A New Paradigm for Plaque Stabilization

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Abstract: The concept of plaque stabilization was developed to explain how lipid lowering could decrease adverse coronary events without a substantial reduction in the regression of atherosclerosis. Plaques were stabilized by reducing serum cholesterol leading to several favorable pathobiological changes in the vessel wall of lipid-rich plaques responsible for a majority of acute coronary events. However, this concept is limited for several reasons including that it does not incorporate strategies directed against either plaques that have already destabilized or non–lipid-rich plaques, which are the substrate for at least one third of major coronary thrombi and may or may not be stabilized by lipid lowering. For the destabilized plaque with overlying thrombus, either percutaneous intervention, long-term antithrombotic and/or anticoagulant therapy, or possibly aggressive lipid lowering stabilizes lesions by reducing subsequent thrombosis at the lesion site and, at least with lipid lowering, by improving endothelial function and possibly reducing inflammation. Short-term, in-hospital antithrombotic approaches alone with agents like the GP platelet IIb/IIIa inhibitors have not been effective in this situation. For other plaques not presently destabilized, the main goal of therapy is reducing future acute coronary events. Several classes of drugs, including ACE inhibitors, β-blockers, and antithrombotic agents in addition to lipid-lowering agents, reduce events, and this may be attributable, at least in part, to plaque-stabilizing effects.

Key Words: plaque stabilization • atherosclerotic plaques

The concept of plaque stabilization was first proposed in the 1990s in an attempt to explain the discrepancy between the small amount of plaque regression demonstrated angiographically in many randomized trials of lipid lowering and the large reduction in clinical events seen in these trials. In the 15 published angiographic lipid-lowering trials, there was an approximate 22% to 34% reduction by pooled analysis in cardiac events, which was similar to the event reduction in the large randomized secondary and primary lipid prevention trials. On the other hand, angiographic regression of stenotic atherosclerotic lesions, although increased with lipid lowering versus placebo, was unlikely to explain the large clinical benefit.

Several factors were hypothesized to contribute to this reduction in clinical events. It had been generally appreciated that a majority of acute coronary events were related to disruption of a “vulnerable” atherosclerotic plaque defined as a lipid-rich plaque with a thinned fibrous cap lacking proper collagen and smooth muscle cell support. At the site of plaque disruption, the fibrous cap was infiltrated by macrophage-derived foam cells and activated lymphocytes. The acute clinical event was precipitated by the formation of an intimal, platelet-rich thrombus followed in some cases by a fibrin, red cell intraluminal thrombus that occluded the vessel in the presence of ST-segment elevation myocardial infarction. Unstable angina and ST depression myocardial infarction were usually associated with a mural, platelet-rich thrombus without total occlusion or with a transient total occlusion.

Based on several lines of evidence from human studies and regression studies in various animal models of atherosclerosis, lipid lowering over time stabilized plaques by several mechanisms, which included the following: (1) depletion of plaque lipid particularly cholesterol ester; (2) a reduction in inflammatory cell activity and even the number of macrophage-rich foam cells; (3) a reduction in thrombosis risk by decreasing platelet reactivity, tissue factor expression by inflammatory cells, and/or improving endogenous fibrinolysis; or (4) overall improvements in endothelial function. All likely contributed in varying degrees to the reduction in clinical events with lipid lowering. The time course of these favorable changes in the pathobiology of the vessel wall varied. Changes in endothelial function could be demonstrated within 1 month of lipid lowering with use of the Hmg Co A reductase inhibitors and may be immediate in cases of low-density lipoprotein apheresis in patients with elevated cholesterol. Reductions in thrombosis risk have been demonstrated at 3 and 6 months after initiation of lipid-lowering therapy. Changes in the lipid and macrophage content of the plaque probably required at least 6 months to occur based on animal data. In most randomized clinical trials of lipid lowering, adverse events began to diverge between placebo...
and treatment arms only after 6 to 18 months, suggesting a long latency between the initiation of lipid lowering and the reduction in myocardial infarction and cardiac death.

**Limitations of the Concept of Plaque Stabilization**

Although the concept of plaque stabilization as described above was based on several lines of investigation, it is limited for several reasons. (1) This concept of a “vulnerable” atherosclerotic plaque would not be applicable to a significant percentage of acute coronary thrombi. At least one third of large coronary thrombi as detected by autopsy originate from non–lipid-rich plaques that usually contain proteoglycan.\(^8\) This number may be higher in women and when clinical events are not exercise-related. In these cases, there is no plaque disruption but only plaque erosion. Lipid-lowering therapy in these individuals may or may not result in the same favorable changes in plaque composition as in the lipid-rich vulnerable plaque. The object of therapy here should be directed against thrombosis and inflammation. (2) The reduction in adverse coronary events with lipid lowering is incomplete as adverse events are still occurring in the treated group. Thus, other factors besides lipids must contribute to on-going, adverse events. Therapies targeted against these factors might be beneficial. (3) The concept of plaque stabilization as originally proposed does not incorporate strategies directed against the plaque that has already destabilized and thrombosed. (4) No distinction is made between short-term (in-hospital) events, intermediate (30-day to 6-month) events, and long-term events and plaque stabilization. The methodology used and the risk of new or recurrent events vary depending on the type of plaque and clinical presentation of the patient. (5) Angiography is an insensitive method for assessing plaque progression or regression.

