CORONARY ARTERY DISEASE IS STILL A MAJOR CAUSE of morbidity and mortality especially in most industrialized and wealthy countries. Great efforts have been undertaken to improve revascularization techniques both surgically as well as by interventional approaches; and the target vessel revascularization rate after percutaneous angioplasty has been reduced to around 10%.1-4

Over the last few years several studies and surveys, however, challenged the treatment of coronary artery disease by angioplasty or bypass surgery, being unable to demonstrate any influence on the natural history by these techniques. Furthermore, deeper insights into the mechanisms of coronary heart disease questioned the value of simple revascularization. Endothelial erosion and plaque rupture leading to thrombosis and occlusion occurs often in minimal narrowing lesions. It was argued that medical treatment might indeed interfere more consistently with the disease process. So, it became important to investigate the two principal different therapeutic approaches in a comparative way. Several disease entities like stable or unstable angina and acute myocardial infarction have to be viewed separately in this context.

Pathophysiological Evidence

Myocardial infarction often occurs in lesions, that had minimal or mild disease at prior angiography. In Nobuyoshi's series, over 50% of infarctions occurred in lesions that had only; 50% luminal narrowing in earlier coronary angiographies, and the ratio of occlusions in lesions; 50% versus 50% was 7.4:1 in the Coronary Artery Surgery Study.6 Also, the severity of lesions is not correlated to the time of myocardi a infarction.7

The predominant pathophysiology of coronary thrombosis is plaque rupture, occurring mainly in the context of hypercholesterolemia and in patients with arterial hypertension. It accounts for about 75% of acute coronary thromboses. Endothelial erosion is not as common, accounting for some 25% of thrombotic events and being more common in diabetics and smokers,8 presumably because of endothelial dysfunction.

While low-grade lesions represent the principal sight of complications of coronary arteriosclerosis, high-grade lesions are often the end-stage after healing of disruptions. Mann found healed disruptions in 73.2% of high-grade, but only 17.3% of low-grade lesions.9

Plaque rupture occurs principally in atheroma, representing a core lesion with liquid cholesterol esters covered by a thin fibrous cap or an endothelial monolayer. This is clearly demonstrated at angioscopic imaging where yellow shiny or glistering lesions have been shown to be associated to unstable angina 10 and unfavourable outcome.11 Rupture occurs at a site of structural weakness and maximal wall stress, usually at the shoulder of lesions and precipitated by arterial hypertension. Inflammation has been shown to be involved in weakening of fibrous caps. Elevated temperature has been demonstrated in vivo in areas of cellular infiltration. 12 The temperature elevation is more pronounced in unstable angina and acute myocardial infarction.13

Therapeutic Goals

Unstable angina has a rather grim progress. The rates of myocardial infarction or death over three months were 20% and 15%, respectively. This
urns us to improve outcomes by making diagnostic and therapeutic progress.

Diagnosis of unstable lesions in vivo is still difficult. Intravascular ultrasound is not able to identify atheroma, angioscopy is still an experimental technique, thermal detection is to invasive needing balloon placement of the thermistor to the wall, and coronary angiography neither identifies the lesions that lead to myocardial infarction nor is able to be a good prognostic guide to therapy.

The principal therapeutic possibilities include bypassing the lesions, gaining lumen and healing the plaque by therapeutic rupture, preventing the thrombotic sequelae of plaque rupture or endothelial erosion by interfering with coagulation and platelet aggregation or by reducing the likelihood of plaque rupture or endothelial erosion. While bypass surgery bypasses the pathophysiologic problem and PTCA precipitates therapeutic plaque rupture, medical therapy aims at either preventing plaque rupture or the thrombotic events to follow. Therefore, numerous studies have been performed over the last few years dealing with the improvement of therapy of unstable angina.

The therapeutic goals in stable severe angina are more straightforward aiming at improvement of symptoms, which has been shown in most studies to be attained most effectively with revascularization. In mild angina both a prognostic and a symptom-oriented approach might be important.

Epidemiological Evidence

While coronary bypass surgery does not reduce the incidence of myocardial infarction, it has prognostic benefit under certain circumstances like left main disease or three vessel disease. The prognostic benefit of angioplasty is less well proven. However, in patients randomized to surgery versus PTCA, no difference in outcome was observed in a meta-analysis, the overall death rate being 4.5% over 2.7 years.

