Conspiracy theories are not uncommon. Indeed, they are a part of everyday life. Stories of aliens controlling the world, sinister hands playing a role in natural disasters, and global warming being a hoax—these are all examples. Studies have shown that these theories arise from a feeling of insecurity.\[^1\] Furthermore, they may commonly follow disasters, crisis, and catastrophes in the world. We do not claim expertise on the subject, nor is this the focus of the article. Mostly, conspiracy theories are harmless intellectual exercises and endless sources of conversation and gossip. However, when these happen in medical circles, they can harm.\[^2,3\] In recent times, given the all-pervasive and viral nature of social media—two new theories have been proposed: One that hyperglycemia is a myth created by the industry to create more people with diabetes, and the other that cholesterol is a friendly Frankenstein invoked by the statin manufacturers. There are many examples which seem to cite these “controversies.”\[^4,5\]

The former theory about diabetes is not worth writing about, and we choose to address the latter one in this article. In recent times, there has been a write-up going around in the lay press and social media circles that cholesterol is a myth and that statins are a bigger myth.\[^5\] Cardiologists and endocrinologists, being accredited leaders of the academic community in this field, are often left to do the explaining to the patients, media, and finally, to other physicians and diabetologists. This article expresses the opinion of the authors on this matter, from an endocrine perspective.

The statin trials are history. Not in the sense that they have made history, but in the sense that they are now really old medications and have been available for over two decades. We see no reason to go through their extensive data again but would like to, nevertheless, list them in an information box [Table 1]. In simple terms, randomized trials have shown 32% and 42% reduction in cardiovascular deaths in primary and secondary prevention studies.\[^7,8\] In these studies, one group of subjects were on statins and the other group was on a control and adding a statin reduced events. In other words, there is a clinching evidence that a statin was responsible for reducing cardiovascular deaths by one-third when compared to people, not on a statin. Were these benefits purely because of low-density lipoprotein cholesterol (LDLc) reduction, which is seen to the tune of about 26–35%?\[^6-11\] This is considered slightly debatable as statins have been shown to have pleiotropic effects that lie beyond LDLc control. Then, is LDLc lowering of no significance? To understand this argument, it could prove instructive to look at other recent studies which have lowered LDLc.

One recent trial on LDL lowering stands out that is the IMPROVE-IT study.\[^12\] This study compared simvastatin + ezetimibe with simvastatin in persons after acute coronary syndrome. Ezetimibe acts on a protein called Niemann–Pick C1-like 1 protein and reduces absorption of cholesterol from the intestine and can reduce LDLc by an additional 23%. The addition of ezetimibe in this study resulted in an incremental improvement in cardiovascular outcomes by an absolute risk difference of 2% points. While this clearly shows that adding ezetimibe to a statin is beneficial in secondary prevention, it does strengthen the hypothesis that an incremental LDLc lowering is beneficial.

### Table 1: A list of statin trials

| Trial          | Abbreviation |
|----------------|--------------|
| AFCAPs/TExCAPs |              |
| 4S             |              |
| HPS            |              |
| PROVE-IT       |              |
| ASCOT-LLA      |              |
| WOSCOPS CARE   |              |
| CARE           |              |
| LIPID trial    |              |
| MEGA A to Z    |              |
| REVERSAL       |              |
| ASTEROID       |              |
| CORONA         |              |
| CARDS          |              |
| TNT            |              |
| JUPITER        |              |
| SEARCH         |              |
| METEOR         |              |
| IDEAL          |              |
| SPARCL         |              |
| ALLHAT-LLT     |              |
| PROSPER        |              |
| 4D             |              |
| MIRACLE        |              |
| AURORA         |              |
| IMPROVE-IT     |              |
The second set of clinical trial evidence relates to studies relating to the new group of drugs called proprotein convertase subtilisin–kexin type 9 (PCSK-9) inhibitors. These medications are injectable, humanized, and monoclonal antibodies. They inactivate PCSK-9 which is an enzyme that binds to the LDL receptor. Inactivation of PCSK-9 can lead to a decreased LDL-receptor degradation, heightened recirculation of the LDL receptor to the surface of cells, and consequent lowering of LDLc levels in the bloodstream. The two well-known forms of PCSK-9 inhibition, alirocumab and evolocumab, both reduce LDLc levels as compared with placebo (LDLc reductions of 39–62%). In the recent ODYSSEY study, 2341 patients at high-risk for cardiovascular events, with LDLc levels of 70 mg/dL or more and on maximal tolerated dose of statins, were randomized to receive alirocumab (150 mg) or placebo as a 1 ml subcutaneous injection every 2 weeks for 78 weeks. In addition to LDLc lowering, a post hoc analysis revealed that the rate of major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab. On the other hand, the PCSK-9 inhibitor evolocumab dramatically reduced the 1-year cardiovascular event rate by 53% compared with standard statin-based lipid-lowering in the randomized OSLER study. New PCSK-9 inhibitors are also researched. All these various studies strengthen the LDLc hypothesis, that lowering LDLc could reduce events. Surely, it is too much to speculate that all three agents – statins, ezetimibe, and PCSK-9 inhibitors – work not by LDL reduction but by pleiotropic effects.