**An Integrated Approach to Plaque Stabilization**

Based on the limitations outlined, an integrated approach to plaque stabilization is proposed, incorporating plaque-specific, process-specific, and time-specific phenomena to reduce future coronary events (Figure 1).

**I. Plaque-Specific Considerations**

The destabilized (disrupted and/or thrombosed) culprit plaque in a patient with an acute coronary syndrome requires a different treatment philosophy and strategy than plaques that have not destabilized. The destabilized plaque is not unlike an active volcano that must be made quiescent. The thrombotic component must dissolve or become organized, the intimal tear heal, and the inflammatory activity reduced. The surrounding endothelium needs to become less dysfunctional with reduced vasoconstrictor, proinflammatory, and procoagulant activity. Here, the issue is treatment. On the other hand, non-destabilized plaques whether or not lipid-rich must remain quiescent and atherosclerotic progression reduced or even reversed. In this case, the issue is prevention. Furthermore, the concept of the vulnerable plaque should be expanded, as originally proposed by Muller et al.\(^9\) to include any plaque that is high-risk and prone to destabilization and thrombosis whether lipid-rich or proteoglycan-rich.

**II. Process-Specific Considerations**

Any process or mechanism that reduces the subsequent occurrence of coronary thrombosis leading to the clinical presentations of unstable angina, myocardial infarction, or sudden coronary death should be considered as either plaque-stabilizing, antithrombogenic in the blood, or passivating the vessel wall (ie, reducing its propensity for vasoconstriction and thrombus formation and decreasing its inflammatory activity). If the plaque is already destabilized and the clinical syndrome acute, short-term medical management cannot completely eliminate thrombus or normalize vessel reactivity. In ST elevation myocardial infarction, thrombus can usually be demonstrated in the culprit lesion for at least 1 month after successful intravenous thrombolysis in patients on aspirin as the only antithrombotic agent.\(^10\) Furthermore, the culprit vessel in both myocardial infarction and unstable angina may be abnormally vasoreactive in comparison to normal-appearing vessels or diseased vessels in stable patients.\(^11\,12\)

**III. Time-Specific Considerations**

Different conditions are associated with recurrent acute or new coronary events (unstable angina, myocardial infarction, or death) that occur at different time intervals. In the medical management of acute coronary syndromes, recurrences occur during hospitalization or early after hospital discharge.\(^13\) Acute recurrent events in general are related to total occlusion (or reocclusion) of the original culprit lesion due to local extension of thrombus.\(^14\) On the other hand, in stable clinical syndromes or in asymptomatic patients, the time frame for the appearance of new, acute coronary events is much longer usually extending over years, and short-term events occur much less frequently. Furthermore, the exact time frame for the transformation of a stable plaque into one responsible for an acute coronary syndrome is unpredictable.

**Stabilizing the Destabilized Plaque**

Stabilization of a disrupted or eroded plaque with overlying thrombus whether the acute syndrome is unstable angina or
myocardial infarction can be accomplished either through percutaneous intervention, with long-term antithrombotic and anticoagulant approaches, or possibly with high-dose lipid-lowering therapy. The prevention of new or recurrent total coronary occlusion at the site of obstruction in the culprit lesion is the predominant mechanism for avoiding recurrent clinical events after an acute syndrome as previously mentioned.

**Percutaneous Intervention**

Although not usually classified as such, percutaneous intervention is an effective method of short-term stabilization of a disrupted and/or thrombotic plaque. Even though percutaneous intervention results in vessel wall injury at the site of the procedure, expansion of the lumen particularly with a properly opposed stent results in an axial redistribution of plaque away from the center of the lesion toward the reference segments, and possibly plaque compression. Theoretically, this change in plaque geometry may seal the intimal tear and allow for intimal healing. Combined with potential improvements in blood flow due to the expanded lumen, reduced percent stenosis, and reduced shear rates, the net result will be a short-term reduction in thrombus locally. Thus, in patients with an acute coronary syndrome of either unstable angina or myocardial infarction, stent placement, usually with the use of adjunctive platelet GP IIb/IIIa receptor inhibition, has proven efficacious in reducing subsequent adverse events. Paradoxically, in this model, the process of restenosis must be considered a form of plaque destabilization secondary to the intervention. In this case, the short-term benefits of percutaneous intervention are reversed by the neointimal proliferation and subsequent lumenal narrowing as a consequence of vessel wall injury at the time of the procedure.