Several studies like the Vanqwish trial and registries like OASIS22 in patients with unstable angina or non-Q-wave myocardial infarction have doubted the value of aggressive invasive work-up and revascularization. All registries and trials had major shortcomings in design and interpretation, the most intriguing problem being the low revascularization rate in all of them. However, light was shed on recently by the well-performed and presented data of the FRISC 11 trial, which demonstrated a benefit of early revascularization therapy with an over 5% absolute event reduction over 6 months in the invasive group. So far, aggressive revascularization in unstable angina is the treatment of choice.

Medical therapy is also thoroughly investigated in unstable angina. Aspirin, beta-blockers, clopidogrel, glycoprotein IIb/IIIa inhibitors, unfractionated heparin, and low molecular weight heparins have all been shown to improve outcome under various circumstances.

In patients with chronic stable and especially mild chronic stable angina, the therapeutic strategy is less obvious. In direct comparison, interventional therapy has not been shown to be superior to medical therapy in the ACME, the RITA 11, and the MASS33 trials except for the improvement of angina. On the other hand, major lipid lowering drug trials have demonstrated the prognostic benefit of statins in patients with symptomatic coronary artery disease. Thus, it may seem to be justified to evaluate lipid lowering therapy versus interventional revascularization in patients with mild chronic stable coronary artery disease.

The First Trial's Evidence: AVERT

The recently published A VERT investigation is the first direct comparison of patients treated with lipid lowering drug therapy in a random fashion versus interventional revascularization. It tested the hypothesis, that medical therapy with aggressive lipid lowering would be at least as safe and effective in terms of outcome events as revascularization mainly by angioplasty. The results do not extend to patients with recent myocardial infarction, three vessel disease, compromised left ventricular function and unstable or severe angina. On the other hand, patients with severe stenoses were included, the average stenosis grade being 80%.

341 patients were followed over 18 months comparing aggressive lipid-lowering with a reduction in LDL-cholesterol by atorvastatin from above 140 to 77 mg/dl to interventional revascularization, mostly with PTCA (including stenting in 30 percent of lesions or 39% of patients) or with CABG (5.1% of patients) plus regular lipid lowering, again mostly with statins, to 115 mg/dl. The weakness of the methods of this trial is predominantly the small number of patients and the limited follow-up period. This method has been
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published in details 37

The endpoints that were prespecified and occurred were severe angina with proof of ischemia, which causes hospitalization, revascularization other than the index revascularization; death; and nonfatal myocardial infarction. Therefore, it was a priori unclear, whether any relevant differences in the composite endpoint would be caused by restenosis, that could be re-intervention massively influence the results against revascularization. Furthermore, it was unclear, whether the high percentage of patients treated with lipid lowering agents in the intervention group would make any relevant differences in the natural history impossible.

The results were quite intriguing. An absolute 8 percent difference in the composite endpoint was reached within 18 months of follow-up and this difference was marginally significant by the prespecified statistics including O'Brien Fleming correction for two interim analyses. However, in a time to event analysis, the difference was significant in favor of the medical treatment. The difference occurred predominantly late after restenosis rate was in the range of only 10 percent. Patients with a LDL decrease beyond the median made up the greatest part of the difference. It is obvious that an influence on the natural history of the disease was responsible for the results, and that aggressive lipid lowering is more efficacious than average lipid lowering, even if it is combined with angioplasty.

Do these Results Change our Attitude Towards PTCA?

PTCA in patient with symptomatic angina is able to reduce angina more effectively and more rapidly and sustained than medical therapy.31,32 It is usually more convenient to the patient than bypass surgery and is readily accepted by patients. There is, however, no reason not to combine two therapies, that have been shown to be efficacious and well tolerated. So the up to date treatment for symptomatic angina would be revascularisation by angioplasty of bypass surgery plus aggressive lipid lowering and for the mildly symptomatic or asymptomatic patient to consider medical treatment only, deferring revascularisation until symptomatic status warrants it. Unstable angina should be treated with revascularisation, predominantly by the percutaneous approach, until more data have been gathered in this field in recently started clinical trials, investigating lipid lowering drugs also in this field.

References