Review

Recurrent angina after coronary revascularization: a clinical challenge

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Coronary revascularization procedures by means of percutaneous coronary interventions or coronary artery bypass graft surgeries are performed worldwide daily for the symptomatic treatment of patients with myocardial ischaemia. Nevertheless, angina remains a significant clinical problem. Management of angina recurring or persisting after coronary revascularization is particularly challenging. This review attempts to summarize the most common causes of recurrent chest pain after coronary revascularization, to analyse the possible diagnostic approaches, and to discuss the potential treatment modalities.

Coronary revascularization procedures by means of percutaneous coronary interventions (PCI) or coronary artery bypass graft surgeries (CABG) are performed daily worldwide for the symptomatic treatment of patients with myocardial ischemia. Nevertheless, angina remains a significant clinical problem.[1] The aim of this article is to review the efficacy and limitations of coronary revascularization procedures for the treatment of angina, to summarize the most common causes of the recurrence of chest pain after revascularization, to analyse the possible diagnostic approaches, and to discuss the potential treatment modalities.

In a series of ~2000 patients diagnosed with chronic angina, of whom 56% had received revascularization procedures in the prior year (PCI in 39% of cases and CABG in 28%), 90% of patients had at least one episode of angina in the prior 6 months and more than one-third of the patients had multiple episodes of angina per week.[2] Angina is inevitably associated with an impairment of the quality of life, and the deterioration in quality of life is proportional to the number of anginal attacks per week.[3]

The major advance of PCI over medical therapy alone in patients with chronic stable angina is mostly limited to improvement in angina severity. Failure to relieve angina by revascularization procedures may therefore represent failure of the procedure itself.[4,5] Accordingly, the American Heart Association (AHA) and American College of Cardiology (ACC) Practice Guidelines for the diagnosis and treatment of chronic angina[6] recommend coronary revascularization for patients with stable angina and significant coronary artery disease only if symptoms are severe and not controlled despite optimal medical therapy. In reality, revascularization is commonly performed in many scenarios with associated ischaemia.

However, it is commonly known that coronary revascularization procedures do not guarantee complete relief of angina and recurrent chest pain after the procedure.

For this review, pertinent studies in the literature were searched in PubMed (updated January 2007) using the following strategy: [angina pectoris(mesh) or coronary artery disease(mesh)] AND recurrent AND [PTCA(mesh) OR coronary artery bypass(mesh)]. Given the design of this work as a narrative review, no formal criteria for study selection or appraisal were enforced. *Table 1* lists the definitions of recurrent angina, refractory angina, and angina with normal coronary angiogram (Syndrome X).

Efficacy and limitations of PCIs for the treatment of angina

The large RITA-2 trial randomized patients with chronic stable angina to PCI or medical treatment alone. While patients randomized to PCI were significantly more likely to be symptom-free at 3 months, the number of patients free from moderate to severe angina (angina score greater than or equal to 2) at 12 months dropped from 60 to 20% in the interventional arm (recurrent angina) but was virtually unchanged in the medical arm.[4] Nevertheless, patients treated with PCI showed a highly significant

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Table 1 Definitions

Recurrent angina
  Occurrence of chest pain due to myocardial ischaemia in a patient previously treated by revascularization (percutaneous or surgical) procedure.[24]
Refractory angina
  Occurrence of chest pain due to myocardial ischaemia in a patient with severe CAD who cannot be managed adequately by medical therapy and who are not candidates for revascularization (interventional or surgical).[6]
Syndrome X (or Cardiac Syndrome X)
  Occurrence of chest pain (usually effort-induced) in a patient with angiographically normal (or near normal) coronary angiogram, usually associated with ST-segment depression during spontaneous or provoked angina, in the absence of spontaneous or inducible vasospasm, and in the absence of other conditions (i.e. left ventricular hypertrophy, valve disease, diabetes, hypertension) likely to be associated with microvascular dysfunction. Angina is indeed thought to be secondary to microvascular dysfunction.[64]

