Chronic Stable Angina: Percutaneous Coronary Intervention or Medication?

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Coronary artery disease is a worldwide hazard today and stable angina is one of its commonest manifestations.1,2 The diagnosis of chronic stable angina is based on the presence of anginal symptoms, a positive exercise test for myocardial ischaemia, and confirmation of coronary artery atherosclerosis by coronary angiography.3

However, the optimum treatment of these patients has been a controversial issue in recent years.2,4 Recent studies, or meta-analyses thereof, have still not fully determined the usefulness of invasive treatment of the coronary arteries with percutaneous coronary intervention (PCI) in comparison with medication. While PCI is known to reduce the incidence of death and myocardial infarction in patients who suffer from acute coronary syndromes, the same benefit does not appear to extend to patients who have stable coronary artery disease.5,6

As the availability of non-invasive methods of diagnosing coronary artery disease steadily increases, asymptomatic patients are often referred for PCI. However, a necessary condition for any preventive therapy is that it should combat a threat— which in the case of stable coronary artery disease is acute myocardial infarction and death— with an acceptable cost.

Review of relevant published studies

One of the first studies to compare the effectiveness of PCI in patients with stable angina, compared to medication alone, was the ACME trial (Veterans Affairs Angioplasty Compared to Medicine).7 The patients in that study had known one-vessel disease and a positive exercise test, and were followed for a total of six months. The investigators found greater improvement of symptoms and better exercise tolerance in the PCI group, although the incidence of death and myocardial infarction was similar in the two groups. PCI, however, was associated with a greater cost and a higher complication rate.

The ACME 2 trial studied men with two-vessel disease, stable angina, and a positive stress test, who were treated with either PCI or medication, and the results were compared with those from the previous study of men with one-vessel disease.8 The study showed that angioplasty was less effective in controlling symptoms in patients with two-vessel disease and stable angina than in those with one-vessel disease.

The ACIP study (Asymptomatic Cardiac Ischaemia Pilot) included patients who were either without symptoms or had symptoms controlled with medication, with asymptomatic ischaemia on 24-hour Holter monitoring and a positive exercise
test.9,10 The study showed, over a two-year follow up, that these patients had a better prognosis when they were reperfused either with angioplasty or surgically.

The AVERT trial (Atorvastatin VERSus Revascularisation Treatment) was designed to examine the effect of aggressive lipid-lowering treatment on the incidence of ischaemic symptoms.11 The study enrolled 341 patients with mild to moderate stable angina and good left ventricular contractility, who were followed for 18 months and were treated either with angioplasty or with medication—the latter included 80 mg atorvastatin per day. The findings of the study showed that medication achieved a reduction in anginal complaints similar to that achieved by angioplasty.

In the MASS study (Medicine, Angioplasty, or Surgery Study), 214 patients with stable angina and good left ventricular function, with >80% stenosis of the proximal anterior descending coronary artery branch, were followed for 5 years.12 The patients were treated with either angioplasty or drugs. Although anginal episodes were reduced in the PCI group, there was no difference in the “hard” endpoints such as myocardial infarction and death.

The ALKK13 study (Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte) enrolled 300 patients with mild or no angina after a recent myocardial infarction (one to six weeks previously) and one-vessel disease, who were followed for 56 months. In these stable patients it was shown that PCI in the culprit artery was associated with a lower use of nitrates and a better prognosis.

In the RITA-2 trial (Second Randomised Intervention Treatment of Angina), 1018 patients without angina who had angiographically documented coronary artery disease were initially treated with only medication or PCI.14,15 Over a seven-year follow up, the PCI group had fewer anginal episodes and greater exercise tolerance, although there was no reduction in acute infarctions or death. It should be noted, however, that 35.4% of the patients in the medication group ultimately underwent reperfusion during the study period.

The TIME study (Trial of Invasive versus Medical therapy in the Elderly) included patients aged more than 75 years who had angina that was refractory to at least two anti-anginal drugs.16-19 The aim of the study was to investigate the effect of medication alone, or in combination with PCI, in reducing major adverse cardiovascular events (death, non-fatal myocardial infarction, hospitalisation for angina with or without reperfusion) and improving the patients’ quality of life, over a six-month follow up. The study demonstrated a small early improvement in quality of life in the group who underwent PCI. Over a four-year follow up there was no difference in mortality between the two groups. Therefore, invasive treatment could be used in elderly patients with refractory angina in order to relieve their symptoms, without promising any prolongation of life.