**High-Dose Lipid-Lowering Therapy and Long-Term Antithrombotic Therapy for Destabilized Plaques**

In the absence of percutaneous intervention, there are other approaches to decrease subsequent coronary events that may stabilize an already destabilized plaque. High-dose lipid-lowering therapy as administered in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial reduced ischemic events at the 16-week follow-up date. Overall, the primary endpoint of either death, myocardial infarction, or recurrent ischemia requiring hospitalization was reduced from 17.4% to 14.8% in the 80 mg/d atorvastatin group (P=0.048). The largest reduction was in the subgroup with the endpoint of recurrent ischemia, which was reduced from 8.4% to 6.2% with high-dose atorvastatin (P=0.02). These beneficial results are likely secondary to improved endothelial function and possibly to either reduced inflammation in the plaque or thrombogenicity of the blood.

Long-term antithrombotic and/or anticoagulant therapy may be another option for plaque stabilization in patients not routinely undergoing percutaneous intervention by reducing the amount of local thrombus formation. Accumulating data also support the concept that antithrombotic therapies may reduce vascular inflammation because thrombosis can augment the inflammatory process through several mechanisms. The preliminary results of the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT)-2 (Dr M.A. Brower, European Society of Cardiology, oral presentation, August 2000) and Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT)-2 trials (Dr R.F. Van Es, European Society of Cardiology, oral presentation, August 2000) suggest a role for coumadin and aspirin (APRICOT-2) or coumadin alone (ASPECT-2) in selected patients. In APRICOT-2, patients with normal TIMI-flow after intravenous lytic therapy were randomized to either aspirin alone or aspirin plus coumadin (the international normalized ratio [INR] was targeted to 2 to 3) and restudied angiographically at 3 months. Angiographic reocclusion was reduced from 30% to 18% (P=0.02) in the aspirin and coumadin arm, and event free survival was increased from 70% to 83%, respectively. These data on aspirin and coumadin complement a previous angiographic study in acute myocardial infarction, indicating that the percent reduction in diameter stenosis of the culprit lesion over a 3-month follow-up was significantly greater in patients given both drugs versus aspirin alone. In ASPECT-2, 993 survivors of an acute syndrome were randomized to aspirin or a combination of aspirin and coumadin or to coumadin alone (INR 3 to 4). The use of coumadin was associated with a significant reduction in the primary endpoint of death/infarction or stroke from 9.2% with aspirin alone to 5.2% with coumadin (P<0.05). These data are similar to large-scale randomized trials after myocardial infarction showing reduced adverse events on follow-up with moderate-dose coumadin alone. However, in the APRICOT-1 study, the use of coumadin alone after acute myocardial infarction without aspirin provided no protection against reocclusion at the site of the culprit lesion at 3 months in comparison to placebo.

The beneficial effects of long-term antithrombotic therapy in reducing adverse events were also seen in the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial. There was a highly significant 20% cardiovascular decrease in the primary endpoint of death/myocardial infarction and stroke at 12 months with the combination of clopidogrel and aspirin versus aspirin alone. Patients with or without revascularization procedures were similarly benefited. The curves began to diverge within a few hours of randomization and were significantly different at 30 days. Obviously, the approaches of intense lipid lowering, long-term antithrombotic or anticoagulant therapy, and percutaneous intervention are not mutually exclusive, although there are presently little or no data on high-dose statin therapy and long-term anticoagulant therapy or other combination approaches. In addition, these approaches have not been compared in a randomized trial in patients presenting with an acute syndrome. In patients undergoing percutaneous intervention, lipid-lowering therapy is routinely administered to decrease progression of atherosclerosis as well as to reduce future coronary events in other lesions not intervened on, but not to reduce restenosis in lesions that underwent intervention. The combination of percutaneous intervention and long-term anticoagulant therapy has also been recently reported in a new randomized trial. The addition of coumadin to aspirin reduced short-term and follow-up events at 1 year versus aspirin alone.
**Short-Term Antithrombotic Therapy in the Medical Management of Destabilized Plaques**