superiority in physical functioning, vitality, mental health, and general health at 3 and 12 months after the procedure and twice as many patients in the intervention arm showed no limitations in physical activity.[7] At 24 months, however, patients treated by PCI and those treated with medical treatment only had similar angina rates.[4] In the large ARTS trial, 5 years after the initial procedure, 42% of patients in the stent group and 22% in the CABG group had experienced recurrence of symptoms and/or required repeat revascularization.[8] While randomized control trials often do not represent real life clinical scenarios, the image depicted by registries in regards to recurrent angina is somewhat similar. A large retrospective cohort study at the Mayo Clinic demonstrated that most of the patients treated by PCI had an improvement in the angina score at 6 months. While this improvement was significant when compared with medical therapy, over 30% of patients in the PCI arm remained symptomatic for angina and 12% had severe angina. Furthermore, the number of prescribed medication for angina was only minimally reduced after revascularization.[9] These results are similar with those reported in the Canadian Rosetta study, an international multicenter registry of patients undergoing coronary revascularization.[10]

In a meta-analysis of nine studies of PCI with bare-metal stent (BMS) placement compared with CABG for multi-vessel disease, 18.4% of patients who underwent PCI had a class II or greater angina score at 16 months after the procedure, and, most importantly, 19.0% required repeat intervention during the same follow-up.[11] With the introduction of coronary stents, and more recently of drug-eluting stents (DES), the probability of restenosis, and thus reintervention, has decreased substantially.[12,13] A meta-analysis showed a 70% reduction in target vessel revascularization with DES when compared with BMS.[13] While the rate of restenosis with sirolimus-eluting stents (SES) appears lower when compared with paclitaxel-eluting stents (PES),[14] there is a debate on the true comparison in target vessel revascularization between different DES. On the other hand, recent data suggest that the profound inhibition of in-stent neointimal hyperplasia may translate in delayed endothelialization

and subsequent risk of late (>30 days) stent thrombosis.[15] The large reduction in repeat revascularization rate with DES is indeed associated with a small but significant increase in subacute stent thrombosis.[15] The excess in stent thrombosis, as well as the potential for other adverse events[16] and lack of true long-term follow-up data, signal a need for more detailed risk assessment studies for DES, especially for their off-label use.

Structural and functional causes of recurrent angina

Following revascularization, different structural aetiologies may explain recurrent angina. The first challenge for the physician is to determine whether the chest pain is anginal in quality or whether it is non-cardiac chest pain. Taking a thorough clinical history is extremely important in helping to determine the aetiology. Structural causes of recurrent angina include (i) restenosis, (ii) disease progression, or (iii) incomplete revascularization. Functional causes of recurrent angina following revascularization are more difficult to fully elucidate and may pose a diagnostic challenge. These are conditions in which inappropriate vasoconstriction in the epicardial or microvascular segments occur. Typically, they present with symptoms of classic angina and may or may not have changes consistent with ischaemia on stress testing. In the Women's Ischemia Syndrome Evaluation (WISE) study, ~50% of women with chest pain and normal coronary angiogram had an abnormal coronary flow velocity reserve[17] and ~20% had an abnormal magnetic resonance spectroscopy (MRS) consistent with ischaemia, which predicted worse cardiovascular outcome.[18] Examples of functional causes of recurrent angina following revascularization include (i) coronary microvascular dysfunction, (ii) epicardial coronary spasm, or (iii) vasoconstriction at the stent edge. Aetiologies of structural and functional causes of recurrent angina are reviewed in detail hereafter.

Of note gender-related differences in pain characteristics of chronic angina and perceived physical limitations exist and raise challenging pathophysiological and clinical questions regarding the role of fixed obstruction vs. microvascular dysfunction.[19–22] Indeed, in the WISE study more than half of women with suspected ischaemia had no evidence of coronary artery disease (34%) or only minimal disease (23%).[23] Furthermore, women have been under-represented in clinical trials that often show inconclusive or contrasting results in women.[20–22]

Recurrence of symptoms after PCI

Recurrent angina is only one of the many causes for recurrent chest pain. *Table 2* lists the most common causes of recurrent chest pain.

