The impact of coronary revascularisation on endothelial and platelet function

Amoroso, Giovanni

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Chapter 2
Drug therapy or coronary angioplasty for the treatment of coronary artery disease: new insights

Giovanni Amoroso
Ad J. Van Boven
Harry J.G.M. Crijns

Department of Cardiology, Thoraxcenter,
University Hospital of Groningen,
The Netherlands

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ABSTRACT

In the last decade percutaneous transluminal coronary angioplasty (PTCA) has become a very popular strategy for the treatment of coronary artery disease, although its efficacy in reducing ischemic events and the subsequent need for revascularization has yet to be proved.

In this article we review the latest trials that compared PTCA and medical therapy. We discuss the potentially favorable effect of lipid-lowering therapy on coronary atherosclerosis and cardiac events, and comment on the results of a recent study (AVERT) that compared lipid-lowering treatment and PTCA in patients with stable coronary artery disease.

Medical treatment aimed at reversing plaque growth and promoting plaque stabilization should probably be considered as the initial therapeutic option. Statin class drugs together with aggressive management of known risk factors show promise as the first step after appropriate early diagnosis. Revascularization procedures should subsequently be considered for all patients who do not respond to medical treatment or in whom the disease shows clear signs of progression.

MEDICAL TREATMENT VS. CORONARY REvascularisation

As reported in 1998 by the Working Group on Coronary Circulation of the European Society of Cardiology 1, in 1994 the ratio of coronary angioplasties (percutaneous transluminal coronary angioplasty, PTCA)/inhabitants in the Netherlands was 797/10^6, while in the rest of Europe it was 458/10^6. This difference reflects the revascularization-oriented approach to coronary artery disease that is common in Western Europe and the United States.

The relative ease and safety, the lower costs when compared to surgical interventions, the continuing improvements in the pharmacological and technological aids that support these procedures, are widening the range of diagnoses for which PTCA is indicated. Patients previously treated with medication or aorto-coronary bypass are now successfully managed with a percutaneous coronary procedure. The question of whether revascularization is always the best option for any patient with coronary artery disease remains controversial.

In 1995 the MASS study investigators 2 compared surgical, interventional (balloon angioplasty) and medical treatment for patients with a single stenosis of the left anterior descending artery, and found a lower incidence of medium-term adverse events only in the surgical group (3%); these authors reported no significant difference between PTCA (24%) and medical treatment (17%). Patients who received medication did not receive lipid-lowering therapy, and no stents were used in patients in the PTCA group, whereas surgically-treated patients received a mammary artery graft. At 3 years’ follow-up the incidence of death and infarction was similar in all three groups.

Percutaneous revascularization has been compared to medical therapy in two large studies: the ACME study 3 and the RITA-2 trial 4. The ACME study, which involved single-vessel patients randomized either to PTCA or medical treatment, demonstrated a significant difference in the number of angina-free patients at 6 months’ follow-up in the PTCA arm (64% vs 46%) and an increase in exercise ischemic
threshold. In the RITA-2 trial, which enrolled also multivessel-diseased patients, PTCA, compared to medical treatment, reduced the percentage of patients with severe anginal status (CCS class greater than 2) at 3 months’ follow-up (-16.5%); exercise ischemic tolerance was also greater in this group.

Despite the improved quality of life and better relief from angina, both these studies clearly showed a higher rate of adverse events in patients who underwent PTCA, so it is less certain whether this procedure is also effective in reducing ischemic events and the need for further revascularization. Interestingly, in these studies also, medical therapy did not include lipid-lowering treatment but only commonly used antiischemic drugs.

**LIPID LOWERING AND CORONARY ARTERY DISEASE**

In 1994 the 4S study brought to our attention that long-term aggressive lipid-lowering therapy alone could be effective in preventing adverse coronary events. Patients with a history of angina or myocardial infarction, and with levels of total cholesterol ranging between 210 mg/dl and 310 mg/dl, were treated with simvastatin (20-40 mg/daily). At 5 years’ follow-up they showed a significant reduction, in comparison to the placebo group, in cardiovascular-related (-42%) and total mortality (-30%) and in major cardiac events (-34%).

