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### Appropriateness of Percutaneous Transluminal Coronary Angioplasty in Stable and Unstable Angina Pectoris. A review

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# Appropriateness of Percutaneous Transluminal Coronary Angioplasty in Stable and Unstable Angina Pectoris. A review

Lars Grip

Coronary artery disease is the main cause of mortality and morbidity in the Western world. In order to reduce symptoms and also to improve survival, revascularization measures are performed on a wide scale. Coronary artery bypass graft surgery (CABG) procedures have escalated since the 70s, and for the past two decades, percutaneous transluminal coronary angioplasty (PTCA) has been performed with increasing volumes and also progressive success. Approximately 100–200 PTCA per 100 000 inhabitants are performed annually in different western European countries (1, 2). Whilst the numbers of PTCA are constantly increasing, the numbers of CABGs seem to be levelling off and today a significant majority of revascularization procedures are done with PTCA. Recently presented results of, among others, the ARTS trial, suggest that PTCA with stent can be safely done also in multivessel disease, with a long-term outcome for survival and rate of myocardial infarction comparable to that of CABG. The results of that study also indicate that PTCA can be an economically attractive alternative in many cases. There is, however, most certainly grounds for considering whether PTCA is appropriate in a number of situations.

## SHORT AND LONG-TERM RESULTS AFTER PTCA

During the 20 years following the advent of PTCA, there has been a continuous improvement in device technology; stents have gained a wide usage, adjunctive medical treatment has been optimized, especially with the introduction of glycoprotein (GP) IIb/IIIa receptor antagonists, and operators and centres have gained experience. All these factors contribute to high-quality performance and good results (3–9).

Thus, today angioplastic procedures can, in stable or unstable angina, be performed with an immediate success rate of approximately 95% (SCAP; the Swedish Coronary Angioplasty Registry, 1998). Procedure-re-

lated mortality from the same registry is 0.03% and the need for emergency CABG approximately 0.4%. This means that if patients with low risk are selected and with proper use of stents and adjunctive therapy with GP IIb/IIIa receptor antagonists, there is no longer a need for on-site surgery back-up. Certain lesion characteristics still remain a challenge. Thus, bifurcation lesions, stenoses in severely curved vessel segments, in ostial location and in small vessels (i.e. <2.5 mm in diameter) are treated with lower success and higher complication rates. For chronic total occlusions in particular, the success rates may be as low as 60%.

Injury to the vessel wall will produce a reaction causing smooth muscle cell proliferation and migration as well as neointima hyperplasia, resulting in shrinking of the vessel, (remodelling), as well as intimal thickening. These processes will lead to a restenosis after balloon angioplasty in 30–50% of cases. The process can be partly compensated for by the use of stents with a reduction of restenosis to 15–25% (10, 11). Restenosis still remains a problem, however, since in-stent restenosis is difficult to treat and may impose a risk of future cardiovascular events. The risk of restenosis depends on clinical and lesion morphological characteristics. Thus, after both balloon and stent angioplasty restenosis rate is increased in diabetic patients, following treatment of long lesions and chronic total occlusions. Furthermore, location in the proximal part of the left anterior descending artery (LAD) is associated with increased risk of restenosis compared with other vessel segments (12). Several targets of pharmacological therapy have been tested in order to reduce the problem of restenosis. Today, compounds with anti-inflammatory, antioxidative or platelet-inhibiting properties seem to be the most promising. Currently, three drugs are being tested, tranilast, probucol and cilostazol, all of which have demonstrated very promising effects in early pilot studies (13–15). Radiation therapy, with both gamma and beta radiation, has also been explored as a mode of restenosis reduction (16). Fear of late adverse effects have, to date, restricted its use to restenotic lesions in which a number of studies have shown very promising preliminary results (17).

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## BENEFIT OF REVASCULARIZATION THERAPY

Results from three major trials performed 20 years ago comparing medical therapy with revascularization with CABG constitute the basis for knowledge on the benefits derived from revascularization therapy. Revascularization in patients with left main stenosis and three-vessel disease, especially when accompanied with impaired left ventricular function, substantially reduces long-term mortality as compared to medical treatment (18–20). There also seems to be some benefit in two-vessel disease if the proximal segment of the LAD is involved. In patients with normal left ventricular function, beneficial effects are smaller, that is if there is any beneficial effect at all. Medical therapies seem, in these cases, to do just as well. When reviewing these results, it is important to remember that they were obtained in an era before the widespread use of aspirin, beta-blockers as well as lipid-lowering and ACE-inhibiting agents.

