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Should Standard Medical Therapy for Angina Include a Statin?

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Summary: Although a wealth of evidence supports the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in patients with clinically evident coronary artery disease, these agents are still underutilized. Statins are the most effective agents in reducing low-density lipoprotein-cholesterol among lipid-lowering drugs, and studies have recently shown that they improve endothelial function and plaque stabilization, and induce regression of atherosclerotic lesions. This article reviews the most recent evidence and guideline recommendations supporting the use of statins in chronic stable angina pectoris and acute coronary syndromes.

Key words: acute coronary syndromes, chronic stable angina, coronary artery disease, statins

Introduction

Chronic stable angina pectoris and acute coronary syndromes (ACS) constitute two distinct syndromes with a common initial pathophysiologic pathway leading to atherothrombosis. The mutual conduit is coronary atherosclerosis, which is characterized by the deposition of lipid (such as cholesterol and its esters) into the artery's subendothelial space. This process, accompanied by the proliferation and migration of smooth muscle cells and inflammatory cells, leads to the development of sclerotic lesions in the intima and inner media.[1] Plaque composition, rather than the severity of stenosis, has been recognized as a major determinant of future coronary events.[2] Cardiovascular risk factors such as dyslipidemia and diabetes mellitus may induce hypercoagulable and hyperthrombogenic states that favor coronary thrombosis.[3]

Current therapeutic approaches to coronary artery disease (CAD) involve preventive nonpharmacologic means for optimal control of risk factors and the combined use of a large number of drugs, such as aspirin and/or clopidogrel, angiotensin-converting enzyme inhibitors, and beta-blockers, all of which have proven effective in decreasing the risk of cardiovascular morbidity and mortality. Nitrates and calcium-channel blockers are used to ameliorate symptoms (i.e., angina), but they have not been shown to influence mortality. Although a wealth of evidence from the landmark trials of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) definitively supports their use in patients with clinically evident CAD (Table I), these agents are still underutilized. We will review the most recent evidence that supports the use of statins for each clinical presentation.

Lipid Lowering and Atherosclerosis

Dyslipidemia is now recognized as the most important risk factor for coronary heart disease (CHD). Increased plasma levels of LDL cholesterol induce endothelial dysfunction, the initial step in atherogenesis, whereas correction of this metabolic disorder by lipid apheresis or treatment with lipid-lowering drugs can normalize endothelial dysfunction.[4–6] In several experimental models and recently in humans, lipid-lowering approaches showed the potential to reduce progression and even to induce regression of atherosclerotic lesions.[7,8] The mechanisms of these effects remain controversial and are a matter of intense research. Stabilization of atherosclerotic lesions by removal of lipid deposits and mitigation of the inflammatory response remain the most likely explanation.[9,10]

Using magnetic resonance imaging (MRI) of aortic and carotid artery plaques in patients with asymptomatic hypercholesterolemia, our group demonstrated that lipid lowering with simvastatin induced regression of atherosclerotic lesions. A significant decrease in plaque size without any change in lumen size was detected at 12 months.[11] This result indicates that statin treatment initially induces vascular remodeling, a

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TABLE I Effect of statin treatment on CAD

Trial	Baseline LDL-C (mg/dl)	Follow-up LDL-C mg/dl (% decrease)	Placebo event-rate (%)	Statin event-rate (%)	Absolute risk reduction (%)	Relative risk reduction (%)	NNT
4S	188	122 (35)	28	19.4	8.6	34	12
LIPID	150	112 (25)	15.9	12.3	3.6	24	28
CARE	139	98 (32)	13.2	10.2	3.0	24	34
WOSCOPS	192	159 (26)	7.5	5.3	2.2	29	46
AFCAPS	150	115 (25)	5.5	3.5	2.0	37	50

Adapted from Ref. No. 38.
4S = Scandinavian Simvastatin Survival Study,
LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease,
CARE = Cholesterol and Recurrent Events,
WOSCOPS = West of Scotland Coronary Prevention Study,
AFCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study,
NNT = number needed to treat to avoid 1 event in 5 years, LDL-C = low-density lipoprotein cholesterol.

process that has been demonstrated in experimental models of atherosclerosis to be a consequence of lipid removal and a decrease in inflammation and metalloproteinase activity.[12] It is of further interest that a longer follow-up of the same study showed not only a further shrinkage of established atherosclerotic lesions but also a small, statistically significant increase in the lumen diameter.[13] These observations seem to indicate that, at least in early, not severely stenotic lesions, maximal plaque regression occurs before lipid lowering affects luminal dimensions.

Our results were confirmed recently in a case-control study that also used MRI and reported smaller plaque size, smaller lipid core, and reduced lipid composition in carotid arteries of patients treated with lipid-lowering drugs for 10 years.[14] These observations on regression in plaque dimensions and changes in composition suggest that statin therapy leads to increased plaque stability.

