Can a Statin Neutralize the Cardiovascular Risk of Unhealthy Dietary Choices?

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The cardiovascular risk reduction associated with different statins for the prevention of cardiovascular disease and the cardiovascular risk increase associated with excess dietary intake of fat have been quantified. However, these relative risks have never been directly juxtaposed to determine whether an increase in relative risk by 1 activity could be neutralized by an opposing change in relative risk from a second activity. The investigators compared the increase in relative risk for cardiovascular disease associated with the total fat and trans fat content of fast foods against the relative risk decrease provided by daily statin consumption from a meta-analysis of statins in primary prevention of coronary artery disease (7 randomized controlled trials including 42,848 patients). The risk reduction associated with the daily consumption of most statins, with the exception of pravastatin, is more powerful than the risk increase caused by the daily extra fat intake associated with a 7-oz hamburger (Quarter Pounder®) with cheese and a small milkshake. In conclusion, statin therapy can neutralize the cardiovascular risk caused by harmful diet choices. In other spheres of human activity, individuals choosing risky pursuits (motorcycling, smoking, driving) are advised or compelled to use measures to minimize the risk (safety equipment, filters, seatbelts). Likewise, some individuals eat unhealthily. Routine accessibility of statins in establishments providing unhealthy food might be a rational modern means to offset the cardiovascular risk. Fast food outlets already offer free condiments to supplement meals. A free statin-containing accompaniment would offer cardiovascular benefits, opposite to the effects of equally available salt, sugar, and high-fat condiments. Although no substitute for systematic lifestyle improvements, including healthy diet, regular exercise, weight loss, and smoking cessation, complimentary statin packets would add, at little cost, 1 positive choice to a panoply of negative ones. © 2010 Elsevier Inc. All rights reserved. (Am J Cardiol 2010;106:587–592)

Despite major strides in prevention, cardiovascular disease remains a leading cause of morbidity and mortality in the developed world, accounting for almost a third of all deaths and just over 10% of disability-adjusted life-years lost.1,2 The prevention of a first cardiac event is haphazard, with systematic control of risk factors only occurring if a patient happens to have contact with the health care system. However, the greatest burden of coronary atherosclerosis nationwide lies in an as yet unidentified “at-risk” population.3 This apparently healthy population is free to make unhealthy choices, yet they have no ready access to powerful primary prevention measures that could mitigate the cardiovascular consequences. Given the frequency of fast food consumption and the adverse health consequences of the foodstuffs supplied,4,5 we propose that the fast food industry is well placed to offer advice and supplements to counteract the cardiovascular harm arising from the foods they purvey. These companies already have an infrastructure for providing a variety of condiments, including salt, tomato ketchup, and other sauces, none of which have any health benefits but are made available free of charge. A generic statin could be added to the panoply of items in the self-service tray, at little marginal cost, in combination with other healthy lifestyle suggestions. However, would a statin be powerful enough to counteract the cardiovascular risk generated by an unhealthy meal? In the present study, we compose a tariff for neutralizing the cardiovascular risk from unhealthy fast food.

Calculating a Neutralization Tariff

No interventional study has examined the ability of statins to neutralize the excess cardiovascular risk arising from consuming fast foods, nor is there ever likely to be such a study. However, a tariff can instead be constructed using only the following assumptions: (1) In an unhealthy diet, each unhealthy meal makes a contribution, pro rata, to the increase in cardiovascular risk; (2) in studies of subjects

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We have chosen the Quarter Pounder® because it is a product that is universally known and universally uniform in its characteristics. We use it, however, solely as a proxy for all foods of certain fat and trans-fat content. We do not suggest that a Quarter Pounder® poses any health threat greater than any other food with the same fat and trans-fat content.

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taking statins, each statin tablet makes a contribution, pro rata, to the decrease in risk; (3) no group of subjects at high atherosclerotic risk has been found in whom statins appear to be ineffective; and (4) if a statin tablet reduces the risk for cardiovascular events by approximately the amount of the increase caused by the meal, the consumer will not care whether the statin achieves this by directly biologically interfering with the absorbed meal or by separate pleiotropic effects with a different time course.