Hambrecht et al studied 101 patients with stable one-vessel coronary artery disease (angiographic stenosis >75%), who were either treated with PCI or followed an exercise regimen (20 min daily on a bicycle ergometer).20 The patients also had angina (Canadian Cardiovascular Society, CCS class I to III) and myocardial ischaemia documented by a non-invasive test. In this study it was found that patients who exercised showed a clinical improvement by one CCS class in comparison with the PCI group, as well as a longer interval free of cardiac events, at half the cost.

A sub-analysis of the DANAMI study (DANish Acute Myocardial Infarction study), including 1008 patients who had undergone thrombolysis because of an acute myocardial infarction and had residual ischaemia (silent or symptomatic), showed that invasive treatment reduced the risk of non-fatal reinfarction, as well as hospital admissions for unstable angina.21

The INSPIRE (adenosine sestamibi SPECT Post-Infarction Evaluation) study followed 205 stable patients after acute myocardial infarction, with ejection fraction >35% and with high-risk criteria on myocardial adenosine scintigraphy (adenosine SPECT).22 The aim of the study was to investigate the possible benefit of intensive drug therapy compared with PCI as regards the reduction in scintigraphically monitored ischaemia. It was found that optimal drug treatment had results comparable with those of reperfusion as regards the reduction in scintigraphic perfusion defect.

In the MASS II study, 611 patients with stable angina on a substrate of multi-vessel coronary artery disease (>70% stenosis in proximal segments of the coronary arteries) and documented myocardial ischaemia on exercise testing were treated either with medication alone or with PCI.23-26 A comparison of the groups revealed no difference in cardiac deaths or total mortality. However, the PCI group had a significantly lower incidence of anginal episodes.

The SWISSI II (SWiss International Study on Silent Ischaemia) trial included 201 patients with a recent myocardial infarction and silent ischaemia.27 The patients were treated either with medication alone
or with PCI and were followed for a mean period of about ten years. The PCI arm showed a benefit in terms of reduced cardiovascular events.

Of particular importance were the results of the recent COURAGE study (Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation). This study was carried out from 1999 to 2004 and included 2287 patients with stable angina and objective evidence of myocardial ischaemia, who were treated with medication either alone or in conjunction with PCI. One limitation of the study was the relatively small number of women included (15%). Patients with left main disease, a strongly positive exercise test, refractory angina CCS class IV, drug-refractory heart failure or cardiogenic shock, or an ejection fraction <30% were excluded, as were those who had undergone reperfusion during the previous six months or who had a coronary anatomy unsuitable for PCI. The patients in this study had either >70% stenosis in the proximal segment of an epicardial coronary artery together with findings of myocardial ischaemia on exercise testing or the resting ECG, or >80% stenosis and typical angina. However, one quarter of the patients did not have anginal symptoms. The mean follow up was 4.6 years. Angina in the medication group improved at one year, with a further benefit at five years. Although angina improved more in the PCI group initially, the difference was not statistically significant after five years. It should be taken into consideration that by the end of the study about a third of the patients in the medication group had undergone reperfusion because of treatment-refractory angina or because of a worsening of ischaemia on a non-invasive ischaemia test. In the COURAGE study, drug-eluting stents were implanted in only 2.7% of the patients. Finally, a recent meta-analysis by Trikalinos et al of all the studies from the last 20 years concerning the treatment of chronic coronary artery disease with PCI showed that, in a total of 25,388 patients, despite the technological advances, PCI did not reduce the incidence of fatal myocardial infarction or death compared to drug treatment alone.

The recent BARI 2D study (Bypass Angioplasty Revascularisation Investigation) was not able to show a benefit from PCI in terms of mortality and cardiovascular events in diabetic patients with chronic coronary artery disease and angina (>70% stenosis of a major coronary artery, or >50% stenosis and a positive exercise test), confirming and reinforcing the results of the COURAGE trial.

Finally, a recent meta-analysis by Trikalinos et al of all the studies from the last 20 years concerning the treatment of chronic coronary artery disease with PCI showed that, in a total of 25,388 patients, despite the technological advances, PCI did not reduce the incidence of fatal myocardial infarction or death compared to drug treatment alone.

The designs and outcomes of the most important of the preceding studies are summarised in Table 1.

Reasons for the results so far – weakness of studies

A recent publication by Katritsis et al, concerning the effect of PCI on prognosis in patients with stable coronary artery disease, points out the relatively short follow-up period in most studies, with the exception of SWISSI II (10.2 years) and COURAGE (4.6 years). The same article also mentions that the myocardial ischaemia was not confirmed by an invasive examination in most investigations.