Studies in Chronic Stable Angina

More than 6 million Americans have angina pectoris, and far more new cases of stable angina (about 400,000) than unstable angina (about 150,000) are diagnosed in the United States each year. Although patients with stable coronary disease are commonly referred for revascularization to reduce the risk of ischemic events, the evidence for the benefits of lipid-lowering treatment with statins is clear. The Atorvastatin VErsus Revascularization Treatment (AVERT)[15] trial indicated that in low-risk hypercholesterolemic patients with stable CAD, aggressive lipid-lowering therapy with atorvastatin was at least as effective as angioplasty and usual care in reducing the incidence of ischemic events.

In patients treated with percutaneous coronary intervention, statin therapy resulted in a longer event-free survival, a 22% relative risk reduction, a 5.3% absolute risk reduction of major coronary events, and reduced the rates of myocardial infarction and need for repeat revascularization when compared with placebo.[16, 17]

Evidence for a systemic inflammatory response has been demonstrated in stable angina as well as in unstable angina,[18] and studies have shown that statin therapy reduces levels of the inflammatory marker C-reactive protein (CRP) in patients with CAD.[19] A recent study in 110 high-risk patients with stable angina and myocardial ischemia showed that aggressive lipid lowering with atorvastatin can lower CRP in this population as well.[20] Intensive LDL lowering resulted in a significant and more rapid decrease in CRP levels (within the first month of therapy) than moderate lipid lowering.

Studies in Acute Coronary Syndromes

Intense cholesterol-lowering with a statin favorably influences interrelated pathophysiologic mechanisms in high-risk plaques that are intimately involved in the pathogenesis of ACS. Statins may improve endothelial function, reduce platelet deposition, normalize hypercoagulability and fibrinolytic activity, and attenuate inflammatory processes.[21] Statin treatment also decreases the hyperthrombogenic state associated with hypercholesterolemia[3, 22] and prevents tissue-factor expression in endothelial cells.[23]

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study[24] was the first large-scale clinical trial to examine the benefits of statin therapy in patients with ACS. More than 3,000 patients were randomized within 24 to 96 h to high-dose atorvastatin (80 mg/day) or placebo. The treatment period lasted 16 weeks, at which time a significant reduction was seen in the combined endpoint. There were no significant between-group differences in the individual endpoints of risk of death, nonfatal myocardial infarction, cardiac arrest, or worsening heart failure, as the study was not powered to detect such differences, but there were significantly fewer strokes and a lower risk of severe recurrent ischemia in patients treated with atorvastatin.

The Randomized Lipid-Coronary Artery Disease Study (L-CAD)[25] randomized 126 patients with ACS to early treatment with pravastatin 20–40 mg/day, alone or in combina-

tion with cholestyramine or niacin, or to usual care. At 24 months, the patients who received early aggressive treatment had a lower incidence of clinical events (23%) than the usual-care group (52%; p = 0.005).

These studies indicate that early initiation of aggressive cholesterol-lowering therapy after an episode of ACS may reduce the risk of future ischemic events. Although evidence from controlled clinical trials is not yet robust or definitive, observational studies support the predischarge initiation of lipid-lowering therapy. In the Swedish Register of Cardiac Intensive Care (RIKS-HIA)[26] of almost 20,000 patients, the adjusted relative risk of mortality was 25% lower in patients in whom statin therapy was initiated before hospital discharge.

Additional evidence of the potential of statin in ACS derives from the observation that cessation of treatment increases the risk of future coronary events. A retrospective analysis of data from the Platelet Receptor Inhibition for Ischemic Syndrome (PRISM) study confirmed the clinical benefit of maintaining statin therapy in ACS, whereas discontinuation of statin treatment after the onset of symptoms of ACS completely abrogated this benefit.[27] The 30-day rate of myocardial infarction and death in patients who continued statins (3.7%) was significantly lower than in patients who had never received statins (7.5%) and also than in those who stopped statin pretreatment during hospitalization (14.0%). As with all post-hoc subgroup analyses, these results need to be confirmed in prospective, randomized trials.