Restenosis after PCI is a complex phenomenon characterized by progressive coronary stenosis due to intimal hyperplasia in the stent and that leads to the recurrence of exertional angina. Recurrent pain, however, is not synonymous with restenosis.[24] Chest pain that resembles the pain for which initial treatment was sought is suggestive of restenosis.[25] A peculiar type of pain after coronary stenting, known as 'stretch-pain', has been described as a 'sharp highly localized pain'. While its pathogenesis remains unclear, it carries a

Table 2 Most common causes of recurrent chest pain after revascularization

Coronary causes
  Post-PCIs
    Acute, subacute, and late stent thrombosis
    Incomplete revascularization
    Restenosis
    Progression of disease not involving the target lesion
    Stent 'stretch' pain
  Post-CABG
    Early recurrence (1 month)
      Technical surgical errors
      Poor target vessel runoff
    Subacute recurrence (1–12 months)
      Graft insertion site lesion
      Incomplete revascularization
    Late recurrence (12 months)
      Degenerative graft disease
      Progression of disease not involving the target lesion
Non-coronary cardiovascular causes
  Myocardial
    Left ventricular hypertrophy (including hypertrophic cardiomyopathy)
    Microvascular dysfunction/inappropriate vasoconstriction
  Valvular
    Aortic valve disease
  Pericardial
    Pericarditis
  Aorta
    Aortic dissection (including intramural haematoma)
Non-cardiovascular causes
  Gastrointestinal
    Gastroesophageal reflux disease/oesophagitis/oesophageal spasm
    Biliary colic/cholecystitis/cholangitis
    Peptic ulcer disease
    Pancreatitis
  Pulmonary
    Asthma/chronic obstructive pulmonary disease
    Pneumonia
    Pleuritis/Pneumothorax
  Musculoskeletal
    Sternal surgical pain (post-CABG)
    Rib fracture
    Costochondritis
    Herpes Zoster
    Fibromyalgia
    Anxiety/panic attack

favourable prognosis, and the duration is usually limited to the immediate post-procedural period.[26]

Another subset of patients will experience persistent symptoms due to incomplete coronary revascularization.[27] In the ARTS trial (of stenting vs. surgery for multi-vessel coronary artery disease), revascularization was considered complete in 84% of surgical cases and only 70% of interventional cases. Patients with incomplete revascularization by PCI had a 7% increase in the absolute risk of 1-year combined endpoint of new cardiac events and additional revascularization procedures (30.6 vs. 23.4%). This difference was largely due to a five-fold increase in the need for subsequent bypass surgery (10.0 vs. 2.0%).[28]

In a series of 102 consecutive patients who had recurrent angina after percutaneous coronary balloon angioplasty,

those presenting within 1 month of the intervention were more likely to have recurrent pain owing to incomplete revascularization. Patients presenting with pain between 1 and 6 months following PCI typically had angina secondary to restenosis, and those presenting more than 6 months after the procedure were likely to have progression of coronary disease other than the target vessel.[27] This paradigm however may be outdated. With the widespread use of DES, restenosis is reduced to a minority of cases, while stent thrombosis appears to no longer be limited to the first few weeks after stent implantation but occurs even several months after implantation.[15] Ong et al.[29] reported the incidence of subacute (1.1%) and late (0.4%) stent thrombosis in patients treated with SES or PES. Of note all cases of late stent thrombosis occurred in patients on antiplatelet monotherapy with aspirin or no antiplatelet therapy. Specific recommendations for patients undergoing DES implantation now include the need to comply with the prescribed double oral antiplatelet therapy (3–6 months or even more of clopidogrel, and lifelong aspirin).[30] While restenosis has been reduced by DES, recurrences owing to progression of disease elsewhere or to stent failure to efficiently inhibit intimal hyperplasia still occurs. In the latter case detailed data are still lacking on the best management strategy, but in a large database study including 803 patients (1376 lesions) binary angiographic restenosis occurred in 15.9% and 17.4% for SES and PES, respectively.[31] Interestingly, only 60% of these restenotic lesions were associated with symptoms of angina or objective signs of myocardial ischaemia, supporting the concept of a difference between angiographic restenosis and clinical recurrence. Moreover, sirolimus-eluting stents were more commonly associated with a focal pattern of restenosis, while PES with a more diffuse or occlusive restenotic phenomenon.[31] This finding may have a relevant clinical impact, as the latter type of restenosis usually needs to be addressed by adjunctive stenting or bypass surgery, while the former can be commonly solved only with repeat balloon inflation.[32]

