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Mechanisms of successful cardiovascular disease prevention

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Coronary artery disease, followed by stroke, is the most significant contributor to morbidity and mortality worldwide.[1] Given the demographics of the aging population globally, the favorable impact of lowering LDL cholesterol is significant and extends beyond mortality or important morbidity such as myocardial infarction and stroke. Atherosclerotic plaque formation and progression, as well as the pathophysiology of endothelial dysfunction, are favorably modified by a decrease in LDL cholesterol levels. Other less well understood measures directed at modification of non-LDL lipid abnormalities may also improve endothelial function or reduce thrombotic potential. This implies long-term benefit not only from a secondary, but also from a primary prevention point of view. Overwhelming evidence has accumulated indicating the importance of early diagnosis and prevention with respect to lowering LDL cholesterol levels. Some of the pathophysiology mechanisms underlying this benefit are reviewed in this paper.

Event reduction beyond lipid lowering

Significant epidemiological evidence has accumulated that demonstrates a direct relationship between elevated serum cholesterol levels and the incidence of coronary artery disease (CAD). Reduction of LDL cholesterol, achieved most efficiently with HMG-CoA reductase inhibitors (statins), results in the reduction of cardiovascular morbidity and mortality. These results are realized not only after long-term treatment, but as early as within three to six months, and are most likely in relation to improved endothelial function. Thus, therapy with a statin reduces cholesterol synthesis, and decreases foam cell accumulation and phagocytic activity. There is also some evidence that statin therapy (eg, pravastatin) results in a reduction of cardiovascular morbidity and mortality beyond that expected from serum cholesterol reduction alone, suggesting that other mechanisms, in addition to LDL cholesterol reduction, may be at play. One convenient way to assess the benefit of statin therapy is through the concept of Virchow's Triad, by examining:

- vascular wall pathology
- abnormalities in blood flow
- abnormalities in blood constituency.

Vascular wall pathology

In addition to improving vascular endothelium function and reducing oxidized LDL at the endothelial surface, statin therapy can result in plaque stabilization. Plaque stabilization has effects on intercellular matrix, smooth muscle cell proliferation, macrophage activity, activation of T lymphocytes, and anti-inflammatory effects. The beneficial effect of pravastatin beyond that of LDL cholesterol reduction was demonstrated in a recently published mammal model (monkeys). In this model, diet was adjusted to maintain total, LDL, and HDL cholesterol in two groups of animals despite pravastatin treatment in one group. The results showed that there was a sig-

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nificant reduction in macrophages in the carotid plaque and an absence of calcification in the treated animals. Calcification was present in all of the control animals, and as well, there was evidence of neovascularization of the plaque in more than 50% of controls.[2] There was a beneficial effect on endothelial function in the pravastatin group as evidenced by a decrease in acetylcholine-induced vasoconstriction.

Abnormalities in blood flow

Healthy endothelium performs a continuous function of balancing between vasodilatation and vasoconstriction, the former being supported by healthy endothelium through secretion of nitric oxide. With endothelial dysfunction — seen early in the atherosclerotic process — comes a lack of physiologic vasodilatation and a vasoconstrictive response in relation to a variety of stimuli, including acetylcholine. Statin therapy normalizes endothelial function and so improves blood flow parameters in epicardial, and most importantly, in smaller vessels.

Abnormalities in blood constituency

In addition to a reduction in total and LDL cholesterol, as well as a mild increase in HDL cholesterol, statin therapy may be associated with a decrease in fibrinogen levels. It should be noted, however, that the impact of statin therapy on fibrinogen levels, as well as the importance of fibrinogen levels with respect to the independent effect of reducing cardiovascular morbidity and mortality, continue to be controversial. However, given the epidemiological evidence linking elevated fibrinogen levels to the incidence of CAD, it appears that fibrinogen reduction may well be beneficial. The statins represent a heterogeneous group of agents, with different pharmacokinetics and pharmacodynamics, and therefore, different effects on fibrinogen levels. The clinical importance of any difference that may or may not exist between various statins has not been studied; however, not all statins have been studied in large clinical trials demonstrating serious cardiovascular event rate reduction. The most significant reduction in fibrinogen level has been seen with a different class of lipid-modifying drugs known as fibric acid derivatives.

Anti-atherosclerotic benefits: Beyond surrogate markers

Significant evidence has accumulated demonstrating that LDL cholesterol lowering can result in retardation of angiographically detected CAD and, in some cases, regression. This suggests, at least to some extent, that a lack of angiographically detected progression can be used as a surrogate endpoint to identify patients who will also experience a reduction in cardiovascular events.[3]

Another independent marker of CAD and its progression is the inflammatory response. C-reactive protein (CRP) appears to predict occurrence of MI or death in high-risk individuals or recurrent events in those with stable or unstable angina. Recent case-control study of CARE participants[4] provide further evidence that inflammation after MI is associated with increased risk of recurrent coronary events. An interesting observation of this retrospective case-control study was that pravastatin may decrease this risk, suggesting a beneficial, non-lipid effect.

