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CLINICAL REVIEW
Controversies in cardiovascular medicine

Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization

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Persistence or recurrence of angina after a percutaneous coronary intervention (PCI) may affect about 20–40% of patients during short–medium-term follow-up. This appears to be true even when PCI is 'optimized' using physiology-guided approaches and drug-eluting stents. Importantly, persistent or recurrent angina post-PCI is associated with a significant economic burden. Healthcare costs may be almost two-fold higher among patients with persistent or recurrent angina post-PCI vs. those who become symptom-free. However, practice guideline recommendations regarding the management of patients with angina post-PCI are unclear. Gaps in evidence into the mechanisms of post-PCI angina are relevant, and more research seems warranted. The purpose of this document is to review potential mechanisms for the persistence or recurrence of angina post-PCI, propose a practical diagnostic algorithm, and summarize current knowledge gaps.

Keywords Coronary microvascular dysfunction • Coronary spasm • Coronary stenosis • Percutaneous coronary intervention • Stable angina

Introduction

Procedural success is routinely achieved in patients with obstructive coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI). In the current European Society of Cardiology guidelines on stable obstructive CAD, coronary revascularization has a Class 1, Level A recommendation on prognostic grounds for patients with left main stem disease or multivessel CAD, and also for symptoms in the presence of limiting angina or angina-equivalent, unresponsive to optimal medical therapy.[1] Persistence or recurrence of angina after PCI is well recognized and may affect about 20–40% of patients during short–medium-term follow-up.[2–7] This appears to be true even when PCI is 'optimized' using physiology-guided approaches [e.g. fractional flow reserve (FFR) or non-hyperaemic pressure ratio (NHPR)][8] and drug-eluting stents (DES) or stents with bioresorbable scaffolds.[9] Importantly, persistent or recurrent angina post-PCI is associated with a significant economic burden. Healthcare costs may be almost two-fold higher among patients with persistent or recurrent angina post-PCI vs. those who become symptom-free.[10] Furthermore, the role of PCI for symptom relief, when added to optimal medical therapy, remains a controversial issue.[11–14] In the ORBITA trial, the benefits of PCI compared with a 'sham control' placebo were unclear. One potential mechanism for persistent angina post-PCI identified by the investigators was microvascular angina,[2]

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although this trial has been criticized because of methodological limitations.[15]

The clinical importance of angina recurrence following successful PCI is evident from developments in clinical quality registries, where post-PCI angina is being utilized as a clinical performance marker for PCI.[16] Despite this, while prospective studies have documented that angina, including with inducible ischaemia, is a contributing factor in many patients with chest discomfort symptoms post-PCI,[17] few studies have systematically addressed the mechanisms responsible for the recurrent angina[18,19] and there are no comprehensive recommendations for its diagnosis or treatment.[1,20]

The purpose of this document, which expands and gives a global perspective to what we have previously published,[3] is to review potential mechanisms for the persistence or recurrence of angina post-PCI, propose a practical diagnostic algorithm, and summarize current knowledge gaps.

Mechanisms of persistent or recurrent angina after percutaneous coronary intervention

Elective PCI in patients with stable angina is routinely successful and procedure-related problems are uncommon. Procedural success reflects effective education and training, the availability of state-of-the-art stent technologies, use of adjunctive intravascular imaging and physiology techniques, and quality assurance.[21]

Despite procedural success, angina may persist or recur in a large proportion of patients, which is frustrating for patients and clinicians. In contemporary practice, clinicians are focused on identifying a 'flow-limiting' stenosis amenable to PCI with stents when sometimes other potential causes are relevant. This issue could be considered as 'detection bias'.

Yet, the pathophysiology of persisting or recurring angina after successful PCI is heterogeneous. Aside from non-cardiac causes of angina, structural and functional alterations in the coronary circulation may be implicated (*Table 1* and *Figure 1*).

Flow limiting epicardial obstructions

Stent thrombosis and in-stent restenosis are infrequent causes of recurrent angina and ischaemia after PCI in contemporary clinical practice with rates of stent thrombosis <1% at 1 year and 0.2–0.4% per year thereafter, and rates of clinically relevant in-stent restenosis of 5% at 1-year follow-up.[22] Recurrence rate of major adverse cardiac events due native vessel disease progression is <5% at 1-year follow-up,[23] although disease progression and cardiac events are higher in patients with diabetes.[24]

Persistence of angina caused by incomplete coronary revascularization may occur in up to 30% in the current era, although definitions of incomplete revascularization are heterogeneous.[25]

Other potential causes of angina post-PCI include diffuse atherosclerosis without a focal stenosis leading in turn to an insidious pressure gradient along the length of the coronary artery, coronary dissection, myocardial bridging, and thromboembolism, all of which may have been overlooked during the index procedure.