We also know that it is mainly the characteristics of the atheromatous plaque, rather than the degree of stenosis (which was used as the indication for PCI in most studies), that determine the risk of plaque rupture and the occurrence of an acute coronary syndrome, and hence the prognosis of the coronary patient. Patients with stable angina have mainly stable
plaques with a thick fibrous cap, small fatty cores, more smooth muscle cells, fewer macrophages, and more collagen.

At the same time, significant progress in modern drug treatments has greatly improved prognosis through the introduction of new medications (thienopyridines, statins, angiotensin-converting enzyme inhibitors) for patients with coronary artery disease, many of which were not available and were not used in most of the trials. Also, compliance with the drug regimen was not the same, not only in different studies, but also in different groups of a given study.

There has also been significant progress in the techniques, methods and materials used in modern PCI of the coronary arteries. However, many of the abovementioned studies used either plain old balloon angioplasty, or bare-metal stents, whereas drug-eluting stents were only used in a small percentage of the patients who were treated invasively. More specifically, as mentioned previously, in the COURAGE trial drug-eluting stents were only used in 2.7% of the patients. On the other hand, in a recent study by Horst et al it appeared that drug-eluting stents are superior in the first year after their implantation, as re-

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**Table 1.** Design and outcomes of the main studies comparing percutaneous coronary intervention (PCI) with medication in patients with chronic stable angina.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Follow up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACME</td>
<td>One-vessel disease + ischaemia on exercise test</td>
<td>6 months</td>
<td>Greater improvement of symptoms and better exercise tolerance in PCI group</td>
</tr>
<tr>
<td>ACIP</td>
<td>Asymptomatic or symptomatic with ischaemia on 24-hour Holter or positive exercise test</td>
<td>2 years</td>
<td>Better prognosis in reperfusion group</td>
</tr>
<tr>
<td>MASS</td>
<td>Stable angina and &gt;80% stenosis in proximal part of anterior descending</td>
<td>5 years</td>
<td>Reduction of angina episodes in PCI group</td>
</tr>
<tr>
<td>ALKK</td>
<td>No or mild angina after recent myocardial infarction</td>
<td>56 months</td>
<td>Improved prognosis in PCI group</td>
</tr>
<tr>
<td>RITA-2</td>
<td>Without angina, with angiographically documented coronary artery disease</td>
<td>7 years</td>
<td>Reduction of angina episodes and increased exercise tolerance in PCI group</td>
</tr>
<tr>
<td>TIME</td>
<td>Refractory to at least two angina drugs</td>
<td>4 years</td>
<td>Early small improvement in quality of life in PCI group</td>
</tr>
<tr>
<td>INSPIRE</td>
<td>Post-infarction with high-risk criteria on myocardial adenosine scintigraphy</td>
<td>62 days</td>
<td>Optimum medication resulted in results comparable with reperfusion in reduction of perfusion defect</td>
</tr>
<tr>
<td>DANAMI</td>
<td>Post-infarction with residual myocardial ischaemia</td>
<td>2.4 years</td>
<td>Reduction of reinfarctions and hospitalisations in PCI group</td>
</tr>
<tr>
<td>SWISSI II</td>
<td>Post-infarction or with silent ischaemia and one- or two-vessel coronary artery disease</td>
<td>10.2 years</td>
<td>Benefit as regards major cardiovascular events in PCI group</td>
</tr>
<tr>
<td>MASS II</td>
<td>Stable angina with multi-vessel disease and documented myocardial ischaemia</td>
<td>5 years</td>
<td>Significant reduction in anginal episodes in PCI group</td>
</tr>
<tr>
<td>COURAGE</td>
<td>Stable angina and findings of myocardial ischaemia</td>
<td>4.6 years</td>
<td>No reduction in mortality or major cardiovascular events in PCI group</td>
</tr>
<tr>
<td>Gu Y et al.</td>
<td>Stable angina and &gt;70% stenosis of one vessel</td>
<td>24 months</td>
<td>No benefit in terms of cardiovascular events in PCI group</td>
</tr>
<tr>
<td>Shaw LJ et al.</td>
<td>Sub-study of COURAGE patients</td>
<td>6-18 months</td>
<td>Reduction of ischaemia as documented by myocardial scintigraphy in PCI group</td>
</tr>
<tr>
<td>Nishigashi K et al.</td>
<td>Stable angina and low-risk coronary artery disease</td>
<td>3.3 years</td>
<td>Reduction in acute coronary events in PCI group</td>
</tr>
<tr>
<td>Katritsis DG et al.</td>
<td>Meta-analysis of 17 studies</td>
<td></td>
<td>Improved survival in reperfusion group</td>
</tr>
<tr>
<td>BARI 2D</td>
<td>Diabetics with chronic coronary artery disease</td>
<td>5 years</td>
<td>No benefit as regards mortality and cardiovascular events in PCI group</td>
</tr>
<tr>
<td>Trikalinos TA et al.</td>
<td>Meta-analysis of 61 studies</td>
<td>Last 20 years</td>
<td>No reduction in incidence of myocardial infarction or death in PCI group</td>
</tr>
</tbody>
</table>
gards restenosis, mortality, myocardial infarction, and cerebrovascular stroke, but that those differences are blunted after the first year.39-41

Special notice should be taken of the lack of homogeneity among the patient populations in the different studies, mainly as regards the angiographic extent of the underlying coronary artery disease and the different severity of the clinical syndrome.