The relationship between lipid change and event reduction

The possibility of primary prevention — that is, the reduction of cardiovascular events with LDL cholesterol-lowering therapy in patients without clinical evidence of CAD — has been clearly demonstrated with pravastatin in the West of Scotland Coronary Prevention Study (WOSCOPS).[5] Subsequent reanalysis[6] has demonstrated that even though reduction in cholesterol of up to 46% was observed, there were no further benefits with respect to reduction in the clinical event rate seen beyond a 24% reduction in LDL cholesterol (Figure 1). In other words, even a modest reduction in LDL cholesterol was associated with a maximal benefit over a period of 4.4 years of follow-up. This interesting observation in the primary prevention trial was supported by a secondary pre-

Figure 1: Similar cardiovascular risk reduction beyond 24% reduction in LDL[8]

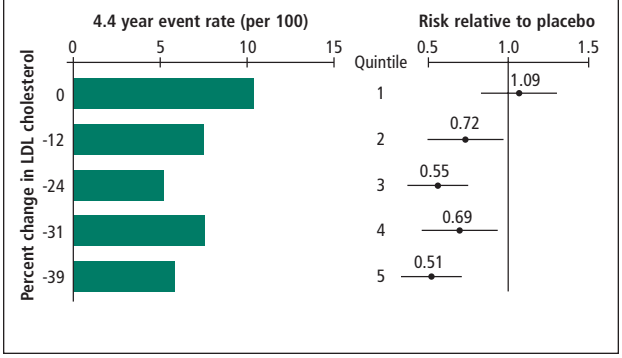
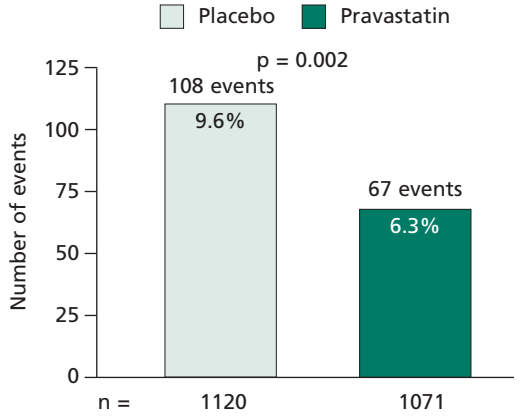


Figure 2: Overlap analysis from WOSCOPS — overlap region was 3.62 to 4.65 mmol/L



vention study with pravastatin, CARE.[7] The results of another large secondary prevention trial, 4S[8], demonstrated reduction of coronary events in direct relation to the LDL cholesterol lowering achieved with simvastatin treatment. Previous epidemiological and primary prevention studies also suggest that for every 1% increase or decrease in total cholesterol, the risk for coronary heart disease rises or falls by 2%, respectively.[9-12] Thus, there may be a divergence of opinion as to how low the goal should be for LDL cholesterol reduction.

Subsequent analysis of the WOSCOPS study[5] has also indicated that reduction in event rate from 9.6% in the placebo group to 6.3% in the pravastatin group after 4.4 years of treatment was greater than expected based on cholesterol reduction alone (Figure 2). In other words, a predicted reduction in event rate (based on serum cholesterol level reduction) was 24%, while the observed reduction was 36%, suggesting that additional mechanisms, beyond those associated with LDL cholesterol reduction, may play a role.

This interesting observation of "greater than expected benefit" was observed in a secondary prevention study with pravastatin, the Cholesterol and Recurrent Events (CARE) trial.[7] In this trial, the predicted reduction in cardiovascular events in patients treated with pravastatin for three or more months after myocardial infarction was approximately 16%, based on cholesterol reduction alone. The observed benefit, however, was 24% or one-third greater than predicted, suggesting that some of the benefit may have been due to other mechanisms. Again in this study, there was the interesting observation that LDL cholesterol did not predict event rate. In fact, reduction in LDL cholesterol beyond 21% and up to 43%, was not associated with further clinical benefit. In other words, a maximal relative risk reduction was seen regardless of a decrease in the cholesterol level as long as a reduction beyond 21% serum cholesterol level compared with a baseline level was achieved, (ie, reduction of the upper 10th percentile of starting serum cholesterol levels was sufficient). These observations suggest, but do not prove, that pravastatin therapy may be associated with benefits beyond LDL cholesterol reduction that may include plaque stabilization, decreased thrombosis, anti-inflammatory effects, as well as the clearly demonstrated effect of improving endothelial dysfunction. These hypotheses are further supported by recent animal data which suggests that pravastatin has effects on the artery wall, independent of its effects on plasma lipoprotein concentration.[2]

