New Developments in Lipid and Medical Management of Vascular Patients: What Every Vascular Surgeon Should Know

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Background

Despite multiple manuscripts and textbook chapters detailing the beneficial results of intensive atherosclerosis management in patients with peripheral arterial disease (PAD) patients still remain undertreated in comparison to established guidelines.[1,2] Fortunately, many vascular surgeons are now realizing the importance of statin therapy for lipid control.[3] Recently it is becoming clear that statins also have benefit, in the prevention of recurrent stenosis following endarterectomy, and angioplasty; in reducing cardiac complications following cardiac and non-cardiac vascular surgery; in improving walking distance; and in improving infrainguinal graft patency. Statins may also prove beneficial in the prevention of colon cancer, Alzheimer's disease, and osteoporosis (all disease frequently seen concurrently with peripheral arterial disease). As such it is becoming all the more imperative that vascular surgeons remain informed about research initiatives related to statin use and lipid management in general.

Statins and Improved Perioperative Mortality

Based on evidence that statins may have benefit in reducing early ischemic events following acute coronary syndromes,[4] investigators began to evaluate whether similar reductions in cardiac morbidity could be achieved with statins in the vascular patient.

The Statins for Risk Reduction in Surgery (StaRRS) study is a retrospective study that recorded patient characteristics, past medical history, and admission medications on all patients undergoing carotid endarterectomy, aortic surgery, or lower extremity revascularization over a 2-year period (January 1999 to December 2000) at a tertiary referral center.[5] Complications occurred in 157 of 1,163 eligible hospitalizations and were significantly fewer in patients receiving statins (9.9%) than in those not receiving statins (16.5%, p = .001). The difference was mostly accounted for by reductions in myocardial ischemia and congestive heart failure. After adjusting for other significant predictors of perioperative complications (age, gender, type of surgery, emergent surgery, left ventricular dysfunction, and diabetes mellitus), statins still conferred a highly significant protective effect (odds ratio [OR] 0.52, p = .001).

Kertai and colleagues studied 570 patients (mean age 69 ± 9 years, 486 males) who underwent abdominal aortic aneurysm (AAA) surgery between 1991 and 2001.[6] The main outcome was a composite of perioperative mortality and MI within 30 days of surgery. Perioperative mortality or MI occurred in 51 (8.9%) patients. The incidence of the composite end point was significantly lower in statin users compared to nonusers (3.7% versus 11.0%; crude OR 0.31, 95% CI 0.13 to 0.74; p = .01).

After correcting for other covariates, the association between statin use and reduced incidence of the composite end point remained unchanged (OR 0.24, 95% CI 0.10 to 0.70; p =.01). ≤-blocker use was also associated with a significant reduction in the composite end point (OR 0.24, 95% CI 0.11 to 0.54). Patients using a combination of statins and ≤-blockers appeared to be at lower risk for the composite end point across multiple cardiac risk strata; particularly patients with three or more risk factors experienced significantly lower perioperative events.

Durazzo and colleagues randomly assigned 50 patients to receive atorvastatin and 50 patients to placebo once a day for 45 days, irrespective of their serum cholesterol concentration.[7] Vascular surgery was performed on average 30 days after randomization, and patients were prospectively followed up over 6 months. The cardiovascular events studied were death from cardiac cause, nonfatal myocardial infarction, unstable angina, and stroke. During the 6-month follow-up primary end points occurred in 17 patients, 4 in the atorvastatin group and 13 in the placebo group. The incidence of cardiac events was more than three times higher with placebo (26.0%) compared with atorvastatin (8.0%; p =.031).

Clearly, the effect of statins occurred more rapidly than can be explained by simple reduction in low density cholesterol levels. This appears to support the concept that statins have an anti-inflammatory effect on coronary vasculature thus reducing sudden coronary thrombosis.[8,9] Olsson and colleagues suggest that a continuous immune system activation takes place in patients with chronic angina pectoris, predominantly involving proliferation of CD4+ T cells.[8] Their findings indicated that statin treatment seems to be able to decrease this inflammatory response.