On the basis that the unhealthy dietary choice is for 1 day, and the corresponding statin use is also for 1 day, the respective harmful and beneficial effects of each undergo the same pro rata attenuation and can therefore be compared directly using relative risks. Relative risks are more helpful than absolute risks in calculating this tariff because, for multifactorial processes such as cardiovascular disease, it is relative rather than absolute measures that are conserved across individuals who vary in baseline characteristics. The tariff of relative risks is best shown on a logarithmic scale, because when exposures are combined, relative risks generally multiply rather than add. On this visual “slide rule,” we will be able to see if “bad” exposures can be offset by sufficiently strong “good” ones.

Exposure to a daily dose of a 7-oz hamburger (Quarter Pounder) with cheese and a small milkshake for a year is used to illustrate the principle of “bad” exposures that can be offset by “good” ones, such as the consumption of a statin tablet. Although it is widely accepted that higher fat intake increases cardiovascular risk, studies to precisely quantify this effect are difficult to perform because of the difficulty in quantifying food intake and adjusting for confounders of dietary behavior. Our best available guidance for quantifying the dose dependence of this risk comes from a large cohort study of 43,757 male health professionals, aged 40 to 75 years, with initially no cardiovascular disease or diabetes from 1986 to 1996. The relative risk for nonfatal myocardial infarction and fatal coronary artery disease after multivariate adjustment to account for other factors contributing to risk was 1.23 (95% confidence interval 0.96 to 1.57) for the highest total fat-intake quintile (89 g total fat) in comparison to the lowest total fat-intake quintile (53 g total fat). A similar trend was also observed for trans unsaturated fat, with a relative risk of 1.4 (95% confidence interval 1.10 to 1.79) associated with intake in the highest quintile of the population (4.3 g trans fat vs 1.5 g in the lowest quintile). Because the study was limited to healthy subjects with no known pre-existing cardiovascular disease, the event rate was low, and therefore the confidence intervals were wide.

We chose to use total dietary fat consumption rather than saturated fat or cholesterol intake for our calculations because total fat provides a more representative marker of the nutritional burden of unhealthy foods, and studies have demonstrated a clear relation between total fat intake and serum cholesterol levels. We performed additional calculations for trans unsaturated fat because recent evidence suggests that it is the trans fat component of the “Western-type” diet that is responsible for the greater part of its adverse cardiovascular risk profile. We obtained nutritional content information for foods from well-known fast food outlets, using data published freely on the Internet. We found food types with total fat and trans fat contents equal to the median values of the third and highest fifths of the population in the cohort described previously and used these foods to illustrate the relative risk associated with those cholesterol intakes.

To determine the relative risk reduction due to statins, we used a recent meta-analysis of statins in the primary prevention of coronary artery disease that included 7 randomized controlled trials, covering 42,848 patients. Table 1 lists study characteristics of the included trials. The primary outcome measure used in our calculations was the relative