Current Recommendations

National and international guidelines have emphasized the importance of preventive strategies in the care of patients at risk for or with CAD. Because dyslipidemia plays a pivotal role in the initiation and progression of atherosclerosis, its optimal management is an essential step in the prevention and treatment of CAD. The guidelines of the National Cholesterol Education Program Adult Treatment Panel III state that the primary goal of cardiovascular risk-reduction therapy is to decrease the level of LDL cholesterol and defines an LDL cholesterol goal of < 100 mg/dl for patients with existing CHD or CHD risk equivalents.[28] Lifestyle modifications (e.g., smoking cessation, exercise) and dietary interventions (such as the Mediterranean diet) have clearly demonstrated efficacy in the prevention of cardiovascular events.[29,30] While lifestyle changes may be the most economical way of achieving LDL cholesterol goals, they are often not sufficient. The second EUROASPIRE survey, undertaken in 1999–2000 in 15 European countries, reported a high prevalence of unhealthy lifestyles, modifiable risk factors, and inadequate use of drug therapies to achieve lipid goals.[31] In fact, 1.4 years after hospital discharge for coronary artery bypass graft, percutaneous transluminal coronary angioplasty, acute myocardial infarction, or myocardial ischemia, 58% of patients did not achieve the Joint European Societies' recommendations for coronary prevention. This disappointing observation should stimulate all physicians involved in the management of patients with CAD to focus their attention on optimal control of risk factors and prompt initiation of lipid-lowering strategies. In this context the Cardiac Hospitalization Atherosclerosis Management Program (CHAMP) study[32] showed that in-hospital initiation of lipid-lowering therapy increased the percentage of patients treated with statins 1 year later from 10 to 91% and of those with an LDL cholesterol of < 100 mg/dl from 6 to 58%.

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines state that patients with chronic stable angina pectoris should receive lipid-lowering therapy with statins if their plasma LDL cholesterol level is > 130 mg/dl and their target goal is < 100 mg/dl.[33] The ACC/AHA guidelines[34] for patients with unstable angina or non-ST-segment elevation myocardial infarction state that drug therapy should be instituted if LDL cholesterol remains > 125 mg/dl after dietary intervention, with the goal of achieving an LDL level < 100 mg/dl. Because about 25% of patients with acute myocardial infarction have low levels of high-density lipoprotein (HDL) cholesterol with normal LDL cholesterol, low HDL cholesterol was recognized as an independent risk factor, suggesting the possible need for therapy with a fibrate or niacin.[34]

Recently published results of the Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study, a trial of 20,536 subjects, many of whom were at high CHD risk because of a past history of cardiovascular disease, diabetes, or hypertension, demonstrated the clinical benefit of statin therapy (40 mg/day simvastatin) across all patient groups (including patients with diabetes, women, and the elderly) regardless of age, gender, or baseline cholesterol values.[35] The Heart Protection Study thus confirms the concept that upon adequate global risk assessment and patient risk stratification, an aggressive control of cardiovascular risk factors, prominently including dyslipidemia, may have significant benefits.

Statin therapy has become an essential component in the prevention of cardiovascular events in both primary and secondary prevention (Fig. 1). The most powerful, consistent, and best-tolerated LDL-lowering agents, statins reduce LDL cholesterol by 24 to 60%.[36] Across the entire range of LDL cholesterol levels studied to date, lower levels of LDL cholesterol are associated with lower event rates (Fig. 2).[37] Statins

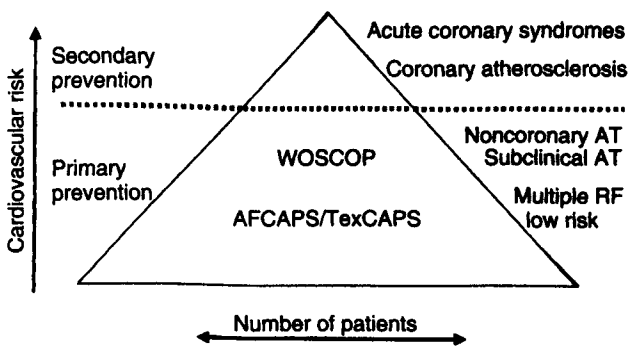

FIG. 1 Primary and secondary prevention trials. AT = atherosclerosis. For abbreviation of trial names see text.

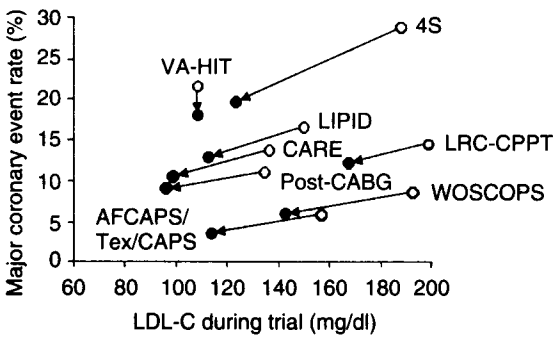

FIG. 2 Relation between low-density lipoprotein cholesterol (LDL-C) levels and the event rates in primary-prevention (blue) and secondary-prevention (red) trials of cholesterol lowering. The lines join the placebo (empty circle) result to the active treatment result (full circle) for each trial. LDL-C = low-density lipoprotein cholesterol, CABG = coronary artery bypass graft. Trial abbreviations: VA-HIT = Veterans Affairs HDL Intervention Trial, LRC-CPPT = Lipid Research Clinics Coronary Primary Prevention Trial. For other trial abbreviations see Table I. Modified from Ref. No. 21.

should be considered standard therapy for patients with angina and elevated LDL cholesterol levels. The results of ongoing statin trials may further elucidate the importance of this approach and stimulate the medical community to a broadened use of these valuable agents.

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