Although widely used, coronary angioplasty has been compared to medical treatment in three minor studies only. In the ACME trial, 212 patients were randomized (21). Results showed that PTCA offered earlier and more complete relief from angina than medical therapy but PTCA was associated with a high risk of complications. In the RITA II trial, 1018 patients were randomized out of 70000 patients screened for inclusion. The number of included patients, when compared with the screened population, revealed a heavy bias towards low-risk patients. Thus patients in whom early myocardial revascularization was deemed necessary for symptom relief or prognostic benefits were excluded. Patients undergoing PTCA had a higher risk of cardiac events, i.e. a composite of death and myocardial infarction that predominantly occurred in the early phase after randomization and must be considered to be more or less procedure-related (22). Quality of life was assessed 3 months, 1 year and 3 years later. The results demonstrated that PTCA was substantially more effective in improving quality of life as well as symptoms such as breathlessness and angina (23). In the AVERT trial, PTCA was compared with a high dose of atorvastatin (24). In this study, medical therapy was associated with a significantly lower risk of ischemic events after randomization (25). These events were, however, related to revascularization procedures and worsening of angina.

All these trials suffered from severe limitations since they obviously have recruited low-risk patients, where neither the physicians nor the patients considered revascularization necessary from pre-existing experience and knowledge. They were probably right. Furthermore, the exact location of the coronary artery disease has not been described and thus conclusions concerning, for example, one-vessel disease with proxi-

mal LAD stenosis cannot be made. PTCA in low-risk patients will only result in procedure-related complication rates and need for subsequent revascularization procedures, which are higher than what should be expected from the natural course of the disease.

In patients with clearly ischemic reactions during daily life or during exercise test, however, revascularization measures have been clearly demonstrated to be beneficial. This has not been described separately for PTCA, but in the ACME trial 558 patients with ischemia underwent either revascularization procedures or had medical therapy (26). More than half of the revascularized patients underwent PTCA. In this study there was a clear benefit of revascularization for late mortality and myocardial infarction. Similar experiences are at hand for patients with unstable coronary artery disease. In the FRISC II trial, unstable patients with either release of markers for myocardial injury or ST-changes indicative of ischemia derived significant benefit from revascularization, PTCA or CABG (27).

## THE OPEN(-ED?) ARTERY

Data from a number of thrombolytic trials provide evidence that an open infarct-related artery in the late course of an acute myocardial infarction is associated with better long-term prognoses than a closed and occluded artery (28, 29). This does not, however, automatically translate into benefits from opening occluded arteries in the late course after acute myocardial infarction, and certainly not in a more chronic phase of coronary artery disease. There are number of unrandomized observations demonstrating relationship between recanalization with PTCA and preserved or improved left ventricular performance in the long term after myocardial infarction (30–32). These trials do not, however, prove that recanalization in itself is of any benefit but rather that long-term vessel patency and left ventricular performance are associated.

In the chronic phase, more consideration shall be focused on what will happen to plaques and stenoses in the long term and what are the risks of progression associated with significant cardiac events. From angiographic studies, it has been demonstrated that critical stenosis progresses to occlusion more often than milder stenosis and non-significant plaques (33, 34). There is, however, not necessarily an association between progression and cardiac events. If progression takes place slowly, collaterals may well have time to develop. Even if this association between severity of stenosis and progression exists, still the vast majority of cases of progression to occlusion, and a probable myocardial infarction, take place in vessels that are non-significantly stenosed (35). The most dangerous moment for patients with coronary artery disease is probably when a

plaque in a non-hemodynamically stenosed artery ruptures and a severe stenosis or occlusions develop within a short period of time. The result of such a rupture is likely to result in a large myocardial infarction or in sudden death. These events cannot be predicted from a coronary arteriogram. They will subsequently not be prevented by any form of coronary angioplasty. On the contrary, coronary angioplasty, even if successfully performed, will have a low risk of subacute occlusions. Furthermore, the restenotic process will lead to progression in the stenosis in at least 20–30% of all patients, despite treatment with intracoronary stents.