Recurrence of symptoms after CABG

Early and late graft failures are the major causes of resistant or recurrent angina after surgical revascularization. Early graft failure is considered to be largely dependent on procedural complications and occurs in up to 15% of cases. Acute thrombosis and technical failure at the site of new anastomoses are common causes. Late graft failure is usually associated with degenerative changes of the graft body. This is usually seen in venous grafts and it is considered to be inevitable over time. In a series of 1388 patients, venous graft occlusion was 19% at 1 year and 25% at 5 years. At 15 years, 50% were totally occluded, and of the remaining 50% of grafts more than half had significant atherosclerotic disease.[33] Though they have a similar risk of acute graft failure, the improved clinical outcome seen with the use of arterial grafts may be explained by the high patency rate at 1-year follow-up (∼95%) and the relative protection from late failure (10–15 year patency of 80–88%).[33,34] In a meta-analysis of nine studies of CABG for multi-vessel disease (3283 patients), the rate of recurrent angina at 16 months was 8.9%. The combined rate of death, acute myocardial infarction, and stroke was 10.8%, with repeat revascularization rate of 4.7% at 16 months.[11]

The data of the recent Project of Ex-vivo graft Engineering via Transfection IV (PREVENT IV), confirmed across 1829 patients undergoing CABG with 12- to 18-month angiographic follow-up, a very high per-patient failure of one or more venous grafts (45%) and per-graft failure of one or more grafts (29%).[35] PREVENT IV trial was a phase-3 multicenter randomized controlled trial in patients undergoing CABG surgery in which autologous vein grafts were treated *ex vivo* with edifoligide, a synthetic oligonucleotide decoy to E2F used to inhibit neointimal hyperplasia. The incidence of venous graft failure in both groups of the PREVENT IV trial appears to be higher than historical controls.[33,34] This may be either related to the selection of older and sicker patients with a higher risk profile than the earlier cohorts,[33,34] or alternatively related to the use of a pressure-mediated delivery system or other vein graft handling techniques used.[35]

Overall, the concept of graft failure over time appears to be no different than stent failure with a loss of long-term angiographic patency and clinical benefit.

Recurrent chest pain: a diagnostic challenge

Recurrent chest pain after coronary revascularization is always a disappointment to both the patient and the cardiologist. The approach to recurrent chest pain should start with an accurate analysis of the initial procedure. In a patient who had a CABG in the last year and symptoms are consistent with angina, one should have a low threshold for early repeat catheterization to determine if an insertion site lesion is present and/or a native vessel can be dilated to resolve symptoms owing to graft failure. It is extremely important, indeed, to identify graft failure as early as possible to allow for PCI as a method to preserve the surgical benefits. Stress tests are often equivocal because of local perfusion abnormalities and/or partial collateral filling of ischaemic zones, especially in the context of functionally adequate but anatomically incomplete revascularization.

In patients having undergone PCI in the last year that present with symptoms similar to those prior to PCI, one may either start with an imaging stress test or consider repeat catheterization without performing non-invasive studies. The longer the time after the initial procedure in years the greater is the probability that recurrent symptoms represent progression of disease rather then restenosis. An accurate history taking in regards to the compliance with dual-antiplatelet therapy is essential to identify patient at greater risk for stent thrombosis, although dual-antiplatelet therapy does not fully prevent stent thrombosis. According to current ACC, AHA and Society of Cardiac Angiography, and Interventions (SCAI) guidelines,[36] dual-antiplatelet therapy should be continued for at least 1 month (for BMS, unless patient at high risk of bleeding in which case treatment may be limited to 2 weeks), 3 months (for SES), 6 months (for PES), and up to 12 months for patients presenting with acute coronary syndromes (in the absence of high risk for bleeding). The role of longer dual-antiplatelet treatment, although advocated by many,[15,29,37] is not supported fully by current literature, and further studies are needed to clarify this issue. Iakovou *et al.* have shown that the risk for stent thrombosis was increased several fold if dual-antiplatelet regimen was inappropriately discontinued, and it was four to six times more frequent in patients with diabetes and/or renal

failure, and six times more likely in bifurcation lesion.[30,38] A recent observational study performed at the Duke Heart Center showed that continuation of clopidogrel beyond duration mandated by stent label was associated with a significant reduction of events in patients with DES (and not in patients with BMS).[37] A hearing of the Food and Drug Administration (FDA) on this issue took place in December 2006. A consensus was reached that although there is evidence for an excess of late stent thrombosis with DES, SES and PES on-label use appears to be safe and not associated with excess mortality. Unresolved issues for their off-label use remain. While awaiting randomized studies, long-term dual-antiplatelet therapy for patients with a DES should be considered on an individual case basis according to clinical and angiographic risk for late stent thrombosis and risk of bleeding.