What then, do we inform our patients regarding the current status of cholesterol and the dangers of statin/other agents? Well, first, we should inform them that statins have benefits as well as risks. The risk of myositis, memory problems, altered liver enzymes, slight worsening in hyperglycemia are among the problems with statins. Therefore, statins have risks; however, this has been hotly debated. Statins also have benefits – one-third lowering of heart disease-related death is by no means a negligible result. Overall, given the mortality and morbidity associated with cardiovascular diseases, the benefits probably exceed the risks of statin therapy, and LDLc lowering is important. Indeed, we as editors would like to take a stance here and suggest that in today’s era, given the important benefits of statins on atherosclerotic event reductions, it may be unethical not to prescribe statins in subjects who need it/benefit from it. This is a resounding message from international clinical care guidelines as well.

Probably, equally important is to offer a nutritionist consultation regarding dietary fat intake as a primary prevention strategy for high-risk population, especially in subjects with obesity, hypertension, diabetes, or prediabetes. In this regard, quite notable is the change in the new US dietary guideline. The guideline suggests avoiding trans-fats altogether, and that <10% of calories come from saturated fat. Thus, the guideline makes a clear distinction between healthy and unhealthy fats. In addition, the guidelines specify that <10% of calories should be from sugar and indicate that “whole grains are to be at least half of total grain consumption, and the limit for refined grains is to be no more than half of total grain consumption.” These guidelines reflect current thinking which is fast shifting from restriction of fat to restriction of carbohydrate. In other words, glucose is emerging as the “new” cholesterol! This has also been a recent media headline – “Is sugar the new cholesterol?”

It seems, however, too early to dismiss “fat” as fiction, and in any case, these dietary guidelines have had their fair share of criticism. Some pragmatic points then must accrue from this discussion.

Restriction of simple sugars and saturated fat is important and at present, moderation in intake of both carbohydrate and fat to attain overall calorie control is advisable. A strict avoidance on trans-fat is necessary. Current guidelines for statin therapy are appropriate, and a reduction of LDLc based on risk stratification is an acceptable strategy. Triglyceride lowering and HDL raising continue to be hotly debated; nevertheless, the American Diabetes Association’s 2016 guidelines continue to suggest the use of medications in a subset of persons with very high triglycerides. Notably, in these guidelines, criteria to base statins therapy have moved from an LDLc-level based guidance to a risk-based guidance. This is a necessary recognition of both the target pleiotropic effects of statins and limitations of setting a particular level of LDLc.

In conclusion, “fat” is really not fiction; benefits of statin lowering in older clinical trials, recent dietary guidelines, evidence from last year’s ezetimibe study, and effects of PCSK-9 inhibitors are all a testimony to the importance of LDLc lowering. The future might see the use of newer research to address residual risk, innovative use of polypill,
and better research on functional foods. Is “sugar” the new cholesterol, or even are sugars the new cigarettes as a new headline proclaims?[23] While this statement by itself is intrinsically and biologically wrong, it does drive home the message that curbing sugar, and in general, reducing refined carbohydrate intake could be beneficial. This is similar to the adage – “sitting is the new smoking,” another witty line to underscore the importance of exercise in an era where efforts on tobacco cessation are finally succeeding.[24] We encourage you to ask your patients to judge the “cholesterol myth” with the measuring tape of science and published scientific research, and by no other parameter, and hope they will see the “fat” of the matter.

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