Coronary vasomotion disorders of epicardial arteries and microcirculation

Functional causes of persistent or recurrent angina following a technically successful PCI include vasomotion disorders of epicardial coronary arteries, as well as coronary microvascular dysfunction (CMD). Accordingly, current European Society of Cardiology guidelines on stable CAD have acknowledged the role of coronary vascular dysfunction in causing angina post-PCI.[1] If vasomotor function has not been specifically assessed in a patient with angina before undergoing PCI, it is impossible to know the time-course of these functional alterations. Of note, stent implantation may cause or enhance coronary vascular dysfunction increasing the propensity of epicardial coronary vasospasm and/or CMD. Overall, these functional mechanisms may be causally implicated in about half of patients with angina post-PCI although, again, prospective studies are lacking.[3]

Significant constriction of epicardial coronary arteries at or distal to the PCI site is a potential cause of recurrent angina.[26] Ong *et al.*[27] documented epicardial spasm (>75% narrowing), associated with reproduction of patient's symptoms, in response to intracoronary acetylcholine (ACh) at increasing doses; up to 200 μg for the left coronary artery or with 80 μg for the right coronary artery (*Figure 2*). Significant constriction occurred in about half of the patients undergoing coronary angiography for post-PCI recurrent angina without haemodynamically significant coronary stenoses. These observations support a mechanistic role for epicardial coronary artery constriction in patients with angina persistence or recurrence post-PCI. Heightened activation of the Rho-kinase pathway, a central molecular mechanism for vascular smooth muscle constriction, might also be involved in the pathogenesis of DES-related enhanced epicardial artery constriction.[28]

Coronary microvascular dysfunction in post-PCI angina, Type 4 by the classification of Camici and Crea,[29] can be caused by impaired microvascular dilation resulting in a reduction of coronary flow reserve (CFR), similar to that caused by an epicardial stenosis, or by microvascular spasm (*Figure 2*). In a study of patients with post-PCI recurrent angina compared with matched patients without angina post-PCI, Li *et al.*[30] observed a more profound reduction in coronary blood flow (CBF) in association with an increase in the index of microvascular resistance (IMR) in response to intravenous adenosine (140 μg/kg/min). The impairment of hyperaemic CBF and increase in IMR was even more relevant in those with abnormal exercise stress test result and persisted at 6-month and 12-month follow-up. These findings are consistent with studies using transthoracic Doppler echocardiography by Milo *et al.*[31] In their study, hyperaemic coronary artery blood flow velocity in the left anterior descending (LAD) was impaired at 1 day, 3 months, and 6 months after successful PCI compared with controls. Importantly, similar impairment of the CBF response to cold pressor testing was also observed, suggesting impaired endothelium-dependent vasodilator function of the coronary microcirculation. Furthermore, a greater impairment of the CBF response predicted restenosis in the LAD coronary artery during long-term follow-up.[32] Among patients who underwent PCI with second-generation DES, Hokimoto *et al.*[33] found impaired CBF response to both ACh (an endothelium-dependent stimulus) and adenosine (mostly an endothelium-independent stimulus). Overall, in this study, evidence of CMD was found in 59% of patients with

Table 1 Cause of persistence or recurrence of angina post-percutaneous coronary intervention

Mechanisms	Diagnostic criteria
Flow limiting epicardial obstructions	
Stent failure	
In-stent restenosis	Presence of ≥70% stenosis in the stented segment and within 5 mm of stent edges at coronary angiography. Intermediate lesions should be interrogated with FFR.
Stent thrombosis (definite)	Presence of intracoronary thrombus that originates in the stent or segment 5 mm proximal or distal to the stent and presence of at least one of the following within a 48-h time window: • Acute onset of ischaemic symptoms at rest • New ischaemic ECG changes that suggest acute ischaemia • Typical rise and fall in cardiac biomarkers
CAD progression	Progression of coronary atherosclerosis in coronary segments |different from those treated with index PCI, with presence of ≥70% stenosis at coronary angiography. Intermediate lesions (40–70% diameter stenosis) should be interrogated with FFR.
Incomplete revascularization	Residual stenosis of ≥50% in the left main coronary artery or ≥70% in another major epicardial coronary artery after index PCI. Intermediate lesions (40–70% stenosis) should be interrogated with FFR.
Diffuse coronary atherosclerosis	Diffuse coronary atherosclerosis at coronary angiography without angiographically significant stenosis, determining myocardial ischaemia as documented by reduced FFR (≤0.80).
Myocardial bridge	Disclosure at coronary angiography of a systolic narrowing, or 'milking' of the vessel, with a 'step-down' and 'step-up' demarcating the affected area, and complete or partial decompression in diastole. Diastolic FFR with dobutamine challenge is a more appropriate approach for testing the haemodynamic significance of myocardial bridges.
Spontaneous coronary artery dissection	Spontaneous coronary artery dissection is defined as a separation within the arterial wall by intramural haematoma, which can occur by an intimal rupture initiating medial dissection or more commonly by a spontaneous intramedial haemorrhage resulting from disruption of the vasa vasorum
Coronary vasomotion disorders of epicardial arteries and microcirculation	
Epicardial spasm	Presence of focal or diffuse epicardial coronary diameter reduction ≥90% during intracoronary ACh or ergonovine administration in comparison with the relaxed state following intracoronary nitroglycerine given to relieve the spasm, associated with reproduction of symptoms and ischaemic ECG shifts.
Microvascular spasm	Typical ischaemic ST-segment changes and angina developed during intracoronary ACh or ergonovine administration in the absence of epicardial coronary constriction ≥90% diameter reduction.
Impaired coronary microvascular dilation	Reduction of coronary flow reserve (CFR <2.0–2.5) in the absence of obstructive epicardial stenoses. Increase in the index of microvascular resistance (>25) or the hyperaemic myocardial resistance (>2.5 mmHg/cm/s)