Considering the diagnostic value of functional studies after coronary revascularization, it is important to recognize that the results of the stress imaging studies are often of limited value in detecting restenosis or graft failure. Microvascular dysfunction and paradoxical increase of microvascular resistance during ischaemia may indeed coexist with epicardial coronary artery disease.[39–44] In addition, coronary microvascular dysfunction alone is capable of generating findings consistent with ischaemia on stress testing.[39–44] While we previously classified microvascular dysfunction as a functional cause of recurrent angina, it is also true that organic disease such as microembolization, ischaemic, and ischaemia-reperfusion damage to the microcirculation may occur during acute coronary syndromes and represent an organic substrate to microvascular dysfunction. During angiography, measurement of fractional flow reserve and coronary flow reserve (representing epicardial and microvascular limitations to flow, respectively) or induction of microvascular spasm with intracoronary acetylcholine may be useful in diagnosing microvascular dysfunction in patients without stenotic lesions that present with recurrent angina following PCI.[45,46]

The ROSETTA investigators have recently shown that practice patterns regarding the use of stress testing varies widely, and there is no general consensus on when and how to order a non-invasive test after coronary revascularization.[44,45] Furthermore, in patients who had undergone coronary stent implantation, outcomes were similar between the group undergoing routine functional testing and the group undergoing symptom-driven functional testing.[47,48]

Since many of the tests used to detect ischaemia actually test for the presence of coronary reserve it is reasonable to consider coronary angiography as the gold standard for the diagnosis of coronary restenosis, especially when supplemented by invasive assessment of fractional flow reserve in cases of intermediate stenosis at angiography. Selection of cases for angiography may be however challenging. The decision should not only be based on the symptoms of the patient but also on the characteristics of the original procedure. A low-threshold for angiography should be present when assessing patients who underwent high-risk procedures such as those involving the left main coronary artery, multiple vessels, proximal branches, bifurcations, multiple stents, or with left ventricular dysfunction, and in those with incomplete revascularization in whom further interventions are considered feasible.

Table 3 Diagnostic tests for recurrent angina after PCI or CABG

Angiography	
Invasive	
Cardiac catheterization	Gold standard
Non-invasive	
CT	Artifacts (i.e. stent, calcium)
Magnetic resonance	Artifacts (i.e. stent, calcium)
Perfusion tests (assessment of coronary reserve)	
SPECT	Requires radioactive material
PET	High maintenance costs
Echocardiograpy	Operator-dependent
Exercise ECG	Low specificity

Non-invasive modalities aimed at detecting restenosis independently from the assessment of coronary reserve are currently highly investigated.[49–52] Large-scale application of these techniques, however, is still hampered by some artefacts related to the visualization of the stent itself and relatively high-costs. CT angiography has been used for evaluating coronary stent patency.[49] Interestingly, MRI/MRA may be shown to be an extremely powerful tool if it shows to be able to evaluate for coronary anatomy and assessing myocardial perfusion reserve at the same time.[51,52] Contrast echocardiography is highly accessible, non-invasive, non-irradiating, and relative low cost procedure to assess perfusion, being however largely operator-dependent and more difficult to standardize.[53]

Positron emission tomography (PET) is considered the gold standard for the assessment of perfusion and function.[54] Because of the high maintenance costs, PET is not largely utilized at present and unlikely to be utilized in the near future for this indication.