#### BALLOON ANGIOPLASTY VERSUS CABG

Balloon angioplasty has been compared with coronary artery bypass surgery for multivessel disease in six major randomized trials (36–41). In the RITA-1 trial single-vessel disease was also included. A common finding in all these trials was that concerning serious coronary events after a procedure, treatment with PTCA seems to be on a par with CABG. The effects on symptom relief and the need for subsequent repeated revascularization procedures were, however, poorer for PTCA as compared to CABG. There are some limitations to the studies; for example, only a very few patients with impaired left ventricular performance were included. Furthermore, it has not been stated to what extent patients with multivessel disease including a proximal LAD stenosis was recruited to the trials.

#### CORONARY ANGIOPLASTY WITH STENT AS COMPARED TO CABG FOR MULTIVESSEL DISEASE

The above-mentioned studies comparing PTCA with CABG were performed before the era of stenting. Since stents improve immediate success rate by providing a tool for treatment of threatened abrupt closure as well as improving long-term results by reducing restenosis, it can be expected that the use of stents may improve late results after PTCA, especially in multivessel disease. This concept has been tested in three recent trials. In the ARTS trial (presented at the XXIth Congress of European Society of Cardiology 1999) it was demonstrated that PTCA with stent had equal short- and long-term results when compared with CABG for two- and three-vessel disease in both stable and unstable angina pectoris. The need for repeated revascularization was higher in the stent group, but this was not associated with a high risk of cardiovascular events. Furthermore, the revascularization need was less than in the previous randomized trials, and an economic analysis revealed that PTCA with stent might be cost effective. The other

studies, the SOS trial and the ERACI II trial, will soon be presenting further data.

#### INCOMPLETE REVASCULARIZATION?

When deciding the treatment modality for patients with multivessel disease, it is important to define whether all lesions should be revascularized or not. Early experiences from the CASS registry demonstrated that patients undergoing coronary artery bypass surgery had better long-term results if complete revascularization was performed (i.e. with at least three grafts to three or more vessels) compared with patients with incomplete revascularization. The benefit also concerned late mortality (42). Data from PTCA procedures are less compelling. Thus, report from the NHLBI PTCA registry did not demonstrate any difference between patients who underwent PTCA with complete or incomplete revascularization (43). Data from the BARI study revealed results in a similar direction. However, incomplete revascularization with PTCA clearly resulted in an increased need for further revascularizations as well as less good results concerning angina pectoris in the long term after the procedure (44, 45). Although there was no significant difference in mortality, there was a clear trend towards higher mortality among patients with angioplasty with incomplete revascularization intended. Thus as of today, there is evidence that incomplete revascularization is less effective in improving symptoms and it may be that incomplete revascularization may be associated with increased late cardiac mortality. Concerning a concept of culprit lesion revascularization in cases of unstable angina pectoris, this has not been tested in any randomized trial.

#### THE LAD STENOSIS

Approximately 50% of all patients undergoing PTCA do so because of a stenosis in the LAD (SCAP 1998). Of patients with coronary artery disease, the presence of stenosis in the LAD represents a special entity, since it is clearly shown that these patients suffer from a worse prognosis in the long term than patients with involvement of other epicardial arteries (46). Angioplasty of a LAD stenosis is often performed without much consideration for alternative strategies. It should be remembered, however, that stenosis location in the proximal part of the LAD is, in comparison with other vessel segments, associated with an increased risk of restenosis after both balloon angioplasty and stent implantation (12, 47). The alternative of coronary artery bypass surgery should be brought forward, especially since analysis of the previous trials on CABG versus medical therapy, demonstrated that much of the benefit

from surgery was revascularization of the LAD with left internal mammaria artery (LIMA) grafts (48). Material recruited early in the era of coronary angioplasty clearly demonstrated a superior long-term effect of bypass surgery to the LAD either by vein graft or by LIMA graft when compared to PTCA (49). This is even more obvious in materials with surgical grafting solely by LIMA grafts (50). The latter material demonstrated that LIMA grafting resulted not only in a reduced need for repeated revascularization procedures but also for a clear tendency towards lower long-term mortality after LIMA-LAD surgery when compared with PTCA.

A randomized trial comparing PTCA with CABG for LAD stenosis demonstrated that both methods were good at improving clinical status but that new revascularizations were needed more frequently after PTCA (51). There was an excess of non-Q-wave myocardial infarction during 5-year follow-up in the PTCA group. Also in this study, there was a non-significant trend towards higher mortality after PTCA compared with after CABG. Preliminary 5-year data from a study also comparing medical therapy with CABG and PTCA came to the same conclusions (52). In this study medical therapy even came out somewhat better than PTCA.

