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Debate

Pro Percutaneous Coronary Intervention (PCI) in Patients with Stable Angina (SA)

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PRO–PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH STABLE ANGINA

In this article, we will defend percutaneous coronary intervention (PCI) — and revascularization as a whole — as a first line treatment in patients with stable angina pectoris. In our opinion, there is strong and sufficient evidence to advocate PCI as an adjunct to medical therapy in the optimal treatment of stable angina (SA). Our argument is based on four pillars: (1) SA patients concern a heterogeneous population; (2) not every SA patient is created equal; (3) obvious limitations of medical therapy; and(4) the issue of symptom control.

COMMON PRACTICE

When one is defending a particular treatment modality, it may be useful to examine the current "common practice." What is already done at this moment in general practice? If we look at the Euroheart survey, it seems that the interventional cardiology community is already pro-PCI in SA. This survey describes PCI practice between 2005 and 2008 in 33 European Society of Cardiology member countries and involves more than 45,000 PCI patients. Of all the PCI procedures included, no less than 48.5% were done as an elective procedure for SA (obviously this is an important observation, but it does not equal evidence-based medicine).[1]

On the other hand, "stent bashing" or "stent nihilism" is generally accepted even in the popular media, certainly since the publication of the Courage trial in 2007, in which PCI failed to reduce death or myocardial infarction compared to medical therapy alone.[2] For instance, on a consumer reports Internet site, coronary stents are among the top five most-overused tests and treatments.[3] This stent unpopularity is largely due to the fact that until now PCI has not shown any real prognostic benefit when compared to medical therapy alone. In our opinion, this can be explained at least partially by the heterogeneity of the SA patient population and the problems this causes in clinical trials.

A HETEROGENEOUS PATIENT POPULATION

Definition

The exact definition and therefore the diagnosis of SA is cumbersome and consists, as the name says, of two parts: angina and stability.

Angina is defined in most cardiology textbooks by the presence of all three of the following characteristics: (1) substernal chest discomfort of characteristic quality and duration; (2) provoked by exertion or emotional stress; and (3) relieved by rest and/or nitrates. When two of these characteristics are present, one speaks of atypical angina; and when one or none of these criteria is met, it probably concerns noncardiac chest pain. The diagnosis is made even more arduous because of anginal "equivalents" such as dyspnea, faintness and fatigue, which are especially common in the elderly. Moreover, the anginal threshold may vary considerably from day to day and even on the same day.[4,5]

Stability is in the first place defined by the absence of instability; this is characterized by new-onset angina, worsening angina or rest angina. Grading is done most often with the Canadian Cardiovascular Society grading system (class I–IV with decreasing activities causing angina, with class IV angina at rest and thus per definition unstable angina). In fact, the diagnosis of angina is a clinical one and depends largely on a correct anamnesis and an accurate patient observation. Even more, SA could be regarded as a diagnosis of exclusion, including every more or less typical chest pain without arguments for unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI).

Pathophysiology

The physiopathological substrate of angina also differs, ranging from a critical epicardial stenosis across a nonsignificant stenosis to microvascular disease. All these very different anatomical entities can cause significant

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angina, with another natural history. But even when a clear culprit lesion combined with a typical clinical scenario has been identified, we do not know for sure whether we have to stent this lesion or not. This is due to the fact that, until now, we have not been able to reliably identify the potentially dangerous coronary plaque that could be responsible for a future acute coronary event.[6] Identifying lesions that are responsible for large areas of ischemia is more feasible, either with noninvasive testing or measurement of fractional flow reserve (FFR), and this can guide treatment, as will be clarified later on in the text.

Natural History

The natural history and thus the prognosis of a patient with SA varies considerably and is dependent on baseline clinical, functional and anatomical factors. Estimates for annual mortality rates range from 0.9% to 1.4% per year, with a large variation in the annual incidence of nonfatal MI ranging from 0.5% to 2.6%. It is clear this risk is way below that observed in acute coronary syndromes.[5]

In conclusion, this heterogeneity caused by the troublesome diagnosis, differing underlying pathophysiology and the large variation in event rate and prognosis is at least partially responsible for the fact that PCI has failed to accrue a prognostic benefit compared to medical therapy. This "PCI failure" has repeatedly been shown in most clinical trials and their most recent meta-analyses,[7,8] although one has to admit not all meta-analyses are neutral or negative for PCI.[9]

NOT EVERY STABLE ANGINA PATIENT IS CREATED EQUAL

As just pointed out, no patient with SA is equal and therefore he or she requires a particular, "personalized" treatment plan. In the guidelines on myocardial revascularization that were published in 2010, this is reflected by the identification of subsets of patients with SA who do benefit from revascularization in terms of prognosis. In short, there are two main categories: "high anatomical risk" and "high clinical risk" patients *(Table 1)*.[10]

Table 1. High Anatomical and High 'Clinical' Risk Subsets of Patients.