The AHA/ACC Clinical Guidelines for the treatment of chronic stable angina recommend the use of nuclear or echocardiographic stress test for the evaluation of patients with prior revascularization who have a change in clinical status.[6,55] This recommendation is graded as Class I (condition for which there is evidence or general agreement) but with a level of evidence of C (based primarily on expert consensus). Although exercise ECG testing in unselected patients has great predictive value for cardiac mortality, the use of exercise ECG testing is discouraged because management decisions are often not only based on the presence or absence of ischaemia but also on the site and extent of ischaemia therefore favouring the use of stress imaging modalities such as single photon emission computed tomography (SPECT) or echocardiography.[55] *Table 3* lists the diagnostic modalities more commonly used to investigate recurrent angina. The role of functional testing is primarily to distinguish between cardiac and non-cardiac pain, evaluating the presence of high-risk features that would prompt early repeat angiography, and to identify the area of myocardium with ischaemia in order to plan revascularization in cases of multiple vessel disease.[6] *Figure 1* shows a proposed algorithm. When symptoms are suggestive of angina, and high-risk clinical or angiographic features are present repeat angiography should be
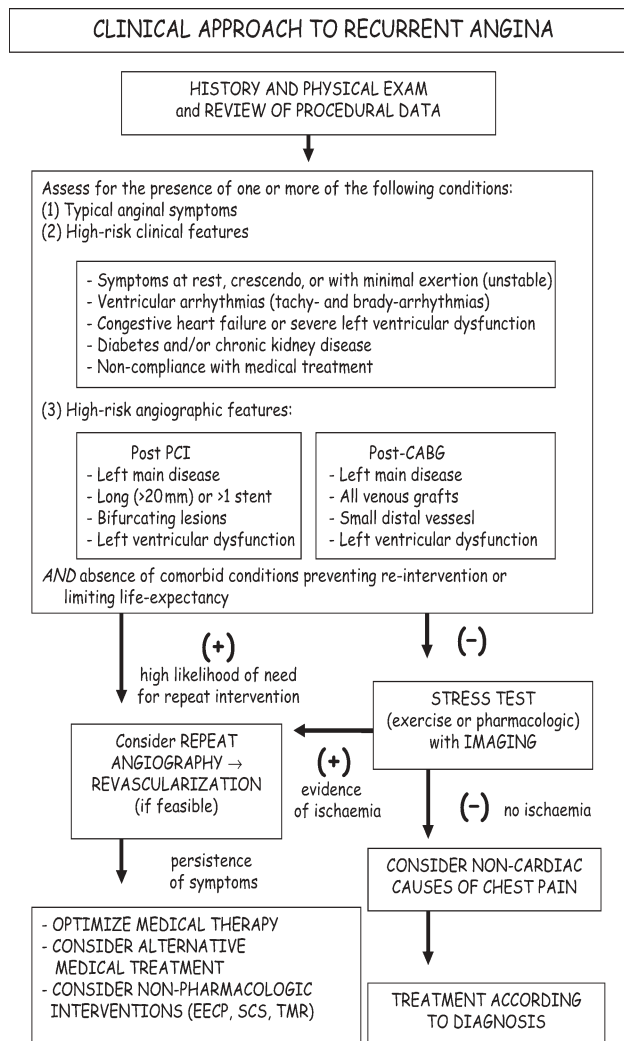
Figure 1 The figure presents a proposed algorithm for the diagnosis and treatment of angina after coronary revascularization.

performed earlier rather than later and revascularization should be attempted. If revascularization is not feasible or not successful, optimization of medical treatment should be made and alternative pharmacologic and non-pharmacologic interventions should be considered. On the other hand, if symptoms are equivocal and possibly due to non-cardiac disease, in the absence of high-risk features, a myocardial perfusion stress test should be performed to distinguish between cardiac and non-cardiac pain and to risk-stratify patients with myocardial ischaemia.

Treatment of recurrent angina

The management of angina after coronary angioplasty largely depends on the cause of the angina. When restenosis is present or suspected, repeat angiography and repeat intervention is usually warranted.

Although recurrent angina may have a different pathophysiologic mechanism to angina than chronic stable angina, evidence in favour of specific intervention in this type of angina is lacking. The AHA/ACC guidelines for the treatment of patients with angina do not distinguish between the different types of angina.[6] Moreover, no controlled randomized trial was specifically designed to assess efficacy in

the subgroup of patients with recurrent angina after revascularization. Beta-blockers, long-acting nitrates, and calcium-channel blockers are considered the mainstay of treatment. *Table 4* lists the more commonly used anti-anginal drugs.