All the above factors provide a rationale for the lack of any consensus among the findings of different studies, while it appears that in order to draw safe conclusions regarding the effectiveness of the two methods of treatment it is essential to perform case-by-case risk stratification for future events. Also, it seems that knowledge of the coronary anatomy is a necessary prerequisite for the choice of the appropriate treatment modality.

**Guidelines for PCI in patients with chronic stable angina**

The guidelines for the treatment of stable angina issued by the European Society of Cardiology in 2006 state that PCI has a Class IIa indication for improvement of prognosis in a patient with reversible ischaemia on functional testing and frequent ischaemic episodes during daily activities.42 Coronary artery angioplasty is indicated (Class I) for improvement of symptoms in patients with one-vessel coronary artery disease who are eligible for invasive treatment and have symptoms that are not controlled by medication (and in whom the periprocedural risk does not exceed the expected benefit). In multi-vessel disease, without high-risk coronary artery anatomy in patients with moderate to severe symptoms, angioplasty improves symptoms and also has a Class I indication. Angioplasty has a class IIa indication in patients with only one-vessel disease, eligible for invasive treatment, with mild to moderate symptoms that are not tolerated. In multi-vessel disease with mild to moderate symptoms, PCI also has a Class IIa indication when the patient cannot tolerate the symptoms.

The corresponding guidelines of the American College of Cardiology and the American Heart Association recommend PCI with a Class IIa indication in patients with asymptomatic ischaemia or angina in CCS class I or II, with one or more significant stenoses in one or two coronary arteries that supply a moderate to large region of viable myocardium, or are associated with a moderate or severe degree of ischaemia on non-invasive examination.43-45 PCI received a Class IIa indication in patients with asymptomatic ischaemia, or CCS class I or II angina and restenosis after angioplasty in an artery that supplies a large region of viable myocardium, or in the presence of high-risk criteria on non-invasive examination. Angioplasty is also recommended in patients with asymptomatic ischaemia, or angina of CCS class I or II, with significant stenosis of the left main coronary artery (>50%) that cannot be treated surgically (Class IIa). In patients with CCS class III angina, angioplasty is recommended in those with one-vessel disease or multi-vessel disease who have one or more significant stenoses in one or more arteries suitable for PCI (Class IIa indication). It is also recommended in those with angina CCS class III with significant left main coronary artery disease who cannot undergo surgery, or in surgically treated coronary arteries with multiple stenoses in grafts that are not susceptible to reoperation (Class IIa).

**Conclusions**

Previous studies, notably COURAGE, and meta-analyses have shown that PCI of the coronary arteries as documented does not improve mortality or the risk of myocardial infarction in patients with chronic stable angina. The controversy continues to grow, however, since some new meta-analyses show an improvement in survival33,46 for patients in this category who undergo PCI, while others do not.35

It appears, however, that in the initial treatment of patients with chronic stable angina who are considered to be at low or medium risk, medication and lifestyle changes are sufficient in most cases, especially if the symptoms do not significantly affect their quality of life.47

In every case where a therapeutic strategy must be laid out, it is essential to take into account features such as symptomatology, quality of life, sex, race, ejection fraction, compliance with medication, prognosis based on non-invasive tests for myocardial ischaemia, angiographic findings, and the characteristics of the atheromatous plaque.

It is very important to keep in mind that the two approaches are not in opposition, but are complementary, with a view to achieving the optimum therapy of the coronary patient. In any case, we know from the results of studies that a significant percentage of patients who are initially treated with medication will eventually undergo invasive treatment.

The need to design new large trials to examine the treatment of patients with chronic stable angina...
is still compelling. In adequately risk-stratified patients who are to be enrolled in such studies, optimal and maximal drug treatment should be administered, based on the guidelines. In the PCI arm the most modern techniques and materials must be used with a view to maximising reperfusion and minimising the ischaemic burden. Only through this approach will it be possible to evaluate the effectiveness of each method in relation to the hard endpoints of death and non-fatal myocardial infarction.

References