Table 1: Modifiable risk factors for stroke (Framingham Study)

Risk factor	Relative risk	Prevalence of risk factor
Hypertension	3-4	25-40%
Cardiovascular disease	2-4	10-20%
Cigarette smoking	1.5-2.9	20-40%
Atrial fibrillation	4-18	1%

Stroke: New paradigms, new options

Stroke is a leading cause of adult disability and the second leading cause of death worldwide. Eighty to 85% of strokes are ischemic and 15% to 25% have a three-month mortality. Nonmodifiable risk factors for stroke include age (doubling with each decade after age 55), male gender, race, diabetes, and family history. Modifiable risk factors based on Framingham Study are shown in Table 1.

Serum LDL cholesterol reduction associated with statin therapy is associated with a favorable effect on reduction in stroke (Table 2).

It should be pointed out that all subgroups of stroke are favorably affected by LDL cholesterol reduction. While cholesterol is a modest risk factor for stroke, unlike hypertension,[10] the benefit achieved in lipid-lowering studies may accrue from mechanisms other than LDL cholesterol lowering alone.

Table 2: LDL reduction with statin therapy reduces the incidence of stroke

Study	Agent	Stroke reduction	p value	% ASA
CARE	pravastatin	31%	0.03	83
LIPID	pravastatin	19%	0.048	83
4S	simvastatin	28%	0.033	37

Successful stroke prevention has been achieved with risk factor modification, a particular emphasis on hypertension treatment, and appropriate anticoagulation therapy in patients with atrial fibrillation, especially in the presence of hypertension or congestive heart failure. In patients with a negative embolic work-up or those who are not candidates for anticoagulation, antiplatelet therapy with Aspirin or ticlopidine (or clopidogrel) should be considered. Carotid endarterectomy is indicated for patients with symptomatic carotid stenosis in the range of 50% to 70% or more and this surgery may also play a role in asymptomatic patients with carotid stenosis.

With respect to cholesterol lowering, direct evidence from the CARE and LIPID studies, as well as analysis of the 4S study, clearly suggests a new era in the treatment of patients at risk for cerebrovascular disease in whom stroke prevention can now be achieved.

Conclusion

LDL cholesterol can be lowered most effectively with HMG-CoA reductase inhibitors. Reduction of LDL cholesterol leads to improved outcome based on a significant amount of evidence accumulated to date. This evidence-based approach is associated not only with improved clinical outcome from cardiovascular events, but also with more basic evidence of atherosclerotic disease regression, plaque stabilization, and improvement in endothelial function. More recent evidence suggests that HMG-CoA reductase inhibitors influence multiple steps in atherogenesis, including monocyte adhesion, proliferation and activation, as well as smooth muscle cell proliferation. These changes likely account for the plaque stabilizing effect thought to be responsible for reducing cardiovascular events. Analysis of the WOSCOPS and CARE studies with pravastatin support these hypotheses, with the finding of clinical benefit beyond that expected with LDL cholesterol reduction alone.

References

1. Murray CJL, Lopez AD. Mortality by cause for either regions of the world: Global Burden of Disease Study. *Lancet* 1997;349:1269.
2. Williams JK, Sukhova GK, Herrington DM, Libby P. Pravastatin has cholesterol-lowering independent effects on the artery wall of atherosclerotic monkeys. *J Am Coll Card* 1998;31:684-691
3. Waters D, Craven TE, Lespérance J. Prognostic significance of progression of coronary atherosclerosis. *Circulation* 1993;87:1067-1075.
4. Ridker PM, Rifai N, Pfeffer MA, et al, for the Cholesterol and Recurrent Events (CARE) Investigators. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation* 1998;98:839-844.
5. Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333;1301-1307.
6. West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation* 1998; 97:1440-1445.
7. Sacks FM, Moyé LA, Davis BR, et al. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events (CARE) trial. *Circulation* 1998;97:1446-1452.
8. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383.
9. National Cholesterol Education Program. Report of the Expert Panel on Population Strategies for Blood Cholesterol Reduction. *Circulation* 1991;83:2154.
10. Davis C, Rifkind B, Brenner H, Gordon D. A single cholesterol measurement underestimates the risk of CHD. An empirical example from the Lipid Research Clinics mortality follow-up study. *JAMA* 1990;264:3044-2252.
11. Lipid Research Clinics Program. The Lipid Research Clinics coronary primary prevention trial results: I. Reduction in the incidence of coronary heart disease. *JAMA* 1984;251:351-364.
12. Lipid Research Clinics Program. The Lipid Research Clinics coronary primary prevention trial results: II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 1984;251:365-374.
13. DeLanty N, Vaughan CJ. Vascular effects of statins in stroke. *Stroke* 1997;28:2315-2320.