Improved Perioperative Outcomes From Carotid Endarterectomy
Yet Another Statin Side Effect?

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A cardiologist colleague at our hospital jokes that he prefers to prescribe medicines when they are first marketed because they have fewer side effects. As a rule, much remains unknown about the unintended effects of pharmaceutical agents at the time of an initial drug launch, and with some regularity, these side consequences yield black box warnings, product recalls, and even congressional hearings. The rule of unintended effects applies also to statins; with each passing month, it seems the literature has several new reports about the unexpected effects of these agents. However, with paradoxical and almost miraculous consistency, the side consequences of statins are health promoting and life prolonging. Through a variety of biochemical pathways, statins exert pleiotropic physiological effects, in addition to their lipid-lowering effects, which include improving endothelial dysfunction, enhancing atherosclerotic plaque stability, increasing NO bioavailability, decreasing oxidative stress, blunting the inflammatory response, increasing bone mineral density, and inhibiting thrombogenesis. These physiologic effects are believed to have potential benefit for a wide variety of disorders, including (but not limited to) preventing Alzheimer disease, slowing progression of chronic kidney disease, treating osteoporosis and rheumatic diseases, preventing type 2 diabetes, preventing prostate and colon cancer, and even reducing mortality in pneumonia and sepsis. These putative effects are so varied and salubrious that readers (of a certain generation) may think of statins as the pharmaceutical equivalent of “Shimmer,” the versatile if fictitious household product from the spoof advertisement on Saturday Night Live: “It’s a floor wax AND a dessert topping!”

In this issue of Stroke, Kennedy et al. add to the growing literature on the Shimmer-like benefits of these miracle agents. They analyzed all carotid endarterectomy procedures performed in four Western Canadian provinces and found that (at least for symptomatic patients) those who take statins had considerably better operative outcomes than those who do not, as measured by mortality and perioperative stroke. Although this is an observational study, the results cannot be dismissed lightly. The database is relatively large (n = 3360), with a good representation of patients with and without statin therapy and with symptomatic and asymptomatic disease. The significance of the effect and the effect-size remained virtually unchanged when the investigators controlled for numerous potential confounders using multivariable logistic regression and propensity scoring. Moreover, the study is consistent with previous studies describing better perioperative outcomes in those who take statins.

However, readers may recall other well-performed observational studies, equally convincing, that were later contradicted by subsequent randomized controlled clinical trials. Indeed, the biochemical and epidemiologic evidence on the effectiveness of hormone replacement therapy (HRT) for the prevention of cardiovascular disease was so compelling that many felt that it would be unethical to randomize postmenopausal women in a placebo-controlled trial. Also, like statins, HRT was felt to have Shimmer-like pleiotropic effects: not only reducing cardiovascular morbidity and mortality but also improving bone mineral density and reducing fracture risk (which was experimentally proven), as well as decreasing the risk of Alzheimer’s disease, depression, incontinence, and other age-related ailments. We now know from the results of the randomized studies Heart and Estrogen-progestin Replacement Study (HERS) and the Women’s Health Initiative (WHI) that far from decreasing risk, HRT increased heart attacks, strokes, thromboembolic diseases, and senility. The increased cardiovascular risk was totally unexpected in light of what can only be described as overwhelming observational evidence.

Why did estrogens appear so beneficial in observational studies and not in the clinical trials? It must have been related to ways in which estrogen takers differed from estrogen nontakers and the limits of statistical methods for adjusting for this noncomparability of the treatment groups. Most especially, estrogen takers apparently differed from nontakers in a cluster of psychological, social, and economic characteristics that are highly influential on health outcomes but not well captured by the usual clinical and demographic variables. And indeed, there is some evidence that statin takers differ from statin nontakers, through disparities in physician prescribing and disparities in patient adherence and persistence, that might be in some ways very similar to the estrogen example. Indeed, as estrogen was last decade, statin therapy is likely to be a general marker of quality of care and of the health-mindedness of the patient, which makes the
results of any observational study highly preliminary. Also, in addition to being a marker generally for good patients being cared for by good doctors, statin use is likely to specifically be closely associated with β-blocker use, and β-blockers are well established to decrease perioperative mortality in patients with cardiovascular risk factors.14 The enormous effect size of statin use among symptomatic patients undergoing carotid endarterectomy seen in this study (nontakers had a 4-fold higher risk of perioperative death and a 2-fold higher risk of perioperative stroke than statin takers) is a hint that patients in the treatment groups might differ in important but unmeasured characteristics since treatment effects of medications are rarely this large. So, in summary, even thoughtful researchers using sophisticated statistical tools cannot convert the sω’s ear of an observational study into the silk purse of a randomized clinical trial (especially when much of clinical importance goes unmeasured).

On the other hand, despite the spectacular failure of observational studies in the estrogen case, this is probably an extreme exception; more often than not, the results of well-conducted observational trials are confirmed by clinical trials.15 Yet, even accepting the potential causative role of statins in reducing perioperative stroke or mortality in patients with symptomatic endarterectomy, it is not clear how one might apply this in clinical practice or in the design of a trial. Given the pleiotropic effects of statins, it is unclear which mechanism(s) might be responsible for their perioperative benefits, and thus the time course for the treatment effect is also unclear. In the small clinical trial testing atorvastatin in patients undergoing vascular surgery,16 patients were pretreated for an average of 30 days before their procedure. Because the risk of stroke is front-loaded in patients with symptomatic carotid stenosis and early surgery is of most benefit,17 any actual benefit of preoperative statins may be outweighed by the risks of delaying surgery if a pretreatment period of this length is needed.

For what it is worth, my personal belief regarding statins is that their anti-inflammatory and plaque-stabilizing properties are likely to be at least as important clinically as their cholesterol-lowering properties, and that many of the putative benefits of these agents, including the perioperative effects, are likely to be causal, and not the result of unmeasured bias. However, I am less sanguine about whether we will have the collective will and resources to rigorously test and fully realize the benefits of these agents in clinical practice, especially as they become generically available, or whether all the “side effects” of statins seen in observational studies, accumulating week after week in the literature, will remain just so many shimmering possibilities.

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References

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