How can lipid-lowering treatment be effective in patients with coronary heart disease other than by simply reducing blood cholesterol levels? All recent studies of coronary atherosclerosis suggest that we should consider this disease as a gradual and continuous process starting long before its clinical manifestation. Several physiopathological factors are probably involved in the favorable effects of HMG-CoA reductase inhibitors on the atheromatous plaque—an effect that in turn helps prevent ischemic events. These factors include restoration of endothelial function, stabilization of vulnerable plaques, and retardation of plaque growth.

**STATINS AND ENDOTHELIUM**

In former years the endothelium was barely considered a mechanical barrier between the vessel lumen and wall. Currently, endothelial cells must be viewed as gatekeepers in the process of sensing and reacting to stimuli, through the production of vasoactive mediators. Early endothelial dysfunction can be identified because of the paradoxical response, seen in diseased vessels, to the endothelium-dependent mediator acetylcholine. Clinical studies of hypercholesterolemic patients without clear anatomical lesions have shown an improvement after lipid-lowering therapy in myocardial perfusion, as assessed by means of SPECT technique, and in coronary flow reserve and coronary resistance, as assessed by means of PET technique. These results suggest that such patients have a basal impairment in endothelial function related to atherosclerosis in early stages, but also that these functional abnormalities are completely reversible with therapy. Several studies have also demonstrated that cholesterol-lowering treatment is able to attenuate and reverse endothelial dysfunction, and also to reduce myocardial ischemia in patients
with proven coronary artery disease: Andrews and colleagues 12, for example, demonstrated a significant reduction (-65%) in daily-life ischemic episodes for patients treated with lovastatin for 6 months.

Reverting endothelial dysfunction should be a primary goal because the imbalance in endothelial function leads not only to impairment of vascular tone and myocardial perfusion, but also to accumulation of oxidized LDL, platelet adhesion, smooth muscle cell growth and the migration of inflammatory cells 13. These events are responsible for the formation of an atherosclerotic plaque, which in the early stages is usually characterized by a thin fibrous cap, a lipid-rich core, a large number of macrophages, and a slight depletion of smooth muscle cells. In recent years evidence has been emerging that soft plaques with an intermediate or minimal degree of lumen narrowing, rather than fibrous and calcified plaques with marked stenosis, are the main factors responsible for acute coronary syndromes. As a result of passive (lipid accumulation) and active (inflammatory process) phenomena, these lesions are prone to disruption and subsequently to thrombosis 14.

STATINS AND PLAQUE STABILISATION AND GROWTH

Whereas surgical or percutaneous revascularization does not address the basic biology of coronary atherosclerosis and therefore may have little effect on plaque vulnerability, experimental studies have shown that lipid-lowering therapy is able to reduce cell replication and the inflammatory response, and to increase collagen content in the atheroma 15, 16, 17, 18, thus contributing to plaque stabilization. In 1995, the results of the REGRESS study 19, a large multicenter trial designed to assess the impact of aggressive lipid-lowering therapy on plaque regression, were first published. In this study symptomatic patients with normal or moderately elevated cholesterol levels were assigned to undergo PTCA, medical or surgical treatment, and were then randomized to receive pravastatin (40 mg/daily) or placebo. At 2 years’ follow-up the pravastatin-treated group showed a significant reduction in the angiographic parameters of plaque growth and progression. Most interestingly, although the luminal changes were modest, these patients also had fewer major cardiac events (-42%) and also showed a reduction (-32%) in transient myocardial ischemia, assessed as ST-segment depression episodes at ambulatory ECG 20. These results highlight the multiple potential roles of lipid-lowering treatment in restoring endothelial function and perfusion and in stabilizing and preventing plaque disruption.

In vivo studies that used ultrasound imaging, and the histological findings in atherosclerotic arteries, have shown that cross-sectional vessel area is not constant because of arterial remodelling. Compensatory or inadequate enlargement and/or shrinkage are common in arteries at the site of atherosclerotic lesions or vascular interventions 21.