Recommendation for Patient Subset Revascularization	
LM > 50%	I A
Proximal LAD > 90%	I A
2–3 VD with impaired LVEF	I B
Large area of ischemia > 10%	I B

Adapted from ESC/EACTS Guidelines on Myocardial Revascularization (2010). LM — left main; LAD — left anterior descending; LVEF — left ventricular ejection fraction. [10]

High Anatomical Risk

These patients have SA and a significant LM or proximal LAD stenosis.

Concerning >50% LM stenosis or left main equivalent (>70% prox. LAD and >70% prox. RCX), we know that these are associated with a high cardiovascular event rate, with a 3-year survival as low as 37% if left untreated.[11] The CASS registry showed a clear survival benefit up to 15 years with CABG compared to medical therapy (median survival advantage of 7 years in 912 patients).[12] So, there is not much room for discussion about the optimal treatment in this subset of patients, meaning that they have to be revascularized.

The discussion of PCI vs. CABG for the treatment of significant LM disease goes beyond the scope of this opinion article. In short, both large registries (MAIN-COMPARE) and prospective studies (SYNTAX LM subgroup analysis, PRECOMBAT trial) suggest a promising role for PCI compared to CABG with similar MACE rates but with a higher rate of target vessel revascularization for PCI.[13–15]

Significant proximal LAD stenosis is also an independent predictor of a worse cardiovascular outcome. When the 5-year mortality rate is stratified according to angiographic severity of coronary artery disease, there is an independent and very strongly negative influence of severe proximal LAD disease, as shown in *Table 2* (assuming only medical treatment).[16] Clearly, these data urge revascularization for these patients.

High anatomical risk is not only restricted to these "classical" high-risk lesions but can also be interpreted in a broader sense: severity of coronary artery disease (CAD) as a whole. Long-term survival estimates in more than 18,000 patients treated either medically or with revascularization were reported in function of three levels of baseline severity of CAD. Revascularization provided significant survival benefit over medical therapy, with 8.1, 10.6 and 23.6 additional months per 15 years of followup for low-severity, intermediate-severity and high-severity disease, respectively.[17]

High Clinical Risk

The second SA patient subset benefits from revascularization because of an elevated clinical risk.

Table 2. 5-Year Mortality Rate Startified According to Angiographic Severity of Coronary Artery Disease With or Without Servere Proximal LAD Stenosis.

Anatomy	**5 Year Mortality**
1-vessel disease	7%
1-vessel disease; > 90% prox. LAD	17%
2-vessel disease	12%
2-vessel disease; > 90% prox. LAD	21%
3-vessel disease	21%
3-vessel disease; > 90% prox. LAD	41%

Adapted from JACC 1996; 27: 964–1047.[16]

Patients with significant CAD and an impaired left ventricular ejection fraction are often excluded from clinical trials (exclusion criterion in COURAGE, <2% in SYNTAX), although there can be a clear benefit from revascularization through an important amelioration of left ventricular function. In general, there are more data proving the benefit of CABG in this subset of patients without any direct comparisons between CABG and PCI available. The Canadian APPROACH registry, however, included 4228 patients with CAD and heart failure, out of whom 2538 were revascularized (half CABG, half PCI). Crude 1-year mortality was 11.8% among those who were revascularized, compared to 21.6% among those who were not. Adjusted survival curves diverged early and continued up to 7 years of followup.[18]

It is paramount to prove the presence of viable myocardium before revascularization, since the expected benefit is largest in patients with viable (hibernating) myocardium. This was elegantly proven in a meta-analysis by Allman et al. which showed an almost 80% reduction in annual mortality in favor of revascularization versus. medical therapy in patients with viable myocardium, while in the absence of viability there was no significant difference in outcome.[19]

Patients with CAD and a large area (> 10%) of demonstrable ischemia compose the second group, which has an elevated clinical risk. This was nicely demonstrated in the much-cited article by Hachamovitch et al., who showed an absolute and relative survival benefit (50% reduction in cardiac death) for revascularization compared to medical therapy in patients with moderate-to-large (>10%) amounts of inducible ischemia on SPECT.[20] More recently, in the nuclear substudy of the COURAGE trial, involving just over 300 patients, patients with >10% ischemic myocardium had a lower risk of death and MI with revascularization (through a >5% reduction in ischemia).[21] In this regard, the results of the ongoing ISCHEMIA trial are eagerly awaited. This trial will compare OMT with OMT + revascularization in 8000 high-risk patients with significant inducible ischemia on noninvasive testing before evaluation of coronary anatomy.[22]

As a third, high-clinical-risk category we want to mention FFR <0.80, as recently published in the FAME II trial. This study was prematurely halted after randomization of 888 patients with SA and functionally significant coronary stenosis (FFR <0.80). Patients were randomly assigned to FFR-guided PCI + MT versus MT alone. In the PCI group there was a significantly lower event rate, mainly driven by a lower rate of urgent revascularization (combined primary endpoint event rate 4.3% in the PCI group versus 12.7% in the medical therapy group).[23] These data highly support the indication of PCI for FFR-positive lesions as an initial treatment option in patients with stable angina pectoris.

