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Review Article

Coronary artery disease: to cath or not to cath? When and how best to cath: those are the remaining questions

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Abstract: Coronary artery disease is the leading cause of death worldwide and it often clinically manifests as stable angina. The optimal diagnostic and therapeutic strategy of patients with stable angina may be controversial. Coronary revascularization with percutaneous coronary intervention (PCI) is associated with a reduction in cardiovascular events in patients with acute coronary syndrome, whereas recent trials have failed to demonstrate the superiority of myocardial revascularization over optimal medical therapy in stable angina. The treatment of a patient with stable angina is still challenging, as the definition of "stable" and "unstable" is not so clear. Moreover, the benefit of PCI in terms of quality of life is evident, and independent from its neutral effect on survival. To date, the best timing of coronary angiography and the role of further investigations on myocardial ischemia still need to be defined. On the other hand, in spite of the clear benefit on clinical outcome of an early invasive treatment of patients with acute coronary syndrome, elderly are often undertreated, whereas the overtreatment with PCI of stable patients undergoing non cardiac surgery might even increase ischemic events due to the premature discontinuation of the antiplatelet therapy, without reducing the perioperative risk.

Keywords: Coronary artery disease, stable angina, diagnostic and therapeutic strategy, coronary revascularization, percutaneous coronary intervention (PCI), antiplatelet therapy

Introduction

Coronary artery disease (CAD) is the leading cause of mortality in most industrialized countries [1] and angina represents one of its common clinical manifestations [2]. The diagnosis and the treatment of stable angina is still a matter of debate. A direct invasive examination should be performed in patients with a high pre-test likelihood of CAD, whereas an exercise testing should be performed only to patients with an intermediate likelihood [3]. On the other hand, coronary revascularization seems to exert favourable effects on survival in patients with extensive CAD and documented moderate-to-severe ischaemia. Recent trials [4-7] have shown no significant difference in outcomes in the treatment of stable angina patients with revascularization versus optimal medical therapy alone (OMT), whereas a routine early invasive strategy is associated with a more favourable outcome in patients with unstable angina and non-ST elevation myocardial infarction (NSTEMI) [8-10]. Of note, the majority of patients admitted with a diagnosis of acute coronary syndrome involve patients older than 65 years of age, who are often undertreated due to their higher risk of procedural complications [11]. On the other hand, in spite of the evident limits of PCI and the lack of evident beneficial effects, PCI is often performed without clear indication in patients undergoing non-cardiac surgery. The peri-operative management of the antiplatelet therapy in these patients is controversial and is often arbitrary. Surgery represents the most frequent cause of premature discontinuation of the antiplatelet therapy, which is associated with an increased risk of stent thrombosis [3, 12-15].

Stable angina

Patient 1 is a 58 year old man. He is a current smoker, on angiotensin-converting-enzyme inhibitors therapy for hypertension. He goes out for jogging 3 times a week. He met a cardiologist because in the last 6 weeks he couldn't run without moderate substernal chest pain, which tended to disappear at rest.

The cardiologist planned an ECG stress test on Bruce protocol, which revealed a mild ST segment depression at 150 Watt. Afterwards, an exercise stress single photon emission computed tomography (SPECT) was scheduled 3 months later. In the meanwhile, the patient was asked not to practice sport any longer, but no specific medication was prescribed. Two months later, before the stress SPECT was performed, the patient experienced an acute ST segment elevation myocardial infarction (STEMI). The urgent coronary angiography revealed the occlusion of the proximal segment of the right coronary and mild atherosclerosis of the left coronary artery. Primary percutaneous coronary angioplasty (PCI) was performed and the course was uneventful.

Coronary artery disease (CAD) is the leading cause of death worldwide, contributing to over 7.2 million deaths annually [1]. A prompt coronary revascularization with PCI is associated with a reduction in cardiovascular events in patients with ACS, whereas the optimal treatment strategy of stable CAD, which clinically manifests as stable angina, is not well defined [9, 10, 16-22].

What are exactly the definitions of "stable" and "unstable" angina? Despite this fairly classic definition, the diagnoses of stable angina and, more concerning, the diagnosis of unstable angina are often missed. Patient 1 experienced the first episode of substernal discomfort 6 weeks before his outpatient visit. Had he met the cardiologist 2 weeks earlier, he would have been defined as an "unstable" patient and an invasive coronary angiography would have been promptly performed.