Statins and Claudication

Mohler and colleagues performed a randomized, double-blind, parallel-design study which included 354 persons with claudication attributable to peripheral arterial disease.[10] Patients were treated with placebo, atorvastatin (10 mg/d), or atorvastatin (80 mg/d) for 12 months. The outcome measures included a change in treadmill exercise time and patient-reported measures of physical activity and quality of life based on questionnaires. Maximal walking time after 12 months of treatment with atorvastatin did not change significantly. However, there was improvement in pain-free walking time after 12 months of treatment for the 80 mg (p = .025) group compared with placebo. A physical activity questionnaire demonstrated improvement in ambulatory ability for the 10 and 80 mg groups (p = .011), whereas two quality of life instruments, the Walking Impairment Questionnaire and Short Form 36 Questionnaire, did not show significant change.

Mondillo and colleagues studied 86 patients with peripheral arterial disease (Fontaine stage II), intermittent claudication, and total cholesterol levels > 220 mg/dL.[11] Patients were enrolled in a randomized, placebo-controlled, double-blind study. Forty-three patients were assigned to simvastatin (40 mg/d); the remaining 43 patients were assigned to placebo treatment. All patients underwent an exercise test and clinical examination, and completed a self-assessment questionnaire at 0, 3, and 6 months. Pain-free and total walking distance, resting and post-exercise ankle-brachial indexes, and questionnaire scores were determined at each follow-up. At 6 months, the mean pain-free walking distance had increased 90 m (95% CI 64 to 116 m; $p < .005$) more in the simvastatin group than in the placebo group. Similar results were seen for the total walking distance (mean between-group difference in the change, 126 meters; 95% CI 101 to 151 m; $p < .001$). There was also a greater improvement in claudication symptoms among patients treated with simvastatin. The effects on walking performance and questionnaire scores were also significant at 3 months.

Statins and Recurrent Stenosis

The relationship between serum lipid levels and recurrent stenosis has been postulated for many years,[12-14] and it has been reconfirmed in recent literature by LaMuraglia and colleagues.[15] These same authors also showed that concurrent administration of a lipid-lowering drug had a profound effect on early recurrent stenosis. In their multivariate model, elevated cholesterol was persistently identified as an independent predictor of CEA recurrent stenosis, despite the effects of lipid-lowering drugs. This would suggest that in addition to their known effect on lowering cholesterol, these drugs might have other relevant properties that might promote the anatomic durability of the CEA reconstruction. Such effects may include the decrease of the inflammatory response in the vessel wall, the increase of circulating endothelial progenitor cells, and the promotion of smooth muscle cell apoptosis; all of which have been described with the use of statins and are known to have a role in the restenotic process.[16,17]

Statins and Graft Patency

Two recent manuscripts suggest that statin therapy may also play a role in graft patency and we are currently evaluating the data in the Prevent III study to see if this data can be confirmed in this large study of infrainguinal vein bypasses.[18,19]