Patients with recurrent angina, however, often represent a real challenge for achieving symptomatic control. Treatment is usually approached in terms of short trials of an intervention. A subgroup of patients will become asymptomatic after initiation or dose optimization of the anti-angina regimen. Anecdotal reports suggest that some of the patients benefit from the addition of calcium-channel blockers as they had an unrecognized vasospastic component to the angina.[56,57]

The benefit of HMG-coA reductase inhibitors (statins) in patients with CAD is clear. High-dose statins also appear to induce regression of atherosclerosis.[58] It is worth noting that the use of vascular protective treatments (i.e. aspirin, statins, angiotensin-converting enzymes, and beta-blockers) is often suboptimal in patients after coronary revascularization.[59,60] The ongoing COURAGE trial will test the effects of PCI on top of 'aggressive' medical therapy (including aspirin, clopidogrel, simvastatin, metoprolol, amlodipine, lisinopril [or losartan], and nitroglycerin).[60]

Several newer therapeutic agents are currently under intense investigation for the treatment of angina.[61] Trimetazidine, a 3-keto-acyl-CoA inhibitor, enhances favourable myocardial metabolism (TRIMPOL II study).[62] Ranolazine, which appears to act via changes in cellular sodium and calcium currents, improved the ischaemic threshold in the CARISA study.[63] Favourable results were also observed with nicorandil, an anti-anginal agent that is thought to act by mediating the opening of potassium (ATP) channels (IONA trial).[64]

The beneficial effects of exercise training should also be considered. Although not specifically tested in patients with recurrent angina, when compared with PCI, exercise training in patients with chronic stable angina was associated with superior event-free survival and exercise capacity.[65]

Due to the lack of universal and standardized recognition of the syndrome of recurrent angina after PCI, observational studies may have enrolled broad and heterogeneous groups of patients. Patients without residual significant coronary artery stenosis (at angiography) and reproducible angina are sometimes enrolled in these studies together with patients with refractory angina who have severe coronary artery disease not deemed treatable with PCI. The former group is usually referred to as having microvascular dysfunction ('Syndrome X'), and prognosis is usually good (*Table 1*).[66] The latter group of patients is often considered to be suffering from refractory angina (*Table 1*). The definition of refractory angina should be reserved to those patients who may have had one or more coronary revascularization procedures in past but are not considered candidate for further interventions (according to coronary anatomy) and remain highly symptomatic despite optimal medical therapy. These patients usually have severe limitation in daily activities and a poor prognosis. Relief of symptoms in these patients is urgent as they are functionally limited in daily activity. In some instances, treatment of refractory angina is to be considered palliative. Several different treatments have been proposed with non-pharmacological treatments being demonstrated to be the most effective.[67,68]

Detailed discussion of non-pharmacological treatments for refractory angina is beyond the scope of this review. Enhanced external counterpulsation (EECP) is currently used in the United States for the symptomatic relief of angina. The recent Report from the International EECP Patient Registry (IEPR) showed significant improvements in anginal status and quality of life that are maintained at 2 years.[69] Logistics and patient preference, however, limit widespread application of EECP.

Transcutaneous electric spinal cord stimulation (SCS) has recently been shown in European studies to reduce angina as well as improve functional capacity with the potential to reduce ischaemia.[70] A pacemaker is implanted in the subcutaneous tissue and leads are guided to the spinal cord. SCS was also shown to be effective in patients with cardiac syndrome X.[71]

Surgical transmyocardial laser revascularization (TMR) is used for the treatment of refractory severe angina. Surgical TMR is associated with a significant improvement of angina and functional capacity at 1 and 5 years, reducing the need for re-hospitalization.[72] The benefits need to be weighed against the potential risks of surgery. However, a survival advantage for patients undergoing surgical TMR has also been reported (5-year survival 65% for

Table 4 Commonly used anti-anginal drugs

Anti-platelet agents	
Aspirin	81–325 mg daily[a]
Clopidogrel	75 mg daily[b]
Beta-blockers	
Atenolol	25–200 mg daily
Metoprolol	25–200 mg daily[c]
Calcium-channel blockers	
Amlodipine	5–10 mg daily
Diltiazem	60–480 mg daily[c]
Nifedipine XR	30–120 mg daily[c]
Verapamil	80–480 mg daily[c]
Nitroderivatives	
Isosorbide mono-/di-nitrate	10–120 mg daily[d]
Nitroglycerin	0.4–1.2 μg/h[d]
Nicorandil	5–20 mg daily[c,f]
Ranolazine	1000–2000 mg daily[e,f]
Trimetazidine	20–70 mg daily[e,f]

This list is not meant to be comprehensive. Regimens need to be adjusted to the individual patient. Indications may vary in the different nations according to their regulation.