Moreover, do we still have "stable" patients? Nowadays, it has become rather infrequent to visit patients (especially if young) with "stable" angina, as we often visit them at the first clinical manifestations of the disease. In such cases of recent onset angina, and thereafter, "unstable" by definition, a coronary angiography should always be performed.

However, even in cases of "stable" angina, the guidelines recommend to submit to direct invasive examination patients with a high pre-test likelihood of CAD, whereas an exercise testing should be performed only to patients with an intermediate likelihood [3]. Our patient's risk factors and his typical symptoms of angina conferred him a high pre-test likelihood of CAD, which should had led him to direct coronary angiography.

Once the diagnosis of CAD is made, how should we approach it? Current guidelines for the management of stable angina emphasize risk factor modification, namely smoking cessation, exercise, diabetes mellitus management, lipid lowering, antianginal, and antihypertensive therapies [23]. With advancements in medical therapies over the last 2 decades, it is unclear whether PCI provides a prognostic advantage over optimal medical therapy (OMT) in the management of stable angina patients. Recent trials [18-21] have shown no significant difference in outcomes in the treatment of stable angina patients with revascularization versus OMT alone. In the COURAGE trial, patients were randomly assigned to undergo PCI and OMT or OMT alone [4]. The Authors demonstrated that PCI did not reduce the risk of death, myocardial infarction (MI), or other major cardiovascular events when added to OMT. Of note, of the 35.539 screened patients, only 2.287 (6.4%) participated to the study and 10% of patients in both groups were lost to follow-up. Moreover, allocation of treatment was made only after coronary angiography, thus excluding patients at increased risk. Half of patients had minimal or no symptoms of angina, 1 out of 4 patients had limited ischemia, and left ventricular ejection fraction (EF) was preserved in both groups. Patients were enrolled between 1999 and 2004, and thereafter drug eluting stents (DES) were used only in 2.6% of the PCI group patients. Six per cent of the patients in the PCI group did not undergo PCI, 14% of the lesions were treated only with balloon angioplasty, and clinical success was achieved in 89% of patients [4]. The definition of peri-procedural MI with any increase of CK-MB could have contributed to the increase of MACE, without clear

prognostic relevance, thus disadvantaging the PCI group [24], whereas cross-over from medical treatment to subsequent revascularization was not considered an adverse event. Thirty per cent of patients in OMT group required revascularization with PCI or CABG at follow up, compared with 19,8% of the PCI group. The latter might be further reduced if DES had been used. Of note, all patients showed high rates of adherence to lifestyle modifications as recommended by clinical practice guidelines [23], and the mean values of LDL cholesterol at 5 years were 76±0.85 for the OMT group and 72±1.21 for the PCI group [4]. This made the patients in the OMT group not fully representative of the *real world* population, for whom we should expect a lower rate of lifestyle modifications. By contrast, *real world* PCI treated patients are currently receiving a higher standard of care, due to the higher use of stents, in particular of DES, which might contribute to the reduction of MACE at follow-up.

The comparison between PCI and OMT in patients with stable CAD was made also in a recent metanalysis, which was conducted on 12 randomized trials [7]. No significant difference emerged in outcomes of all-cause mortality, cardiovascular death, nonfatal MI, or need for symptom-driven subsequent revascularization with PCI when compared with OMT alone. However, the point estimate for all-cause mortality and cardiac death favored PCI and was most prominent in trials with longer duration of follow up. Of note, PCI was associated with a greater freedom from angina in the overall analysis and at all studied time points [7]. However, some limitations of this metanalysis are evident. Angioplasty without stenting was performed in the majority of included trials, as the first patients were enrolled in 1987. Moreover, in the vast majority of stented patients BMS were used and the use of DES was reported in a very low percentage of patients only in the COURAGE and BARI 2 trials [4, 6]. It is therefore unknown whether these results can be extrapolated to contemporary cohorts of patients. The COURAGE and MASS-2 notably included a high proportion of patients with triple vessel CAD, where surgical revascularization options should also have been considered [4, 25]. Obviously, no trial was blinded, the analysis of symptom-driven revascularization and freedom from angina outcomes was subjective and, subsequently, prone to reporting bias by providers and participants, respectively. Moreover, there was notably significant statistical heterogeneity among trials included in this analysis at all time points. The older MASS-1 and ACME trials were outliers showing greater proportion of early repeat PCI or CABG required in the PCI group, possibly due to less experience and more complications during this era [26-28]. Finally, there existed no standard definition for stable CAD, as the trials had varying angiographic definitions for significant coronary stenosis and only a minority clearly described a requirement for clinical symptoms of angina.