previous PCI. Finally, Ong *et al.*[27] suggested coronary microvascular spasm might contribute to post-PCI recurrent angina in approximately one in five affected patients. Specifically, following intra-coronary infusion of ACh, affected patients experienced angina and ischaemic electrocardiographic (ECG) changes without evident epicardial constriction, suggesting that microvascular spasm rather than epicardial constriction was causal for the angina.

Mechanisms underlying CMD post-PCI are poorly understood, heterogeneous, and potentially more than one problem may be operative in any given patient.[34] First, chronic coronary microcirculation adaptation to reduced perfusion pressure distal to a stenosis or to an occlusion would be expected to negatively influence microvascular remodelling and its capacity to maximally dilate after restoration of a more physiologic perfusion pressure. Furthermore, the time required for the coronary microcirculation to recover to baseline vasomotor reactivity is likely to be variable among patients.[35]

Second, PCI might contribute to CMD by causing microembolization by debris material, which may obstruct small coronary arteries, arterioles, and/or capillaries to cause perivascular inflammation and even capillary obliteration and cardiomyocyte injury.[36] Furthermore, the DES *per se* causes vasoconstriction in the adjacent and downstream coronary macro- and microcirculation, potentially due to elution of the active drug and polymer constituents downstream. Although these detrimental effects of DES might be mediated by endothelial dysfunction,[37] more recent studies suggest that they are mainly mediated by activation of Rho-kinase in smooth muscle cells and, accordingly, are prevented by Rho-kinase inhibitors.[38,39]

Third, CMD may have pre-dated the index PCI procedure, type 3 by the classification of Camici and Crea,[29] which was 'unmasked' when the epicardial obstruction was relieved by PCI. In particular, CMD with microvascular rarefaction is implicated in heart failure with preserved ejection fraction.[40,41]