### Table 1

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Primary Prevention</th>
<th>Study Population Characteristics</th>
<th>Statin</th>
<th>Mean Change in LDL-C</th>
<th>Years of Follow-Up</th>
<th>RR for Major Coronary Events (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS (1995)</td>
<td>6,595</td>
<td>83.8%</td>
<td>100% men, increased cholesterol</td>
<td>Pravastatin 40 mg</td>
<td>−26%</td>
<td>4.9</td>
<td>0.70 (0.58–0.85)</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS (1998)</td>
<td>6,605</td>
<td>100%</td>
<td>Men aged ≥45 yrs, women aged ≥55 yrs, 85% men</td>
<td>Lovastatin 20–40 mg</td>
<td>−26.5%</td>
<td>5.2</td>
<td>0.60 (0.43–0.83)</td>
</tr>
<tr>
<td>PROSPER (2002)</td>
<td>3,239</td>
<td>100%</td>
<td>Mean age 75 yrs, ≥3 risk factors</td>
<td>Pravastatin 40 mg</td>
<td>NA</td>
<td>3.2</td>
<td>0.91 (0.71–1.15)</td>
</tr>
<tr>
<td>ALLHAT-LLT (2002)</td>
<td>5,355</td>
<td>85.8%</td>
<td>≥3 CV risk factors</td>
<td>Pravastatin 20–40 mg</td>
<td>−16.7%</td>
<td>4.8</td>
<td>0.91 (0.79–1.04)</td>
</tr>
<tr>
<td>ASCOT-LLA (2003)</td>
<td>10,305</td>
<td>82%</td>
<td>Mean age 63 yrs, 81% men, ≥3 risk factors</td>
<td>Atorvastatin 10 mg</td>
<td>−27.6%</td>
<td>3.3</td>
<td>0.65 (0.50–0.83)</td>
</tr>
<tr>
<td>HPS (2003)</td>
<td>2,911</td>
<td>100%</td>
<td>High-risk patients with diabetes</td>
<td>Simvastatin 40 mg</td>
<td>NA</td>
<td>4.8</td>
<td>0.57 (0.41–0.79)</td>
</tr>
<tr>
<td>CARDS (2004)</td>
<td>2,838</td>
<td>100%</td>
<td>T2DM, ≥1 risk factors, low LDL-C</td>
<td>Atorvastatin 10 mg</td>
<td>−33.9%</td>
<td>3.9</td>
<td>0.53 (0.35–0.82)</td>
</tr>
</tbody>
</table>

Adapted from Arch Int Med. AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Arm; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; CI = confidence interval; CV = cardiovascular; HPS = Medical Research Council/British Heart Foundation Heart Protection Study; LDL-C = low-density lipoprotein cholesterol; PROSPER = Pravastatin in Elderly Individuals at Risk of Vascular Disease; RR = relative risk; T2DM = type 2 diabetes mellitus; WOSCOPS = West of Scotland Coronary Prevention Study.
risk for a major cardiovascular event (nonfatal myocardial infarction and coronary artery disease death).

We acknowledge that the underlying physiologic mechanisms by which the 2 opposing exposures, fat intake versus statin consumption, affect cardiovascular risk are complex and multifactorial; however, the quantitative juxtaposition of their relative risks is not reliant on these mechanisms’ being matched. This approach can be likened to the routine clinical practice of prescribing statins to patients with diabetes with normal lipid levels. Despite the risk-reducing agent’s acting through a different biologic pathway from the risk factor, the overall cardiovascular risk is reduced. Although effect on risk can be measured adequately only at a population level, this is only because we quantify risk by counting events that are dichotomous, so the only way to obtain a continuous risk variable is to average many individuals. It is not because individuals are not affected; effect on the population can arise only from effects on its component individuals.

Neutralization by Matching Relative Risks

Risk prediction equations are generated from cohort studies that measure risk exposures in all the subjects and follow the participants for outcomes. The basis of most statistical models fitted to the data is that after accounting for age and gender, the remaining risk exposures, such as cholesterol and blood pressure, act multiplicatively to increase a subject’s risk. Thus, for example, if the relative risk for death due to a 1 mmol/L increase in cholesterol is estimated to be 2, and if that due to a 10 mm Hg increase in blood pressure is estimated to be 3, then a subject with the combination of the 2 will have a total relative risk of 6. In published research, a number of studies suggest that this simple model (adding the logarithm of relative risk or multiplying the actual relative risk) is a reasonable approach. In practice, simple multiplicative risk scores appear to work as well as more complex models when whole populations are stratified into categories of high, medium, and low absolute total cardiovascular risk. Thus, although it is possible that there is an interaction term
between the risk factors that contribute to cardiovascular disease risk scores, in practice, we use simple tools to estimate individual risk, and it would be reasonable to use equally simple and transparent tools to estimate risk reduction.