What is the principal goal of revascularization in stable CAD? Even if it does not seem to reduce mortality, it confers the relief of ischaemia, improves quality of life and exercise capacity, reduces the amount of anti-angina drugs, and ultimately improves prognosis on top of the beneficial effect of medical treatment [24]. Symptomatic and asymptomatic ischaemia are of prognostic importance in patients with CAD particularly when occurring at low workload [29, 30]. Compared with medical therapy, revascularization has been consistently shown to more effectively relieve angina, relieve myocardial ischemia, reduce the use of anti-angina drugs, improve exercise capacity and quality of life [31, 32]. In the RITA-2 and COURAGE studies angina frequency and quality of life were assessed systematically [33]. PCI relieved angina and improved self-assessed health status to a greater degree than medical therapy alone up to 24 months. This benefit from PCI was greatest among patients with severe and frequent angina, and one-third of patients in the medical therapy group subsequently underwent PCI for symptom relief during follow-up.

However, in cases of intermediate stenosis at coronary angiography, the ESC guidelines for revascularization recommend a functional assessment, non-invasive or invasive [3]. Even experienced interventional cardiologists might not predict accurately the significance of most intermediate stenoses on the basis of visual assessment or quantitative coronary angiography [34, 35]. The FAME 1 trial demonstrated that in patients with multivessel CAD, routine measurement of fractional flow reserve (FFR) during PCI, as compared with the standard strategy of PCI guided by angiography, significantly reduced the rate of the primary compos-

Table 1. Baseline clinical and angiographic characteristics in the COURAGE, FAME, and FAME 2 trials patients

Trial	Courage	FAME	FAME 2
Enrolled/screened patients (%)	6.4	52.7	NA
DES (%)	2.6	96.9	100*
Angina status CCS 0-2 (%)	PCI group: 78, OMT group: 80; P=NS	angiography group: 56.5, FFR group: 59.3; P=NS	PCI group: 75.8, OMT group: 77.6; P=NS
Triple vessel CAD (%)	PCI group: 30, OMT group: 31; P=NS	Overall patients 23	PCI group: 8.9, OMT group: 7.7; P=NS
MACE definition	All cause death, MI	Death, MI, repeat revascularization	Death, MI, urgent revascularization
Overall MACE (%)	PCI group: 19, OMT group: 18.5; P=NS	angiography group: 18.3, FFR group: 13.2; P=0.02	PCI group: 12.7, OMT group: 4.3; P<0.001
Death (%)	PCI group: 7.6, OMT group: 8.3; P=NS	angiography group: 3, FFR group: 1.8; P=NS	PCI group: 0.2, OMT group: 0.7; P=NS
Periprocedural MI (%)	PCI group: 3.0, OMT group: 0.7	angiography group: 3.2, FFR group: 2.3; P NS	NA
Revascularization (%)	PCI group: 21.1, OMT group: 32.6; P<0.001	angiography group: 9.5 FFR group: 6.5; P=0.08	PCI group: 3.1, OMT group: 19.5; P<0.001

*second generation DES. CAD=coronary artery disease; CCS=Canadian Cardiovascular Society; DES=drug eluting stent; FFR=fractional flow reserve; MACE=major adverse cardiac events; MI=myocardial infarction; OMT=optimal medical therapy; PCI=percutaneous coronary intervention; NA= not applicable.

ite end point of death, MI, and repeat revascularization at 1 year [35]. The combined rate of death and MI was also significantly reduced. Of note, only half of the screened patients were enrolled in the trial and the majority of patients at the time of enrolment were asymptomatic or had only mild angina. Moreover, the lower incidence of the composite primary end-point of death, MI, and repeat vascularization in the OMT patients compared with PCI patients was mainly due to a lower incidence of MI and repeat revascularization, the latter probably influenced by the investigators. Of note, it is not clear how repeat revascularization was driven and only first generation of DES were used. Moreover, the 1-year rate of death or MI was surprisingly high, being 11.1% in the angiography group and 7.3% in the FFR group, similar to those emerged in acute coronary syndromes trials, like TRITON-TIMI 38 and PLATO [36, 37].