In conclusion, there will often be an indication for revascularization in patients with SA because of the common presence of these high-anatomical-risk or high-clinical-risk features — although, even in the absence of these features, there will often be a need for revascularization because of the troubles encountered with medical therapy, as will be explained in the next section.

THE ISSUE OF MEDICAL THERAPY

In a very recently published large observational study, common practice for the treatment of stable CAD was described in New York. The study was done in a real world population, in a setting apart from a randomized controlled trial. Between 2003 and 2008, 9586 patients with SA and significant CAD were included, with a mean followup of 2.87 years. First, treatment practice was described in the whole population: 11% received routine medical treatment (RMT) alone, and 89% received RMT + PCI. This is a confirmation of what we said in our introduction about common practice: it seems that we are already pro-PCI in SA (certainly in New York), given these very high rates of percutaneous revascularization. Second, 1866 patients were propensity-matched (933 pairs) to correct for factors that could have a bearing on outcomes. RMT + PCI patients versus RMT patients had a significantly lower adverse outcome rate for mortality/myocardial infarction (16.5% vs. 21.2%), mortality (10.2% vs. 14.5%) and subsequent revascularization (24.1% vs. 29.1%).[24] In our opinion, this result is in large part due to the fact that in a real world population, as in this study, patients are treated with routine medical therapy (RMT) and not with optimal medical therapy (OMT), and this brings us to the actual issue of medical therapy. OMT, ideally combined with lifestyle changes, can be accomplished in a clinical trial setting, often with the aid of a nurse manager (as was done in the COURAGE trial)[25] RMT, on the other hand, is what a patient takes without coaching, in a real world setting and with the usual (sporadic general practitioner) care. Self-reported adherence to the combination of aspirin, a beta blocker and a lipid-lowering agent in patients with CAD has been reported to be <40% in long-term followup surveys. Patients with high adherence rates have a significantly lower risk of cardiovascular events than those with low adherence rates.26 Furthermore, OMT means a cocktail of medications (aspirin, statine, ACE inhibitor for disease modification and nitrates, calcium antagonists, beta blockers for symptom control) and often in escalating doses, which makes intolerable side

effects and nonadherence more likely. In conclusion, OMT is in general very difficult to achieve, certainly in combination with the necessary lifestyle changes. Therefore, in real world clinical practice (meaning RMT) the added beneficial effect of PCI on outcome will likely be greater than the effect in the ideal world of a trial (meaning OMT). This is true not only for outcome but also for symptom control, as will be clarified in the next part of the text.

THE ISSUE OF SYMPTOM CONTROL

When one is evaluating PCI versus medical therapy in SA, the focus is predominantly on outcome. Of course, this is of paramount importance, but when one is treating this heterogeneous and rather low-risk population the importance of symptom control and quality of life cannot be overemphasized. As with outcome, the expected beneficial effect of PCI on symptom control is dependent on how optimal the patient's medical therapy is. This was demonstrated in a meta-analysis focused on angina relief (14 trials, 7818 patients). In the most contemporary trials, in which evidence-based medications were used more often, the benefit associated with PCI for symptom relief was diminished. On average, with each additional medication class, the advantage of PCI over medical therapy decreased by 31%.[27]

Overall, PCI is very effective in relieving angina through a direct effect of a reduction in the ischemic burden through improved myocardial oxygen supply without the side effects of medication. It can even decrease the need for antianginal medications and increase exercise capacity and quality of life. Patients with the most significant anginal burden at baseline obtain the greatest benefit from PCI. This has repeatedly been shown in recent randomized trials and their meta-analyses.[8,27–30] Moreover, we want to emphasize in this regard the importance of early revascularization for SA: it will prevent future (semi) urgent revascularization for unbearable angina and we do not see the utility of a patient's continued suffering despite the numerous medications that he or she is possibly taking irregularly or at an insufficient dose. PCI improves the ischemic burden immediately, whereas medical therapy has a much slower onset of action through plaque stabilization, plaque regression, reduction in myocardial oxygen demand and ischemic preconditioning.[31] After all, there is nothing wrong with treating a patient's symptoms by means of an invasive procedure without a major beneficial effect on his or her outcome. Entire medical specialties are devoted to this practice.[32]

CONCLUSION

Patients with SA represent a very heterogeneous population for which a highly individualized treatment strategy is needed. We believe that PCI should be considered a first-line treatment modality in conjunction with medical therapy in selected patients, since there is a prognostic benefit in the often encountered "high-risk anatomical" and "high-risk clinical" patient subsets and since it is very effective in relieving angina with a very rapid onset mode of action. In this predominantly

low-event-rate population, the effect of a particular treatment on symptom control is as important as the effect on outcome. PCI is a very effective tool for symptom control without the drawbacks of medical therapy. These drawbacks consist not only of medication side effects but also of the fact that it is extremely difficult to achieve an optimal medical therapy in real world practice, where a more pragmatic real world routine medical therapy will pertain. Of course, as always, the final treatment decision has to be personalized to the patient after informed consent, taking into account risk stratification, the patient's personal preference and medication adherence.

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