Abbruzzese and colleagues performed a retrospective analysis of consecutive 172 patients (1999 to 2001) who underwent 189 primary autogenous infrainguinal reconstructions with a single segment of greater saphenous vein.[19] Patients were categorized according to concurrent use of a statin (94 statin, 95 control). Graft lesions (identified by duplex surveillance) and interventions were tabulated. Interestingly, despite the earlier section on improved mortality with statin use, perioperative mortality (2.6%) and major morbidity (3.2%) were not different between groups. There was no difference in primary patency (74% ± 5% versus 69% ± 6%; $p = .25$), limb salvage (92% ± 3% versus 90% ± 4%; $p = .37$), or survival (69% ± 5% versus 63% ± 5%; $p = .20$) at 2 years. However, patients on statins had higher primary-revised (94% ± 2% versus 83% ± 5%; $p < .02$) and secondary (97% ± 2% versus 87% ± 4%; $p < .02$) graft patency rates at 2 years. Of all factors studied by univariate analysis, only statin use was associated with improved secondary patency ($p = .03$) at 2 years. This was confirmed by multivariate analysis. The risk of graft failure was 3.2-fold higher (95% confidence interval, 1.04-10.04) for the control group. Perioperative cholesterol levels (available in 47% of patients) were not statistically different between groups. Henke and colleagues evaluated 293 patients (mean age, 64 years; 67% men) who underwent 338 infrainguinal bypass procedures with autologous vein (n = 218), prosthetic grafts (n = 88), or composite prosthetic-vein grafts (n = 32).18 Limb salvage was the operative indication in 75% of procedures. Coexisting diseases included hypertension (70%), diabetes (52%), hyperlipidemia (37%), coronary heart disease (51%), congestive heart failure (14%), and active tobacco use (30%). Statin drugs were taken by 56% of patients, ACE inhibitors by 54% of patients, and antiplatelet agents or warfarin sodium by 93% of patients. Postoperative graft surveillance was done in 39% of patients. Cumulative graft patency was 73%, limb salvage was 85%, and mortality was 9%, with a mean follow-up of 17 months. Statins were associated with increased graft patency (OR 3.7; 95% CI, 2.1 to 6.4) and a lower rate of amputation. Once again, however they were not associated with decreased mortality

Beneficial Effects of Statins in Statins Non-vascular Conditions

Many elderly patients with PVD are also at risk for other nonrelated conditions and statins have shown to be beneficial in many of these.

Colon Cancer

Statins inhibit the growth of colon-cancer cell lines, and secondary analyses of some, but not all, clinical trials suggest that they reduce the risk of colorectal cancer.

The Molecular Epidemiology of Colorectal Cancer study is a population-based case-control study of patients who received a diagnosis of colorectal cancer in northern Israel between 1998 and 2004 and controls matched according to age, sex, clinic, and ethnic group.[20] They used a structured interview to determine the use of statins in two groups and verified self-reported statin use by examining prescription records in a subgroup of patients for whom prescription records were available. The analysis included 1,953 patients with colorectal cancer and 2,015 controls. The use of statins for at least 5 years (versus the nonuse of statins) was associated with a significantly reduced relative risk (47%) of colorectal cancer (OR 0.50; 95% CI 0.40 to 0.63). This association remained significant after adjustment for the use or nonuse of aspirin or other nonsteroidal anti-inflammatory drugs; the presence or absence of physical activity, hypercholesterolemia, and a family history of colorectal cancer; ethnic group; and level of vegetable consumption (OR 0.53, 95% CI 0.38 to 0.74). The use of fibrates was not associated with a significantly reduced risk of colorectal cancer (OR 1.08, 95% CI 0.59 to 2.01). The use of statins was associated with a 47% relative reduction in the risk of colorectal cancer after adjustment for other known risk factors. It should be noted, however, that the absolute risk reduction was low and so further investigation of the overall benefits of statins in preventing colorectal cancer is still warranted.

Alzheimer's Disease

The role of statins in this debilitating mental disease remains controversial.[21] Also there is a suggestion that statins may cause memory problems in some susceptible patients.[22]

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Osteoporosis

Statins have also been shown to reduce osteoporosis in post-menopausal women.[23,24] Whether this is another anti-inflammatory effect or whether this is related indirectly to the beneficial effects of statins on the bone vasculature or some as yet unidentified statin pharmacologic effect is still not known. Interestingly bis-phosphonates, drugs used to increase bone density, may improve lipid profiles.

Summary

Patients with PAD will usually manifest an abnormality of lipid metabolism that will often require pharmaceutical assistance. In general, statins will be the first line therapy, and these can usually be prescribed with minimal risk although severe side effects may occur. It is important to realize that the beneficial effects of these drugs go beyond changes in cholesterol levels and affect not only atherosclerosis but also its effects on morbidity and mortality.

The complete vascular surgeon needs to stay abreast of these exciting advances in our knowledge about these pluripotential statins. Once again, I suggest that the vascular surgeon should be a "center of excellence of one," someone who is able to operate, dilate, and medicate.