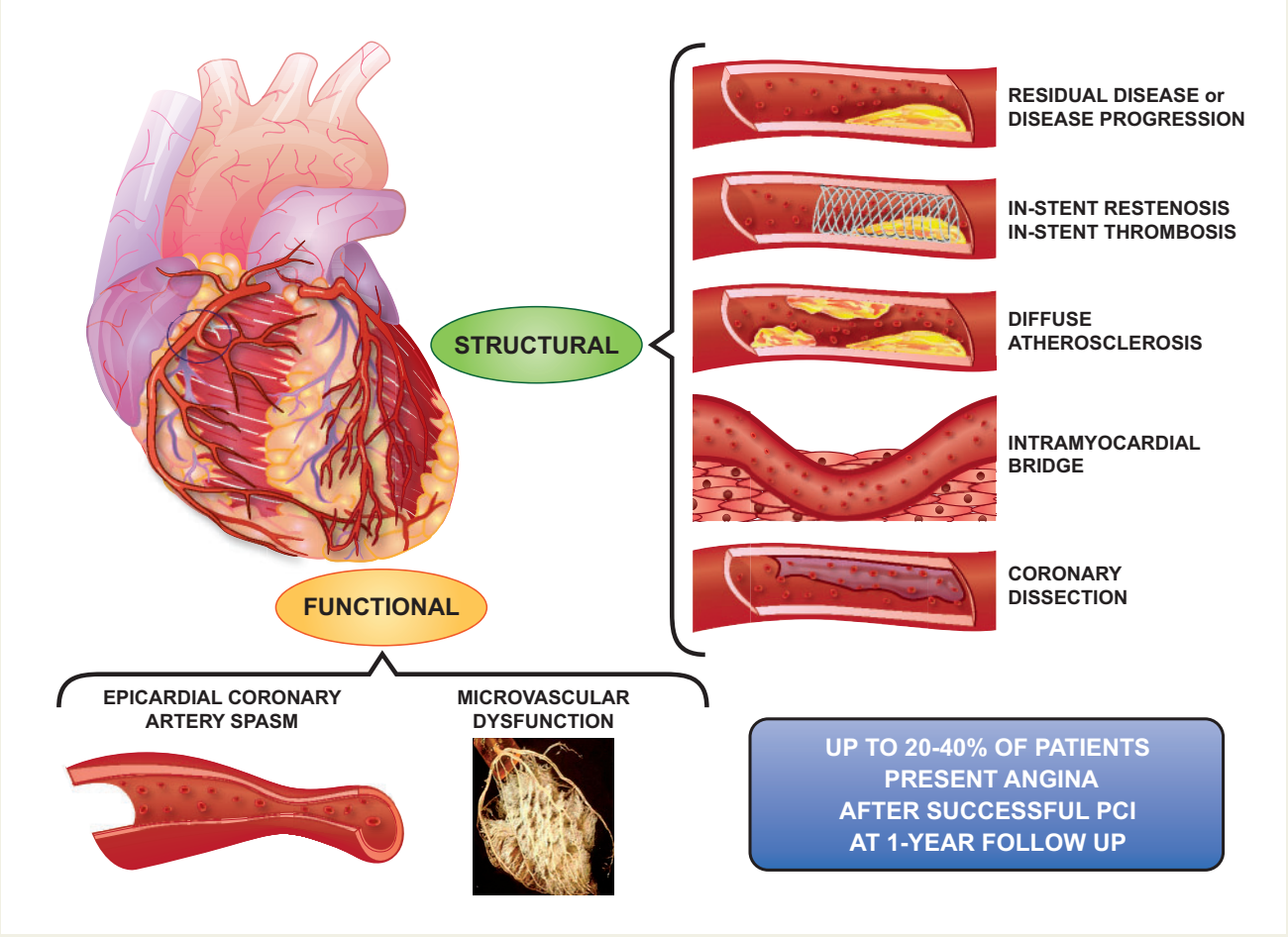

Figure 1 Structural and functional alterations of coronary circulation responsible for persistence or recurrence of angina after percutaneous coronary intervention.

Last but not least, coronary microcirculation regulates myocardial blood flow, and therefore, shear stress in large epicardial arteries which in turn directs vessel remodelling and plaque formation.

Diagnostic evaluation of persistent or recurrent angina after percutaneous coronary intervention

Non-invasive diagnostic tests

European Society of Cardiology guidelines for stable obstructive CAD recommend a stress test at follow-up in patients with persistent or recurrent angina post-PCI, preferably a stress test that is combined with imaging (Class I, level of evidence C).[1] Thus, non-invasive stress tests represent, in most cases, the first diagnostic assessment for patients presenting with angina post-PCI.

ECG stress testing in the diagnostic and prognostic assessment of patients with stable ischaemic heart disease is well established as it helps guide the initial treatment strategy.[1] The diagnostic performance of computed tomography coronary angiography for the evaluation of in-stent restenosis is generally lower than in a native vessel, and adjunctive estimation of FFR-computed tomography in a vessel with a stent is relatively contra-indicated.[42] The role of ECG stress testing alone after PCI is debated because the positive predictive value for obstructive stenosis/restenosis is only moderately high.[43] A key issue is that an abnormal ECG stress test can be caused by both obstructive CAD and functional mechanisms (CMD, epicardial vasoconstriction, etc.). In both clinical scenarios, evidence of exertional angina and ECG abnormalities consistent with ischaemia provide objective evidence that should be useful for onward management.

Similar considerations apply to stress myocardial perfusion imaging by single-photon emission tomography (SPECT). Positron emission tomography (PET) is a well-validated technique that provides non-invasive, accurate, and reproducible quantification of both global and regional myocardial blood flow (mL/g/min) and CFR. Clinical research using PET has provided substantial new knowledge on CMD in various clinical settings. Indeed, evidence of segmental abnormalities more often reflects an epicardial problem while CMD is associated with a global reduction of CFR.[44,45] Recent studies suggest that cardiac magnetic resonance may discriminate between epicardial and microvascular causes of myocardial ischaemia.[46,47]

