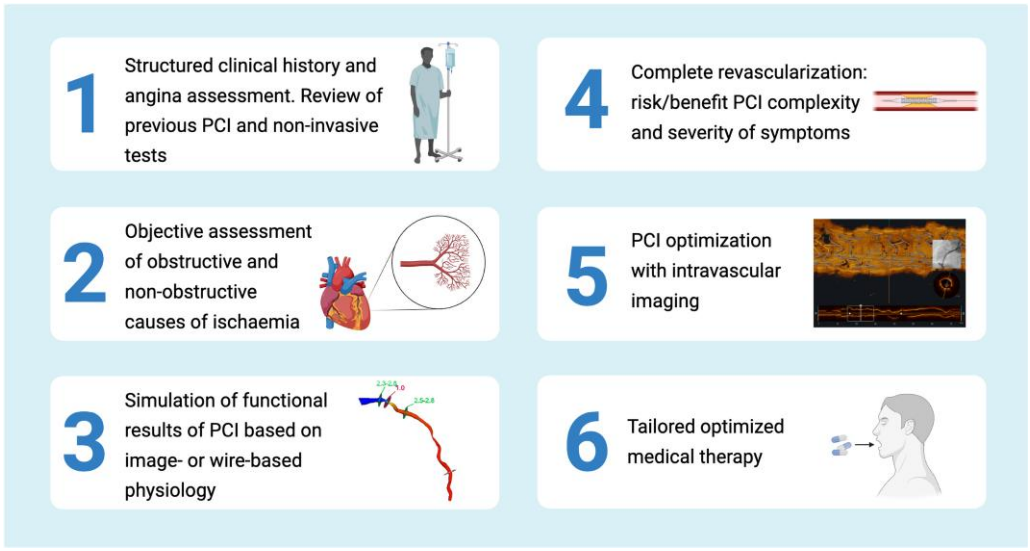

Figure 5 Key aspects related to prevention of the occurrence of post–percutaneous coronary intervention angina. PCI, percutaneous coronary intervention

Second line anti-ischaemic drugs include long-acting nitrates, ivabradine, nicorandil, trimetazidine, and ranolazine.[7,72] Drugs indicated for event prevention in CCS include low-dose aspirin, statins, and renin-angiotensin-aldosterone system blockers.[7,72] Exercise training and cardiovascular rehabilitation should also be encouraged since it increases exercise tolerance and quality of life also decreasing angina occurrence and myocardial ischaemia.[84] This finding is additionally confirmed by a *post hoc* analysis of the TARGET-FFR study, which found that engagement with/completion of cardiac rehabilitation programmes occurred more frequently in the group of patients who were free of angina at 3-month follow-up (86.2% vs 75%, $P = .03$).[56]

Patients with non-obstructive cause of myocardial ischaemia should receive counselling on lifestyle factors and maximal risk factor control, particularly through smoking cessation, drug-related cause detection and management.[7] Symptomatic treatment is empirical because of the limited knowledge of its causes and inconclusive results of therapeutic trials. Chronic prevention of epicardial coronary spasm is based on the use of calcium channel blockers and long-acting nitrates can be added in some patients to improve the efficacy of treatment.[85] Avoidance of beta-blockers is recommended as they might favour spasm by alpha-mediated vasoconstriction unopposed by beta-mediated vasodilatation.[86] In patients with microvascular angina, treatment should address any concomitant cardiovascular risk factors that may account for changes in microvasculature.[7,87] Statins are recommended due to their pleiotropic anti-inflammatory effect.[7,87] Angiotensin-converting enzyme inhibitors may improve microvascular function by counteracting the vasoconstrictor effects of angiotensin II and, thus, may improve symptoms and exercises tolerance.[7,87,88]

In selected patients with end-stage CAD, further PCI may no longer be indicated or technically feasible. These include cases with multiple layers of stents, markers of poor PCI durability (e.g. long-segment disease in small-calibre vessels, diffuse CAD, or diabetes mellitus), or conditions that contraindicate further intervention, such as high bleeding risk or frailty. In such patients, where durable PCI results are unlikely and procedural risks outweigh potential benefits, OMT remains the cornerstone.

However, in presence of long-lasting symptoms (>3 months) despite escalating medical therapy due to reversible myocardial ischaemia (refractory angina),[8] non-pharmacologic therapies should be considered.[89] The coronary sinus reducer has demonstrated its value in patients with refractory angina due to obstructive CAD not amenable with revascularization in two randomized, sham-controlled trials.[90,91] Other options —such as extracorporeal shockwave therapy, enhanced external counterpulsation, neuromodulation, and emerging cell-based therapies— may offer potential benefit in selected cases.[89]

In cases of non-cardiac chest pain, it is of utmost importance to make a correct diagnosis. For example, anxiety disorders may be relieved by benzodiazepines and psychotherapy, or gastro-intestinal pain by administration of antiproton pump.[8] Finally, psychosomatic causes of angina should be addressed by specific targeted therapies.

Conclusion

Evaluation of post-PCI angina must consider the evolving knowledge on ischaemic heart disease. The established practice of using angiography alone to define the procedural success of PCI has led to under recognition of this clinical conundrum as that outdated approach fails to consider the angiographically-inapparent causes of ischaemia, which may underlie a patient's symptoms. The assessment of the type and intensity of symptoms, existence of non-invasive evidence of ischaemia, and the results of physiology-based intracoronary studies (including post-PCI FFR and the assessment of microvascular function and coronary spasm) are critical in an effort to inform subsequent decisions. A more comprehensive perspective on the causes of angina in these patients may lead to a better diagnosis and invasive and non-invasive therapeutic management.

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Figure 5 was created with BioRender (licence to Marco Lombardi).

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

No data were generated or analysed for or in support of this paper.

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