It has been demonstrated that the potential benefit of revascularization is correlated with the presence and extent of myocardial ischemia [38-40]. In the myocardial perfusion substudy of COURAGE, PCI compared with OMT showed a greater absolute reduction in myocardial ischemia and more patients exhibited a relevant reduction in ischaemia, particularly among those with moderate to severe ischaemia [40]. Again, there was a graded relationship between reduction of ischaemia and subsequent risk of death or MI with improved event-free survival in patients with significant reduction of ischemia [40]. The FAME 2 study demonstrated that in patients with stable CAD and functionally significant stenoses, FFR-guided PCI plus the best available medical therapy, as compared with the best available medical therapy alone, decreased the need for urgent revascularization [41]. **Table 1** shows the clinical and angiographic characteristics of the patients enrolled in the COURAGE, FAME, and FAME 2 trials.

The National Heart, Lung, and Blood Institute is sponsoring The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial to find the best management strategy for patients with stable ischemic heart disease and moderate to severe ischemia [42]. The trial will compare angiography and revascularization plus OMT with the conservative strategy of OMT only and is designed to answer questions raised by the seminal COURAGE and BARI 2D trials, which found no mortality benefit for revascularization over OMT in patients with stable ischemic heart disease [42].

In the FAME-2 trial, in patients without ischemia, the outcome appeared to be favorable

with the best available medical therapy alone [41]. But, on the other hand, according to the ESC guidelines on myocardial revascularization, revascularization should be *anatomically-driven* and 50% lesion of proximal left anterior descending artery or left main have a class I recommendation of revascularization in patient with stable angina or silent ischemia [7]. So, how should we cope with these apparent contradictory indications? Might a recent onset angina be considered as a clear marker of ischemia? In patients with recent onset (even if > 4 weeks), typical angina and a single "intermediate" lesion, do we really need to further investigate the severity of the stenosis? Angina is a marker of ischemia itself, and, even though a PCI probably might not condition long term prognosis if the lesion, the patient will experience a clinical benefit in terms of quality of life. Moreover, in cases of (quite) recent onset of angina, an haemodynamic assessment of the coronary stenosis may not be conclusive, whereas the evaluation of the plaque morphologic features might provide more relevant information.

Elderly patients

Patient 2 is an old woman, aged 85 years old, who lives alone and has no relevant comorbidities. In the last 2 months, she refers worsening, typical, substernal chest pain which wakes her up every night. The symptoms are also associated with mild exertion during the day. Since the first manifestations of angina, she has been visited by 3 cardiologists, who have prescribed her statins, aspirin and nitrates. No beta-blocker was prescribed due to significant bradycardia. At first, she experienced some relief of the symptoms, but in the last 2 weeks the symptoms worsened and the patient was visited by 2 more cardiologists who titrated nitrates at the maximum dosage. No benefit was obtained, though, the patient could not sleep any more at night, and angina was associated with any level of physical activity. Finally, she underwent coronary angiography which revealed 99% proximal left anterior descending artery lesion with an ulcerate plaque, no other lesion was found. PCI with the implantation of a BMS was performed and the patient was discharged on day 2. After 1 month she was completely asymptomatic, slept every night, and did a 30 minute walk every day.

Most of the admissions for acute coronary syndromes involve patients older than 65 years of age, and increased age has been identified as an important risk factor for death or recurrent MI [11]. In the RITA trial, age was the strongest predictor of death or MI, with more than a doubling of risk for every 10 years of age over 60 years [43]. Physicians caring for these patients are faced with immediate decisions about substantially different management strategies that may significantly affect short- and long-term outcome. It has been widely demonstrated that routine early invasive management yields superior outcomes in a broad population of patients with unstable angina and NSTEMI [8-10]. However, because elderly persons are at greater risk for complications with catheterization and revascularization procedures, the benefit of such a strategy in this subgroup remains uncertain. Moreover, elderly persons have traditionally been underrepresented in clinical trials of acute coronary syndromes [11, 44]. In current clinical practice, older patients with acute coronary syndromes are less likely to undergo invasive procedures than are younger patients [45-49]. The subgroup analysis of the TACTICS TIMI 18 trial demonstrated that, compared with younger patients, elderly patients with unstable angina and NSTEMI had a markedly increased rate of adverse ischemic outcomes and a routine early invasive strategy reduced death or nonfatal MI among elderly patients [11]. This strategy had greater absolute benefit for reduction of death or nonfatal MI in older patients than in younger patients, and both the absolute and relative benefits increase with increasing age. Of note, the early invasive strategy significantly increased major bleeding among patients older than 75 years of age, who showed an absolute increase of 10.1 percentage points in major bleeding with early invasive therapy. The high rate of bleeding might be explained by the use of glycoprotein IIb/IIIa inhibitors and underlines the need of a drug dosage reduction for elderly people, not adequately represented in randomized clinical trials.