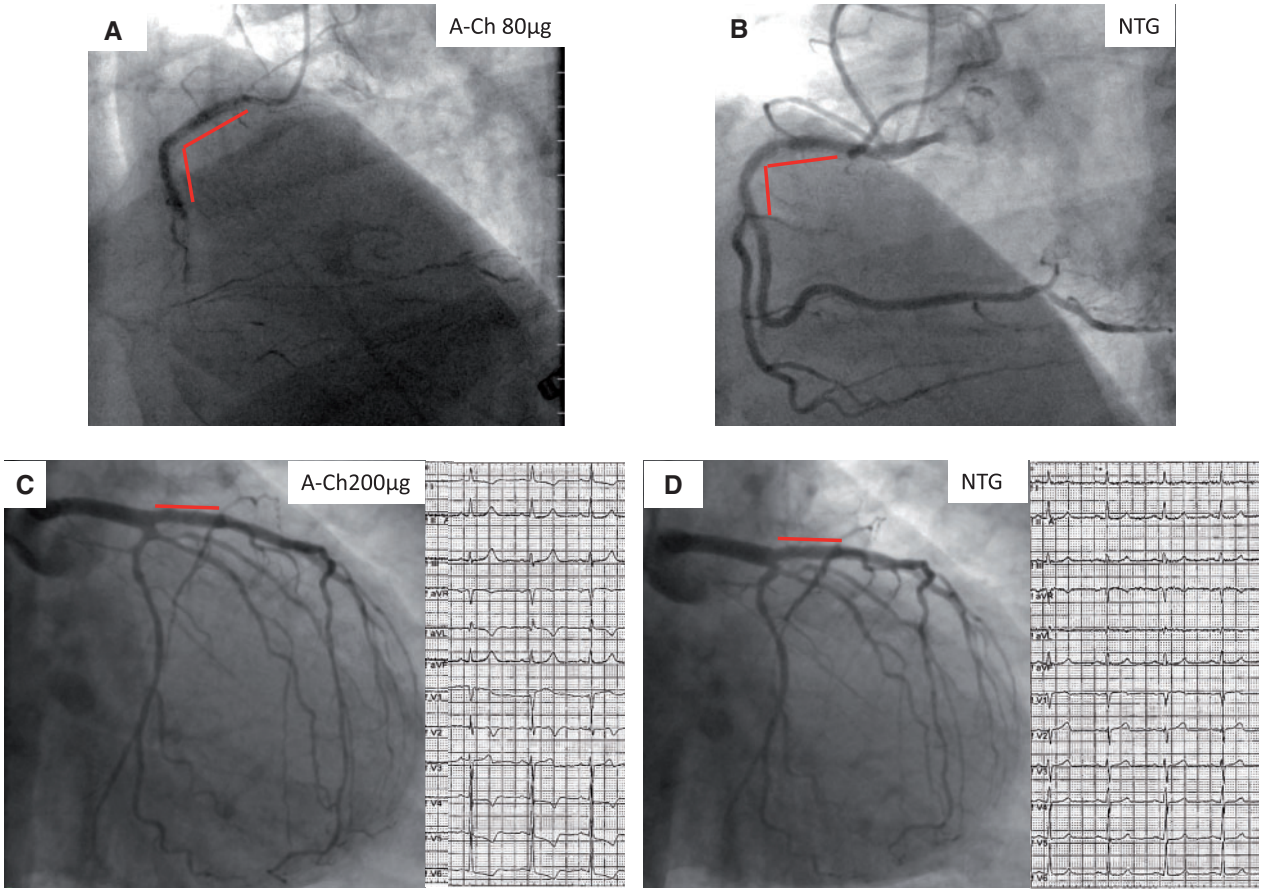

Figure 2 (*A* and *B*) Epicardial coronary spasm: representative images of a 55-year-old male patient with several previous stent implantations in the right coronary artery (red lines). The patient-reported recurrent resting angina and underwent invasive coronary angiography. The right coronary artery showed mild in-stent proliferation. Intracoronary acetylcholine testing revealed spasm of the right coronary artery distal to the stents at 80 μg with reproduction of the reported symptoms (*A*). After intracoronary nitroglycerine injection (400 μg) the spasm and the symptoms resolved (*B*). (*C* and *D*) Coronary microvascular spasm: representative images of a 64-year-old female patient with previous stent implantation in the left anterior descending artery (red lines). The patient-reported recurrent angina at rest as well as during exertion and underwent invasive coronary angiography. The left anterior descending showed mild in-stent proliferation. Intracoronary acetylcholine testing revealed no epicardial spasm at 200 μg, but reproduction of the reported symptoms together with ischaemic ECG shifts on the simultaneously recorded 12-lead ECG (*C*). After intracoronary nitroglycerine injection (200 μg) the ischaemic ECG changes and the symptoms resolved (*D*).

Stress echocardiography (with either exercise or pharmacological stressor) may be useful to distinguish between epicardial and microvascular coronary mechanisms. Indeed, a dissociation between angina and ischaemic ST-segment changes on the one hand and lack of regional wall motion abnormalities on the other hand, is a typical feature of microvascular angina due to the patchy distribution of ischaemia.[48–51] In sharp contrast, as established in the ischaemic cascade concept where regional wall motion abnormalities precede electrical abnormalities and both precede symptoms, it is very unlikely for patients with epicardial coronary stenoses to experience angina and ischaemic ST-segment changes in the absence of regional wall motion abnormalities.[48]

Invasive diagnostic tests

Current European Society of Cardiology guidelines on stable CAD recommend invasive coronary angiography in clinically stable patients with high-risk ischaemic findings (>10% of myocardium) at stress imaging (Class I, level of evidence C).[1] However, the threshold for coronary angiography might be lower after high-risk PCI (Class IIb, level of evidence C).[1] Considering the limited negative predictive value of a non-invasive test, then an invasive approach may be chosen independent of non-invasive test results, particularly when the history is strongly supporting angina recurrence because it offers the opportunity to test both structural and functional alterations of coronary circulation (*Figure 3*). Multi-territory ischaemia (both