Median total fat intake above the lowest fifth of the cohort (53 g total fat or 1.5 g trans fat per day, relative risk 1) is associated with an increase in (multivariate-adjusted) relative risk for a major cardiac event, which can be approximated by a log-linear relation (Figure 1). Dietary modification to reduce fat intake shows a trend toward reducing cardiovascular risk, but interventional studies have not always achieved significance, perhaps because the intervention is slow to take effect or because of poor long-term compliance or difficulties in measuring diet accurately. In contrast, a daily dose of statin reduces the relative risk for fatal ischaemic heart disease and non-fatal myocardial infarction by 20% to 70%, depending on the type of statin and the dose taken (Figure 2). In a recent meta-analysis focusing only on primary prevention trials, the combined relative risk across all included trials was 0.71 (95% confidence interval 0.60 to 0.83).

We plotted the logarithm of the reduction in relative risk for cardiovascular disease associated with different statin trials against the logarithm of the increase in relative risk associated with consumption of foods of increasing total fat and trans-fat content (Quarter Pounder hamburger [19 g total fat, 1 g trans fat], Quarter Pounder with cheese [26 g total fat, 1.5 g trans fat], small milkshake [10 g total fat, 1 g trans fat]). We juxtaposed the changes in relative risk to illustrate the extent to which statins have the power to offset the increased risk for cardiovascular disease associated with unhealthy lifestyle choices. We found that most statin regimes are able to compensate for the increased relative risk associated with eating an additional Quarter Pounder with cheese and a small milkshake above the baseline daily fat intake of the lowest quintile of the population (Figure 3).

Discussion

The calculations show that statins can be expected to neutralize the increased relative risk for cardiovascular disease associated with the regular consumption of unhealthy foods. Most of the primary prevention statin regimes we examined, with the exception of pravastatin, had the strength to counteract the increase in risk caused by an unhealthy diet or eating an additional 36 g of total fat or 2.8 g of trans fat per day, approximately equivalent to a Quarter Pounder with cheese and a small milkshake.

Science is a mechanism for resolving controversy. The role of the diet, particularly fat, in influencing serum cholesterol levels and cardiovascular mortality has been questioned in the past, but there are extensive data to corroborate its adverse effects. The beneficial effects of reducing dietary saturated fat on serum cholesterol and cardiovascular disease is suggested by a number of studies, but the data remain inconclusive. This does not mean that we should disregard nutritional education in prevention of cardiovascular disease, but it should be recognized that nonpharmacologic measures alone may sometimes be insufficient, thereby prompting us to move toward incorporating dietary advice and pharmacotherapy into a coherent strategy for primary prevention.

Until recently, there has been relatively little evidence for the role of statins in the primary prevention of cardiovascular disease. Primary prevention trials by definition target a low-risk population with a low event rate, so benefits of interventions may be more difficult to demonstrate. However, we argue that it is unlikely that the mechanism by which atherosclerosis causes a first myocardial infarction differs substantially from that causing subsequent infarctions. It could therefore be targeted in a similar manner to secondary prevention. In support of this, evidence has now emerged from a number of recent large meta-analyses in favor of the use of statins in primary prevention, thus forming the basis of new United States guidelines.

We acknowledge the significant variability in background cardiovascular risk between the different statin trials and the dietary fat intake observational study. We have controlled for this as far as possible by using multivariate-adjusted relative risk in the dietary fat study, accounting for confounding factors such as body mass index, smoking status, and blood pressure. Clinicians frequently make similar extrapolations between populations in prescribing drugs to patients whose personal characteristics differ from those of published trial populations, because it is impossible to conduct every dietary, behavioral, and interventional trial in every subpopulation. Practical decisions must be made on the basis of the best information that is available.