References

1. Rehring TF, Sandhoff BC, Stolcpart RS, et al. Atherosclerotic risk factor control in patients with peripheral arterial disease. J Vasc Surg 2005;41: 8l6-22.
2. Samson RH. Pharmaceutical initiatives to combat atherosclerosis-what to do with the good, the bad, and the ugly lipoproteins. Semin Vasc Surg 2002;15:204-15.
3. Samson RH. Medical management of the vascular patient. In: Rutherford R, editor. Vascular surgery. 6th ed. London: Elsevier Publishing; 2005.
4. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001;285:1711-8.
5. O'Neil-Callahan K, Katsimaglis G, Tepper MR, et al. Statins decrease perioperative cardiac complications in patients undergoing noncardiac vascular surgery-the Statins for Risk Reduction in Surgery (StaRRS) study. J Am Coll Cardiol 20051;45: 336-42.
6. Kertai MD, Boersma E, Westerhout CM, et al. A combination of statins and beta-blockers is independently associated with a reduction in the incidence of perioperative mortality and nonfatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery. Eur J Vasc Endovasc Surg 2004;28:343-52.
7. Durazzo AE, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. J Vasc Surg 2004;39:967-75.
8. Olsson AG, Schwartz GG, Jonasson L, Linderfalk C. Are early clinical effects of cholesterol lowering mediated through effects on inflammation? Acta Physiol Scand 2002;176:147-50.
9. Kinlay S, Schwartz GG, Olsson AG, et al. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. Circulation 2003;108:1560-6.
10. Mohler ER III, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation 2003;108:1481-6.
11. Mondillo S, Ballo P, Barbati R, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. Am J Med 2003;114:359-64.
12. Rapp JH, Qvarfordt P, Krupski WC, et al. Hypercholesterolemia and early restenosis after carotid endarterectomy. Surgery 1987;101:277-82.
13. Cuming R, Worrell P, Woolcock NE, et al. The influence of smoking and lipids on restenosis after carotid endarterectomy. Eur J Vasc Surg 1993;7: 572-6.
14. Colyvas N, Rapp JH, Phillips NR, et al. Relation of plasma lipid and apoprotein levels to progressive intimal hyperplasia after arterial endarterectomy. Circulation 1992;85:1286-92.
15. LaMuraglia GM, Stoner MC, Brewster DC, et al. Determinants of carotid endarterectomy anatomic durability: effects of serum lipids and lipid-lowering drugs. J Vasc Surg 2005;41:762-8.
16. Erl W, Hristov M, Neureuter M, et al. HMG-CoA reductase inhibitors induce apoptosis in neointima-derived vascular smooth muscle cells. Atherosclerosis 2003;169:251-8.
17. Laws PE, Spark JI, Cowled PA, Fitridge RA. The role of statins in vascular disease. Eur J Vasc Endovasc Surg 2004;27:6-16.
18. Henke PK, Blackburn S, Proctor MC, et al. Patients undergoing infrainguinal bypass to treat atherosclerotic vascular disease are underprescribed cardioprotective medications: effect on graft patency, limb salvage, and mortality. J Vasc Surg 2004;39:357-65.
19. Abbruzzese TA, Havens J, Belkin M, et al. Statin therapy is associated with improved patency of autogenous infrainguinal bypass grafts. J Vasc Surg 2004;39:1178-85.
20. Poynter JN, Gruber SB, Higgins PD, et al. Statins and the risk of colorectal cancer. N Engl J Med 2005;352:2184-92.
21. Zandi PP, Sparks DL, Khachaturian AS, et al. Cache County Study investigators. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. Arch Gen Psychiatry 2005;62:217-24.
22. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy 2003;23:871-80.
23. Hamerman D. Osteoporosis and atherosclerosis: biological linkages and the emergence of dual-purpose therapies. QJM 2005;98:467-84.
24. Burnett JR, Vasikaran SD. Cardiovascular disease and osteoporosis: is there a link between lipids and bone? Ann Clin Biochem 2002;39(Pt 3):203-10.

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