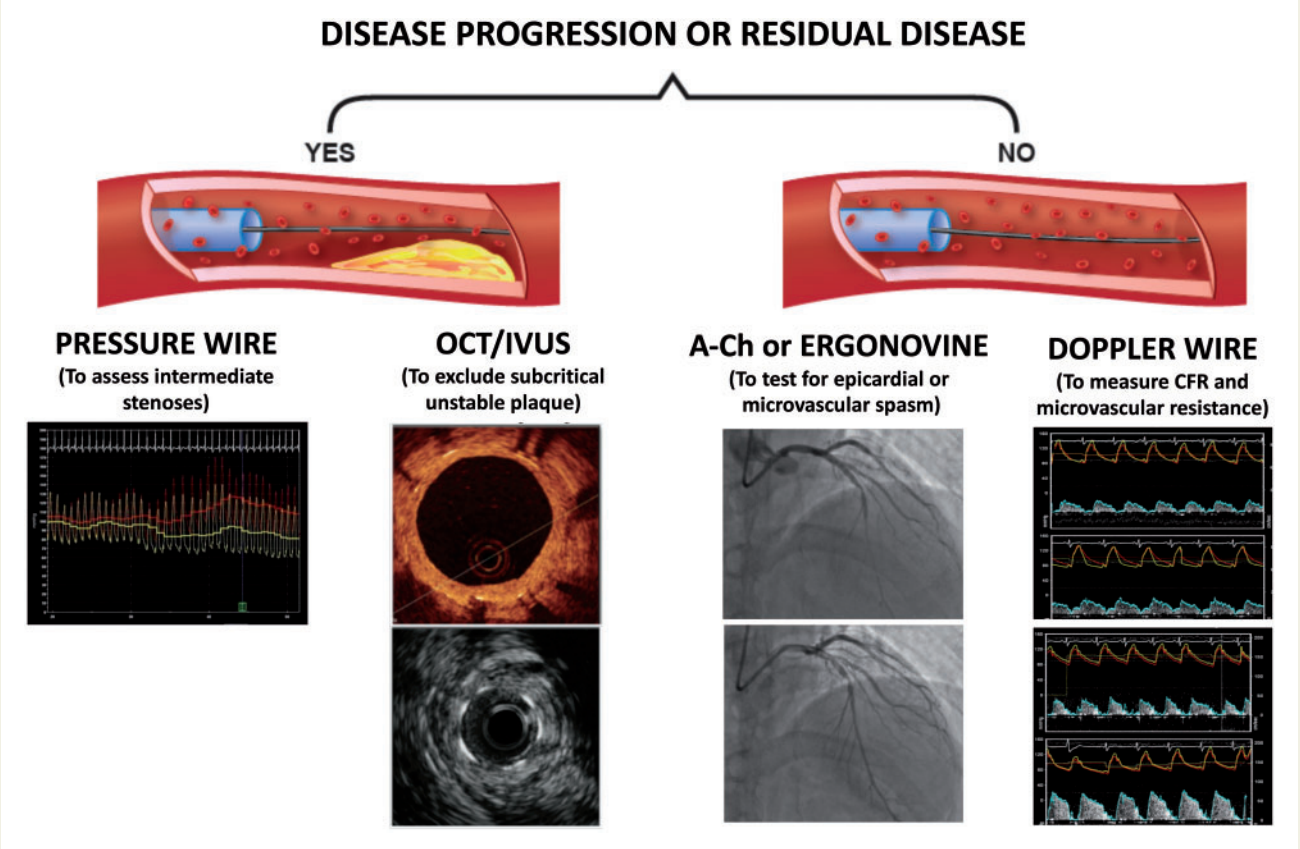

Figure 3 A full investigation of the mechanisms of persistence or recurrence of angina after percutaneous coronary intervention in the catheterization laboratory should include the assessment of both structural and functional alterations of epicardial coronary arteries and of coronary microcirculation. A-Ch, acetylcholine; CFR, coronary flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography.

transmural and regional) may not be detected by most non-invasive tests.[3] Moreover, patients with persistent or recurrent angina and incomplete revascularization need to be reassessed if additional revascularization is considered to be technically feasible. Finally, in case of an intermediate stenosis on coronary angiography, FFR or NHPR measurements can be helpful to confirm the presence of a haemodynamically significant epicardial stenosis. However, the caveat is that in the presence of CMD, it may be unclear whether near maximal hyperaemia is achieved, thus limiting the usefulness of FFR measurements without measuring CFR or indices of myocardial resistance.[52]

A second indication for coronary angiography is the occurrence of angina at rest, despite optimal medical treatment and negative non-invasive testing. This scenario should strongly suggest functional coronary alterations. In this patient subset, invasive coronary angiography might sometimes establish the presence of subcritical unstable coronary plaques, which can be further investigated by intravascular imaging (optical coherence tomography, intravascular ultrasounds, etc.). In the absence of subcritical unstable plaques, the assessment of epicardial and microvascular coronary vasomotion may reveal functional causes of persistent angina. In both scenarios, invasive coronary angiography is necessary to elucidate the causes of angina.