[a]Current ACC/AHA guidelines recommend a dosage of 325 mg daily after coronary stenting. This recommendation is based on consensus rather than direct evidence of a superiority of 325 mg dosage vs. lower regimens.

[b]The duration of dual-antiplatelet therapy with aspirin and clopidogrel is based on the type of stent used [1 month (BMS), 3 months (SES), and 6 months (PES)] and on the clinical scenario 12 months for acute coronary syndromes. Longer treatments, although advocated by many, are not supported by current evidence, and should be determined on an individual case basis according to the clinical and angiographic risk of late thrombosis.

[c]Regimen to be administered in divided doses; extended release formulation may be available for some of the drugs.

[d]Regimen to be administered in divided doses, a drug-free period of >6 h during the 24 h should be observed.

[e]Ranolazine and Trimetazidine are available in extended release tablets (500 mg and 35 mg, respectively) that are administered on a twice daily basis.

[f]Nicorandil and Trimetazidine are commercially available in Europe but not in the USA. Ranolazine, on the other hand, is commercially available in the USA but not in Europe.

TMR vs. 52% for medical therapy only, $P = 0.050$.[72] Percutaneous transmyocardial revascularization to date has not been shown to be effective but new studies are still ongoing.[67,68]

Neovascularization of ischaemic myocardium is the objective of intense research. The possibility of restoring oxygen supply/demand balance by increasing its supply through the formation of new vessels in the ischaemic myocardium is indeed very appealing.[73–75] This goal has been attempted by means of exogenous vascular growth factors administration, cell transplantation, and vascular growth factors gene therapy. To date there are too few studies and results that are promising although somewhat inconclusive.

Technical challenges of repeat interventions

Strategic planning prior to re-intervention is essential. Assessment of coronary and bypass anatomy is pivotal. Previous angiograms should be viewed, as this simple comparison might enable the identification of the most likely culprit lesion. If such a culprit cannot be identified by morphological assessment, two approaches can be proposed. The first is based on the selective treatment of the functionally most important lesion, on the basis of the results of imaging testing, morphologic features at angiography, quantitative coronary angiography, intravascular ultrasound, and/or fractional flow reserve. Another approach is to aim towards anatomically complete revascularization. There is still no conclusive evidence that one strategy has a better risk-effectiveness profile than the other for recurrent angina.

Treatment of restenotic lesions has different implications in case restenosis occurs after balloon-only angioplasty or after stenting. Nonetheless, considering the results of the more recent studies, DES implantation can be advocated in both settings given the better results provided by these devices.[76] Repeat balloon-only angioplasty, BMS implantation with or without debulking, or brachytherapy have all shown suboptimal results. The recently published SISR trial has randomized 384 to brachytherapy or sirolimus eluting-stent implantation for in-stent restenosis.[76] The use of SES and of PES were associated with a $>50\%$ relative risk reduction in target-lesion revascularization at 6 months.[76–78] Whenever recurrent angina is not due to restenosis but rather due to lesion progression, the approach to PCI is the standard one.

Re-do CABG is fraught by a significant increase in morbidity and mortality, and usually only vein grafts or second-choice arterial conduits can be employed.[79]

PCI in patients with recurrent angina due to bypass failure is particularly challenging, owing to the diffuse nature of their native CAD, older age, and different physiopathology of graft disease, in particular in the case of vein grafts (which are still the most commonly used grafts).[33–35] Due to procedural difficulties and incidence of complications, any attempt to treat the native artery should be done if feasible, considering that procedures may be required not only in the segment proximal to the graft insertion site but also distally. When attempting PCI of vein grafts, best available evidence suggests the use of stents in association with distal protection devices, even if recurrent events are still likely.[80–82] The use of DES is promising in reducing target-lesion revascularization,[83–85] keeping

in mind, however, that long-term (>1 year) events after PCI in vein grafts is mainly a result of progression of other lesions that were considered non-significant ($<50\%$ in diameter stenosis) at the time of initial procedure.[85]

Conclusions

Angina recurring or persisting after successful coronary revascularization affects a substantial number of patients, with morbidity and potential mortality implications. Both diagnosis and treatment may prove challenging, especially in patients treated with CABG or multi-vessel PCI. Despite these diagnostic and management hurdles, there may still be room for interventions leading to symptomatic and prognostic benefit, especially given the recent advancements in medical therapy, percutaneous coronary devices, and cardiac surgery.

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