Statin therapy may help reduce plaque growth, but this effect may be underestimated by coronary angiography due to late vascular remodelling. Nevertheless, in the PTCA subgroup in the REGRESS study, pravastatin treatment not only had a positive effect on clinical restenosis when compared to the placebo (7% vs 29%), but also reduced angiographic restenosis (mean stenosis diameter at follow-up 32% vs 45%) 22.
Newer and less invasive techniques are under development to improve the assessment of atherosclerosis. In a study that used electron-beam CT and considered the volume of coronary calcifications as a reliable index for the total burden of atherosclerotic plaques, Callister and colleagues recently demonstrated that long-term therapy with statins can have a beneficial impact on slowing the progression of coronary atherosclerosis.

STATINS AND/OR CORONARY ANGIOPLASTY

The 1996 AVERT study was designed to compare the effect of lipid-lowering therapy and PTCA on the incidence and timing of ischemic events. In this trial, patients with stable angina, LDL-cholesterol levels ≤115 mg/dL and one or two vessels suitable for revascularization were randomized to either atorvastatin (80 mg/daily) or PTCA. At 18 months’ follow-up the atorvastatin group, compared to PTCA/usual care group, showed a decrease in overall ischemic events (-36%) and a significant delay in time to the first ischemic event (36% risk reduction). No differences were reported in safety and quality of life, and patients who were treated with PTCA showed a small improvement in anginal class. These data suggest that aggressive lipid-lowering therapy, when compared to PTCA in stable patients with coronary artery disease, may be useful in reducing ischemic events and in preventing or delaying revascularization.

Further studies are needed to understand and defeat atherosclerosis, but in the light of the present results, and considering that coronary artery disease is a continuous, gradual, long-term process, medical treatment aimed at reversing plaque growth and promoting plaque stabilization should probably be considered as the first therapeutic option. Statin class drugs together with aggressive management of known risk factors show promise as the first step after appropriate early diagnosis, and revascularization procedures should subsequently be considered for all patients who do not respond to medical treatment or in whom the disease shows clear signs of progression.
References


Aim of the thesis
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As previously described in part I, coronary revascularisation is performed upon a substrate that has already been altered by the atherosclerotic process. However, revascularisation procedures can also be responsible for a further dysregulation both of endothelial and platelet function (chapter 1). Furthermore, medical interventions aimed at modulating endothelial and platelet function have demonstrated to be an effective aid and possibly a feasible alternative to coronary revascularisation (chapter 1 and 2).

The aims of the thesis are: 1) To confirm that endothelial dysfunction and platelet activation preexist to coronary revascularisation and to assess whether they can influence the outcome of percutaneous and surgical interventions. 2) To clarify the direct effects of coronary revascularisation on endothelial and platelet function. 3) To determine how to reduce endothelium/platelet interaction, and possibly to improve the outcome of coronary revascularisation.

Given the primary involvement of endothelium in vasoregulation, in part II are described the vasomotoric response of normal and atherosclerotic coronary arteries during cardiac catheterisation (chapter 3), the endothelial release of vasoactive substances induced by percutaneous coronary intervention (chapter 4), and the long-term effect of stent deployment on coronary vasomotion, with its clinical consequences (chapter 5).

As platelet contribution is fundamental in determining the outcome of percutaneous coronary revascularisation, in part III the question whether geometry and design of stents (chapter 6), and how different antiplatelet therapies (antiaggregants or GpIIbIIIa inhibitors) (chapter 7) can influence platelet activation during stenting will be considered.

Finally (part IV), endothelium-dependent and independent vasomotion of grafted internal thoracic arteries long-term after surgery (chapter 8), and the effect of various risk factors (smoking in particular) on arterial graft vasomotion (chapter 9) are investigated.

A comprehensive overview of our results with conclusive remarks and clinical implications complete the thesis. Summaries both in Dutch and in Italian are also provided.