Coronary artery vasomotion is mainly assessed invasively, usually by intracoronary administration of drugs, such as ACh or ergonovine.[1,3] The safety of intracoronary provocative testing has been convincingly proven in previous studies.[53] Some have advocated non-invasive assessments using ergonovine stress echocardiography in patients known to have non-obstructive CAD.[54] Coronary vasomotion in response to ACh reflects the interplay between endothelial and smooth muscle cell responses. Acetylcholine elicits endothelium-dependent vasodilatation when the endothelium is functional, but in pathological conditions, characterized by endothelial dysfunction and/or smooth muscle cell hyper-reactivity, it may result in no dilatation or even trigger vasoconstriction or spasm via stimulation of smooth muscle cell muscarinic receptors. Ergonovine acts primarily via serotoninergic receptors on vascular smooth muscle cells but also on α-adrenergic and dopaminergic receptors, unmasking predisposition to vasoconstriction or spasm. Acetylcholine is preferred because it is relatively short-acting, specific in its selectivity for muscarinic receptors and the intracoronary dosing is devoid of systemic effect; whereas ergonovine effects multiple receptors, is longer acting and even with intracoronary dosing may have some systemic effects (blood pressure increases). Nevertheless, at present, it is unclear whether ACh or ergonovine is superior to

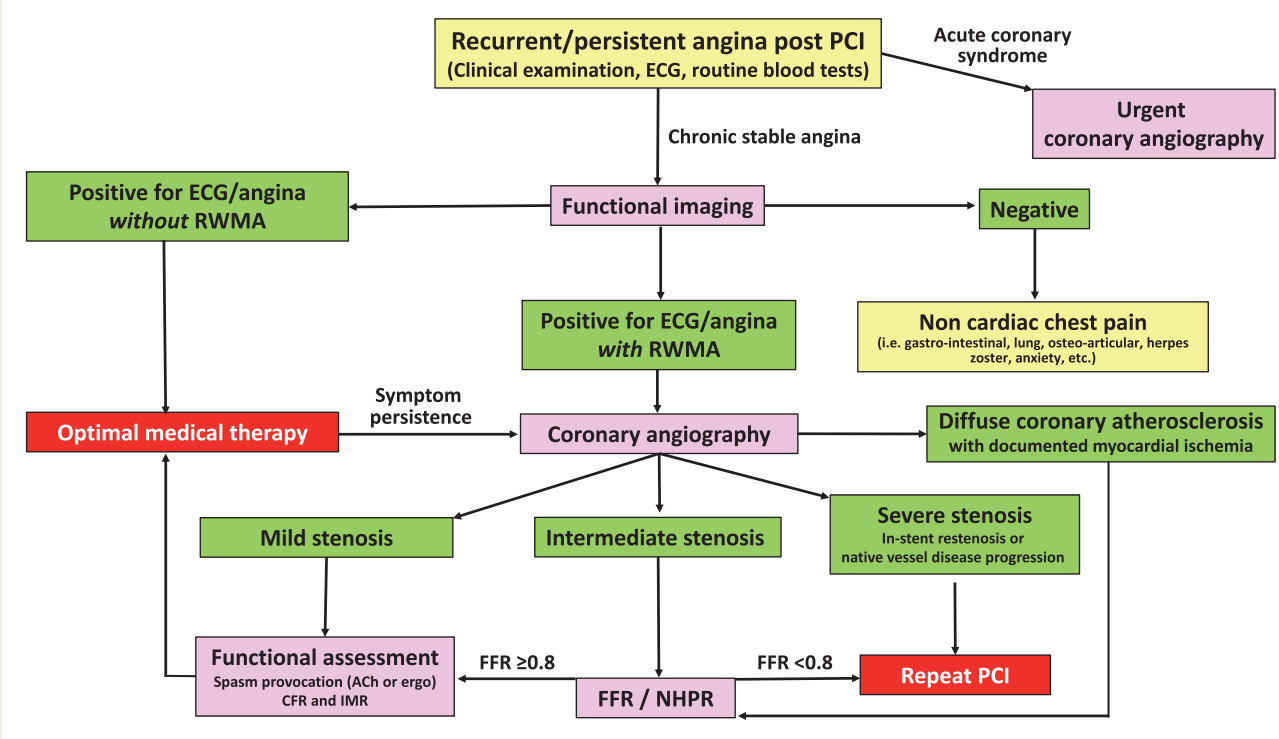

Figure 4 Diagnostic flowchart in patients with persistent or recurrent angina after percutaneous coronary intervention. Colour coding: symptoms in yellow, diagnostic tools in purple, diagnostic findings in green, and therapeutic recommendations in red. ACh, acetylcholine; CFR, coronary flow reserve; Ergo, ergonovine maleate; FFR, fractional flow reserve; IMR, index of microvascular resistance; NHPR, non-hyperaemic pressure ratio; RWMA, regional wall motion abnormalities.

detect spasm in patients with persisting angina post-PCI also because they might identify different subsets of patients with vasospastic angina.[55]

Coronary artery spasm is defined as a transient (e.g. reversible) coronary artery occlusion/subocclusion (>90% narrowing) with signs (ST changes) and symptoms of myocardial ischaemia.[56,57] Spasm may involve discrete coronary segments in one or multiple arteries, or can be diffuse and, when it involves distal coronary vessels, can be suspected to also extend into the microvasculature.[56]

Lack of epicardial coronary spasm by angiography in the presence of ischaemic ECG changes and angina suggests microvascular spasm.[58] When epicardial spasm occurs, objective determination of concomitant microvascular spasm is difficult.