Statin safety: The widespread clinical use of statins has permitted extensive review of their safety profile. Reports have concluded that statins have a favorable “benefit-to-risk” ratio, with only rare adverse effects reported in hepatic, renal, and muscle tissue and no associated increase in non-cardiovascular mortality. If statins are to be made more readily available by fast food outlets, statin toxicity might become a greater concern, but statins have been shown to be safe even at high doses. We can conclude that the documented safety record of statins is substantially better than that of fast foods, which carry not only direct cardiovascular risks but other risks due to obesity. It cannot therefore be reasonably argued on safety grounds that individuals should be free to choose to eat lipid-rich food but not be free to supplement it with a statin. It would be no more sensible than allowing individuals to drive without training or a license but at the same time restricting access to seatbelts and airbags. Despite this, we would advocate that appropriate studies be conducted to evaluate the potential risks of “unsupervised” statin availability.

“Occasional” versus “regular”: Our calculations are based on statin trials of a daily dose over an extended time period. There is currently no evidence for the use of a single “one-off” dose of statin for the primary prevention of cardiovascular disease, just as there may never be any evidence for the adverse mortality effect of eating a single cheeseburger. However, we argue that an unhealthy lifestyle is no more than the sum of a series of regular unhealthy choices. For an individual who eats a cheeseburger once a year and thus takes a statin only once a year, the risk offset will be minimal. Individuals who have a more frequent habit of fast
food consumption will have greater risk and greater opportunity to neutralize that risk. Importantly, even partial adherence to statin therapy conveys a mortality benefit, suggesting that statins do not need to be taken daily to have some protective effect.

Can statins work against all risk factors? Although statins cannot eliminate cardiovascular risk, it is worth remembering that in trial data, there is no consistent “high-risk” subgroup that does not show a cardiovascular benefit from statins. Although “individuals who eat fast food frequently” is not a subgroup that has ever been formally studied in a statin trial, it seems implausible that they would turn out to be an undiscovered subgroup in whom statins are peculiarly ineffective. Importantly, statins have proven risk-reducing benefits for cardiovascular risk factors other than high low-density lipoprotein cholesterol and cholesterol, such as type 2 diabetes mellitus and elevated C-reactive protein.

Not taking the easy way out: We hope to empower individuals with the awareness of their own cardiovascular risk by creating a visual sliding scale of the relative risks associated with different lifestyle choices. We emphasize that in no way are we encouraging individuals to eat unhealthily by coaxing them into the belief that a simple pill is a panacea for all risks. We stress that there should be greater pressure on fast food corporations to develop healthier menus and to encourage regular physical activity and weight control. However, the current epidemic in obesity and cardiovascular disease is proof that many individuals fail to follow a healthy lifestyle. Although statins do not provide protection against obesity or diabetes arising from high-calorie, high-sugar diets, they may provide protection against impending cardiovascular disease in this as yet subclinical but high-risk population.

We envisage a future in which fast food restaurants encourage a holistic approach to healthy living. On ordering an unhealthy meal, the food will arrive labeled with a warning message similar to those found on cigarette packets (“This meal increases your risk for heart disease and death”), and on the tray, next to the ketchup, will be a new and protective packet, “MacStatin,” which could be sprinkled onto a Quarter Pounder or into a milkshake. This could easily be provided at no extra charge, just as sugar and salt currently are (despite being harmful). To prevent individuals from believing that the packet is a “cure-all,” it should be accompanied by a leaflet stating, “No tablet can counteract the full spectrum of harm that comes from unhealthily. Better ways to reduce your risk for death from heart attack include eating healthily, exercising, maintaining a healthy weight, and not smoking” (Figure 4). The leaflets should contain suggestions for healthy eating, exercise tips, and perhaps even membership vouchers for local gymnasiums.

We suggest that the MacStatin concept not be rejected on the grounds of condemning unhealthy diets, any more than seatbelts should be rejected on the grounds of an appearance of conditioning speeding. Indeed, it is providing a free opportunity for someone who has already decided to eat unhealthily, and may well already be rejecting medical advice for a healthier lifestyle, to remain alive for longer than they might otherwise.

We emphasize that the medical advice must continue to place pharmacologic therapy into context as a secondary adjunct to nonpharmacologic measures, such as healthy eating, smoking cessation, and regular exercise. However, those who decline sensible medical advice should not be denied access to health-preserving tools.

Figure 4. New concept in fast food risk reduction.