Several randomized trials in patients with an acute syndrome and a destabilized plaque have included patients in whom medical management alone was utilized without percutaneous intervention or bypass surgery. In an overview of randomized trials with the intravenous glycoprotein IIb/IIIa receptor inhibitors, there was only an insignificant 8% reduction in recurrent events in patients treated medically with GP IIb/IIIa inhibitors but without intervention. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-4 ACS trial, there was a slight but insignificant increase in adverse events at 30 days with a 24- to 48-hour infusion of abciximab compared with placebo. It is plausible to suggest that the lack of benefit seen with abciximab was, in part, related to the very low rate of acute intervention performed in this trial. These data appear similar to the results of GUSTO IIb in that other new and powerful antithrombotic agents, such as the direct thrombin inhibitor hirudin, given over a short period of time did not significantly reduce 30-day adverse events in comparison to unfractionated heparin. On the other hand, the universal failure of the trials with the oral glycoprotein IIb/IIIa inhibitors should not necessarily be attributed to the lack of concomitant percutaneous intervention but to other factors possibly related to their pharmacology or mode of administration. These adverse mechanisms include a prothrombotic tendency at low plasma drug levels or toxic effects of these agents on the myocardium. Thus, in contrast to the studies with long-term antithrombotic or antithrombotic/anticoagulant approaches, there are no data that powerful antithrombotic therapy alone administered short-term, in-hospital will prevent subsequent events in patients with a destabilized plaque and an acute syndrome.

**Stabilization of Vulnerable Plaques**

To reduce subsequent events, vulnerable plaques (utilizing the broadened definition of vulnerable as any plaque prone to destabilization and thrombosis) must remain stable and quiescent. The benefits of lipid lowering in reducing coronary events by preventing destabilization of lipid-rich vulnerable plaques have been previously mentioned. The effects of these drugs on preventing plaque destabilization with subsequent thrombus in non–lipid-rich plaques are unknown. Nevertheless, the antiinflammatory and antithrombotic properties of lipid lowering may provide some protection.

Several other drug classes are routinely used in the management of coronary disease patients that reduce the incidence of subsequent acute coronary events and may have plaque-stabilizing effects. These include angiotensin converting enzyme inhibitors, β-blockers, and standard antithrombotic agents such as aspirin. There are several potential mechanisms for these agents to favorably affect atherosclerotic plaques. A reduction in blood pressure and pulse rate at rest or with exercise with β-blockers or ACE inhibitors may reduce the propensity for plaque disruption by reducing circumferential stress on the fibrous caps of lipid-rich plaques. ACE inhibitors have been shown to improve endothelial dysfunction. Angiotensin II within an atherosclerotic plaque also induces the synthesis and release of interleukin-6 from macrophages. Theoretically, ACE inhibition would reduce inflammatory processes within the vascular wall that lead to the development of an acute coronary syndrome and/or promote thrombus formation. Finally, aspirin will, of course, reduce platelet aggregability and its ability to reduce future myocardial infarction appears greatest in individuals with serologic evidence of increased inflammation.

In addition to the potential plaque-stabilizing effects, these agents have other properties that might also explain a reduction in adverse events. ACE inhibitors favorably influence myocardial remodeling, and β-blockers are both antiischemic and antiarrhythmic. Thus, it may not be possible to ascertain which effects are primarily responsible for reducing future events with the possible exception of aspirin as an antithrombotic agent. Other drug classes that might possess plaque-stabilizing properties include antioxidants and possibly macrolide antibiotics. Other antiinflammatory agents, such as inhibitors of the matrix metalloproteinases, are likely to be studied in the near future in large clinical trials.

**Conclusions**

Based on the above, we conclude the following. (1) The concept of plaque stabilization should be expanded to include treatment for plaques that have already destabilized as well as preventing future destabilization in quiescent plaques. The concept of a vulnerable plaque should be broadened to include all high-risk plaques prone to destabilization and thrombosis secondary to plaque disruption or erosion whether or not lipid-rich, proteoglycan-rich, etc. (2) For the destabilized plaque, percutaneous intervention is an effective method of short-term stabilization in selected cases. As an alternative, new randomized trials with either long-term aspirin therapy in combination with coumadin to an INR of 2 to 3, the combination of aspirin and clopidogrel, or high-dose lipid-lowering therapy will reduce subsequent coronary events potentially through plaque-stabilizing effects. Short-term powerful antithrombotic agents alone such as GP IIb/IIIa inhibitors in this setting do not appear effective in reducing events on follow-up. More data in this area combining different approaches are needed and some studies are in progress. (3) ACE inhibitors and β-blockers in addition to lipid-lowering agents potentially possess plaque-stabilizing properties that contribute to their beneficial effects on reducing subsequent events. Aspirin reduces future events by its antiplatelet effects and possibly through an antiinflammatory mechanism. (4) These concepts may require modification subsequent to the publication of new regression trials based on more sensitive methods than angiography for assessing atherosclerotic lesions such as intravascular ultrasound.

**References**


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