The few studies performed so far, addressing the treatment of LAD stenosis, have compared conventional CABG with balloon angioplasty. In recent years the technique for CABG has been developed to be less invasive (MidCab) and, above all, operating without a heart and lung machine ("off-pump"). This may reduce the risk of the operation and, it is hoped, with good results preserved (53). At the same time, stents have become accepted as a general treatment during an angioplasty procedure. While studies big enough to make a meaningful comparison are awaited, preliminary reports of comparisons between MidCab/"off-pump" surgery versus PTCA with stent have yielded results that confirm that both methods can be used with excellent clinical results, but with somewhat better effects on angina after surgery (54). For treatment of complex lesions in the LAD (B2- or C-type of lesions), it seems that surgery may offer a superior alternative to PTCA with stent (55).

## THE DIABETIC PATIENT

Although patients with diabetes fare significantly worse than non-diabetics after both PTCA and CABG, it has now been clearly demonstrated that diabetic patients seem to have a poorer long-term outcome after coronary angioplasty compared with after CABG, especially if suffering from multivessel disease (56, 57). Furthermore, diabetics have a less favourable long-term outcome in comparison with non-diabetic patients after

both coronary angioplasty and stenting (47, 58). There may be several mechanisms responsible for this finding.

Retrospective analyses from previous trials (56, 57) have indicated that the results were partly due to more incomplete revascularization with PTCA compared with bypass surgery. It has furthermore been demonstrated in several trials that progression of the disease is more intense in diabetics than in non-diabetics (59). Thus grafting of all major vessel segments with CABG may provide better protection against the consequences of future progression in proximal vessel segments than treatment with PTCA.

There is some controversy about whether the worse outcome complies with both insulin-dependent and non-insulin-dependent patients (60). Insulin, being a growth factor, may predispose for later restenosis after an angioplasty procedure. On the other hand, one interesting finding is that in patients with coronary artery disease, the prognosis in diabetics is related to the glucose levels (61), and one possible link may be the endothelial function. Thus, one possible way to improve outcome after PTCA in diabetics may be better glucose control with insulin.

Platelets play a major role in acute thrombotic complications in association with angioplastic procedures, but may also have an impact on the long-term results and restenosis. In recent years it has been shown that intense platelet inhibition using the GP IIb/IIIa receptor antagonists abciximab and integrilin both reduces complications and improves long-term results, especially in diabetics. Thus in the EPISTENT trial, the 6-month results in diabetic patients treated with abciximab were equal to those in non-diabetic patients (62). If confirmed over longer observation periods and in other trials, this may point to a solution to the diabetic problem in interventional cardiology.

## THE IMPORTANCE OF AGE

Coronary artery disease is a life-long chronic disease. Coronary artery bypass surgery may be done once and, where there are less good results and increasing complications, a second operation may be offered. Coronary angioplasty can, on the other hand, be performed for, in principle, an unlimited number of times. Thus, there is a widespread belief that it is preferable to wait for coronary artery bypass surgery for as long as possible. In young patients PTCA can be performed with excellent short- and long-term results (63, 64). In the long term, however, new revascularization procedures are usually needed because of restenosis but also because of progression of the coronary artery disease. Although repeated procedures are often needed, it seems that the restenosis process in itself is less common in patients of young age than in older patients

(65). On the other hand, the long-term prognosis after coronary artery bypass surgery in young adults is poor and discouraging (66). This may be due to selection bias, as young patients referred for coronary artery bypass surgery are often at a more advanced stage of the disease and suffer from diabetes and hypercholesterolemia more often than patients referred for PTCA. These experiences, although not based on randomized trials, may advocate the choice of PTCA as the method of choice for revascularization in younger patients. In doing so, however, some considerations are in place. Younger patients often have a more aggressive coronary artery disease per definition. Thus, a more rapid progression than in older patients can be expected, which is why patients should be closely followed-up, with repeated exercise tests, to reveal occurrence of ischemia. Furthermore, if a young patient suffers from widespread coronary artery disease, where experience from previous randomized trials between medical and surgical treatment have shown that surgery may prolong survival, then bypass surgery should be considered and PTCA performed only if complete revascularisation can be done.