Coronary reactivity testing is only performed in a limited number of cardiac catheterization laboratories worldwide. The reasons for the low adoption of coronary reactivity testing are multifactorial and include lack of evidence from randomized controlled trials, and lack of education and training in who to administer the tests. The European Society of Cardiology (ESC) and the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines make spasm provocation testing only Class IIa and Class IIb, respectively.[1,20] However, the Japanese Circulation Society and the Coronary Vasomotion Disorders International Study Group (COVADIS) have recommended routine testing in selected patients.[56–58]

Coronary flow reserve and microvascular resistance can be measured using a pressure- and flow-sensitive Doppler catheter or a thermodilution guidewire. These techniques can be performed during coronary angiography enabling a comprehensive assessment of CMD by assessing microvascular dilatory function,[59,60] which may complement coronary reactivity testing within the same procedure.

The Coronary Microvascular Angina clinical trial (CorMicA) is the first to prove the diagnostic, health and economic value of an interventional diagnostic procedure, which combines a guidewire and coronary vasoreactivity testing, to inform the diagnosis and treatment of patients with angina and no obstructive CAD, where the primary outcome is Seattle Angina Score at 6 months.[61]

Diagnostic flowchart

We recognize that randomized controlled trials for management of post-PCI angina are lacking. Nonetheless, given the clinical necessity, practice guidelines are needed. Although symptom assessment is important, it is frequently insufficient to establish the cause of persistent or recurrent angina after PCI, the only distinctive feature of vasospastic angina being angina at rest, frequently nocturnal, with preserved effort tolerance[62] and the only distinctive feature of microvascular angina being prolonged chest pain not immediately responsive to nitrates.[63] We propose a diagnostic algorithm that may assist in the evaluation of patients in this setting (*Figure 4*). The rationale prioritises

a person-centred approach with diagnostic tests according to local availability and onward management, including coronary angiography, as appropriate. A non-invasive assessment will be sufficient in some patients, but in many cases, invasive management including to assess coronary vascular function will be needed.

Knowledge gaps

Patients with persistent or recurrent angina post-PCI present an unmet clinical need. Recent studies suggest that PCI may not be relied upon to improve angina.[2] The large International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) clinical trial is assessing the benefits of revascularization in addition to optimal medical therapy to improve health outcomes.[64] A recent study demonstrated that a simple non-invasive assessment of peripheral artery endothelial function during index PCI admission predicted the persistence or recurrence of angina/ischaemia at follow-up,[65] suggesting that assessment of endothelial dysfunction[66] may be useful for prediction of structural treatment benefit. We recognize that such tests are not feasible in daily practice, but the implication is that treatments which improve endothelial dysfunction may be beneficial. This possibility merits further prospective research.

In clinical practice, PCI for stable angina patients is currently a 'one-size-fits-all' approach, potentially useful for symptom relief in some symptomatic patients found to have epicardial obstructive CAD. In other patients, a significant epicardial stenosis may reflect more extensive vascular dysfunction, where PCI alone may be ineffective. We think more research is warranted into the prevalence and clinical significance of coronary vascular dysfunction in patients undergoing PCI.

When obstructive CAD is ruled out, post-PCI angina may be due to coronary vascular dysfunction caused by either increased IMR, epicardial or microvascular spasm, or both. In these circumstances, repeat PCI would be unlikely to be beneficial. An important knowledge gap is treatment of CMD.[67] Importantly, early evidence suggests that an empirical treatment of angina in the absence of obstructive coronary atherosclerosis guided by the assessment of functional coronary alterations is associated to a better outcome as compared to a strategy guided by angiography only.[61]

Finally, while current guidelines on percutaneous coronary revascularization do not fully address the issue of persistent/recurrent angina, it would be desirable to do so in the future.[68]

Conflict of interest: F.C. reports speaker fees from AstraZeneca, Amgen and Servier and institutional agreements between his employer, the Catholic University, and Biotronik, Boheringer Ingelheim. C.N.B.M. reports lecturer fees from Abbott Diagnostics and Board Director fees from iRhythm. C.B. declares institutional agreements between his employer, the University of Glasgow, and Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Coroventis, DalCor, GSK, HeartFlow, Novartis, and Philips. P.G.C. reports personal consultant fees from Servier. P.O. reports personal fees from Menarini Berlin Chemie and grants from Sanofi. None of the declared interests regard the submitted work. All other authors have nothing to disclose.

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