Also the analysis of the FIR (FRISC II- ICTUS-RITA 3) trials shows that the long-term benefit of the routine invasive strategy over the selective invasive strategy was evident for patients aged 65-74 years (HR 0.72, 95% CI 0.58 to 0.90) and those aged ≥75 years (HR 0.71, 95%

CI 0.55 to 0.91), but not in those aged <65 years (HR 1.11, 95% CI 0.90 to 1.38) [50].

In the Elderly ACS trial, patients with an initially conservative treatment experienced significantly more ischemic events during index admission, although these were mostly episodes of recurrent ischemia prompting urgent angiography [51]. Within 1 year, a 20% difference in the rates of the primary endpoint between the early aggressive and the initially conservative cohorts was observed. This difference was not statistically significant in the present trial, which was powered for a 40% difference in the primary endpoint rate. However, patients with elevated troponin levels on admission randomized to an early aggressive approach had a significant 57% reduction of the primary endpoint rate. Of note, the rate of dual antiplatelet therapy with aspirin and clopidogrel at discharge was significantly higher in the initially conservative group and this might have contributed to the reduction of adverse events in this group.

Our patient had a fortunate and uneventful outcome, but had to wait 2 months for an invasive approach in a setting of acute coronary syndrome. In the meanwhile, a dramatic event like a large anterior STEMI might have occurred, with the need of an emergent PCI and a less favourable outcome.

Coronary angiography and non cardiac surgery

Patient 3 is a 55 year old man who had been submitted to elective PCI with DES on circumflex artery 2 years earlier. His medication were aspirin 100 mg, atenolol 100 mg, simvastatin 20 mg. The patient was completely asymptomatic and played tennis 2-3 times a week. He underwent regular cardiologic follow-up. Due to hematuria, the patient was referred to abdominal scan which revealed a 2 cm mass in his bladder. An endoscopic bladder resection was scheduled. In the preoperative cardiac evaluation, an ECG stress test was suggested. The test showed a mild ST segment depression at 175 watt, while the patient was completely asymptomatic. A preoperative coronary angiography was then performed, which showed a 70% stenosis in the mid RCA. The patient underwent a new PCI with BMS implantation and the surgical intervention was postponed of 6 weeks.

Did PCI really reduce the perioperative risk of this patient? The ACC/AHA guidelines on non cardiac surgery state that PCI before noncardiac surgery is of no value in preventing perioperative cardiac events, except in those patients in whom PCI is independently indicated for an acute coronary syndrome [52]. Patients undergoing low-risk surgery (class I) and patients with functional capacity greater than or equal to 4 METs without symptoms (class IIa) are recommended to proceed to planned surgery [52]. Noninvasive testing might be considered only if it will change management for patients with poor (less than 4 METs) or unknown functional capacity and 3 or more clinical risk factors [52]. Our patient is undergoing undeferrable, low risk surgery, and has a functional capacity greater than 4 METs without symptoms. In highly functional asymptomatic patients, management will rarely be changed based on the results of any further cardiovascular testing. According to ACC/AHA guidelines, it is therefore appropriate to proceed with the planned surgery [52].

The balance of the evidence to date suggests that routine preoperative coronary revascularization in patients with stable Class I, II or III angina will not alter perioperative risk, unless cardiac catheterization reveals high-risk surgical anatomy [52]. Even in patients with unstable coronary syndromes depending on the results of the coronary angiography and the risk of delaying surgery, it may be appropriate to proceed to the planned surgery with maximal medical therapy. Of note, previous studies on prophylactic revascularization before non cardiac surgery are often small and not conclusive [53-55].