Although high age is an independent predictor of mortality after coronary angioplasty (67), both PTCA and CABG can be performed with good short- and long-term results in elderly patients (68, 69). With advancing age, PTCA may become a more attractive alternative as coronary artery bypass surgery is conceivably related to high-risk for cerebral, renal as well as cardiac complications. At high age the prognostic importance of the procedure is of less significance. Thus PTCA can be performed as a palliative measure also in patients with advanced multivessel disease.

#### AD HOC PROCEDURES

In order to save time and ultimately money, coronary angioplasty activities are, in many centers, organized with the possibility of an ad hoc procedure, i.e. a diagnostic coronary angiography immediately followed by coronary angioplasty. This approach seems to be attractive from logistic and economic points of view, and when performed selectively it appears safe in the short perspective (70). The strategy may, however, impose a certain risk – namely that decisions are made on the basis of impulse and feelings rather than on a sound knowledge of the expected risks and long-term outcomes with different treatment modalities. Taking these considerations into account, patients with a single-vessel disease may, in many instances, preferably be treated pharmacologically. Only if symptoms are severely incapacitating or if the patient presents with high-risk, unstable coronary disease, is it usually necessary to perform an angioplasty. On the other

hand, lesions located in the proximal part of the LAD may be treated with coronary artery bypass surgery for prognostic reasons. Other considerations apply to multivessel disease, incomplete revascularizations and diabetic patients.

For most patients with coronary artery disease, the decision to carry out a revascularization procedure may be one of the most important decisions to be taken in that particular patient's life. It is therefore reasonable that such a decision is made in compliance with the patient, who should be well informed and in a state of alertness (not sedated). Furthermore, the decision should, from the physician's side, be safeguarded by unbiased considerations of all treatment alternatives, where risk during the procedure should be weighted against the expected long-term outcome. If ad hoc procedures are to be performed, which may well be warranted, especially in unstable angina, it requires that the patient is thoroughly informed before the diagnostic catheterization and that current indications and contraindications for PTCA are carefully followed. If any doubts arise after the coronary angiography, the patient's case should be discussed in collaboration with the interventional cardiologist, a thoracic surgeon and the physician with primary responsibility for the patient.

#### FUTURE DIRECTIONS

Rapid technical development is taking place in the field of coronary angioplasty. Development concerning guide wires and balloons will allow more complex lesions to become more accessible for coronary angioplasty, and with the development of improved stents it is foreseen that smaller vessels, lesions in curved vessel segments as well as bifurcation lesions, may be effectively treated. It can therefore be anticipated that the success rate will improve even more, to close on 100% of attempted procedures. Establishment of treatment with GPIIb/IIIa receptor antagonists has provided an antithrombotic treatment that is effective in prohibiting thrombotic complications. Furthermore, this type of therapy may have a greater impact on reducing myocardial injury during angioplasty procedures and thereby improving long-term results.

The Achilles' heel of coronary angioplasty is still restenosis. A few promising pharmacological compounds are currently being tested against restenosis and it is hoped that in the coming years we can expect the results of large randomized trials to reveal whether any of these drugs are effective in the reduction of restenosis. If the restenosis problem can be reduced substantially, this will have a great impact on the use of coronary angioplasty as an alternative to other treatment modalities in coronary artery disease. Technically,

complicated lesions as well as lesions in widespread three-vessel disease can be treated, and if the restenosis rate can be controlled, this will enhance coronary angioplasty as the treatment of choice for the majority of patients with coronary artery disease.

## CONCLUSIONS

Coronary angioplasty is a safe and effective treatment method for revascularization of patients with single- and multivessel disease. Complications are low with the use of stents and effective antithrombotic treatment. Restenosis, however, still remains a problem.

Single-vessel disease without severe ischemia on exercise test can be treated with medical therapy alone. For patients with ischemia on an exercise test or with incapacitating symptoms, coronary angioplasty is the treatment of choice. An exception may be a lesion situated in the proximal part of the LAD, where bypass surgery with the use of LIMA graft may have better results for long-term symptom relief and prognosis.

Coronary angioplasty may be considered for multivessel disease if lesion morphology is suitable for angioplasty. Complete revascularization should be aimed for in either one or a staged procedure. Since angioplasty is perhaps, in comparison with coronary bypass surgery, less effective in relieving symptoms, the patient should have some say in the choice of therapy. Thus a first attempt with coronary angioplasty may be worthwhile, with a later coronary artery bypass surgery if the initial procedure does not result in sufficient relief of symptoms in the long term.

Diabetics should be considered for bypass surgery, especially if presenting with multivessel disease.

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