If prophylactic revascularization has been not demonstrated to reduce perioperative events, on the other hand noncardiac surgery in a patient who has undergone a prior PCI presents special challenges, particularly with regard to the management of the antiplatelet agents. The management of antiplatelet therapy in patients with coronary stents undergoing surgery is a growing clinical problem and often represents a matter of debate between cardiologists and surgeons. It has been estimated that about 4-8% of patients undergoing coronary stenting need to undergo surgery within the next year [56-62]. Surgery represents one of the most common reasons for premature antiplatelet therapy discontinuation, which is asso-

ciated with a significant increase in mortality and major adverse cardiac events, in particular stent thrombosis [63, 64, 12-14]. In addition, surgery confers an additional risk of perioperative cardiac ischemic events, being high in these patients because of the pro-inflammatory and pro-thrombotic effects of surgery [65-67]. Practice guidelines recommend that elective noncardiac surgery be delayed until surgery can be performed safely using antiplatelet therapy with aspirin alone [52]. Delaying surgery for at least 2 to 4 weeks after balloon angioplasty to allow for healing of the vessel injury at the balloon treatment site is supported by the study by Brilakis et al [68]. In case of PCI with stent implantation, current international guidelines recommend to postpone non-urgent surgery for at least 6 weeks after bare metal stent implantation and for 6-12 months after DES implantation [52]. Previous studies showed an increased risk of adverse cardiac events when noncardiac surgery was performed shortly after stent implantation [56, 59, 69-71]. Specifically, urgent-to-emergent procedures, which are likely to necessitate noncardiac surgery soon after PCI, are associated with an almost 4-fold increased risk of mortality [72]. A recent study by Wijeysundera and Colleagues suggests that elective noncardiac surgery can be performed reasonably safely in carefully selected patients once at least 6 months have elapsed since DES implantation [73]. There may also be an optimal time window for performing surgery within the year after bare-metal stent implantation, namely from 46 to 180 days after PCI. Although the presence of this optimal window is not certain, this window is biologically plausible. It represents the period when re-endothelialization is largely complete after bare-metal stent implantation but when in-stent restenosis has yet to completely manifest itself [74, 75]. Conversely, once >1 year has elapsed since either bare-metal stent or DES implantation, physicians can be reassured that the associated perioperative cardiac risk has reached a plateau, with risks similar to that of individuals with remote histories of previous PCI (ie, 2 to 10 years before surgery) [73].

How should we manage the antiplatelet therapy in patients recently implanted with coronary stent and undergoing undeferrable surgery? Current international guidelines provide little support with regard to managing antiplatelet therapy in the perioperative phase in case of urgent operations and/or high hemorrhagic risk [46]. Furthermore, ischemic and hemorrhagic risk is not defined in detail on the basis of clinical and procedural characteristics. Finally, guidelines shared with cardiologists and surgeons are lacking.

A consensus document on the management of antiplatelet therapy in the perioperative period in patients with coronary stents undergoing surgery has been recently published [76]. Cardiologists and surgeons contributed equally to its creation. An ischemic risk stratification has been provided on the basis of clinical and procedural data. All surgical interventions have been defined on the basis of the hemorrhagic risk. A consensus on the most appropriate antiplatelet regimen in the perioperative phase has been reached on the basis of the ischemic and hemorrhagic risk. Dual antiplatelet therapy should not be withdrawn for surgery at low bleeding risk, whereas aspirin should be continued perioperatively in the majority of surgical operations. In the event of interventions at high risk for both bleeding and ischemic events, when oral antiplatelet therapy withdrawal is required, perioperative treatment with short-acting intravenous glycoprotein IIb/IIIa inhibitors (tirofiban or eptifibatide) should be considered [76].

Conclusions

Coronary angiography should be performed in patients with stable angina especially if it is of relatively recent onset. PCI should be considered as a valuable adjunct rather than an alternative to medical therapy. Of note, the benefits of revascularization are associated with a low peri-procedural risk and therefore justify their implementation for symptomatic as well as prognostic reasons. As with most other therapeutic interventions in medicine, the relief of symptoms remains a noble task of physicians caring for patients with stable CAD, particularly in today's executive society where only few would opt to accept angina symptoms impeding their otherwise active life style.

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