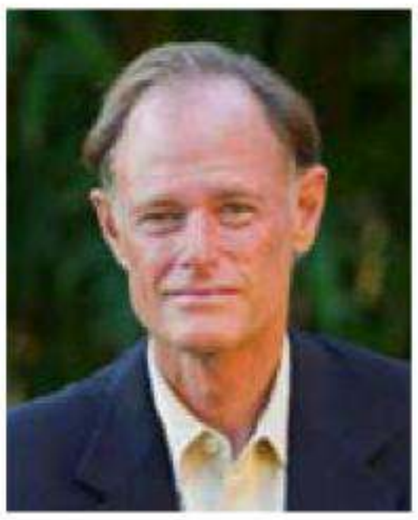
ROUNDTABLE

Appropriate Clinical Use of Statins: A Discussion of the Evidence, Scope, Benefits, and Risk



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Beatrice Golomb, *MD, PhD, is an associate professor of medicine at the University of California, San Diego in the division of General Internal Medicine. She is a staff physician at the San Diego Veterans Affairs Medical Center and a primary care physician for a panel of about 280 patients. She has been principal investigator on a number of studies and clinical trials. Her research interests can be captured in two broad themes: medical reasoning; and the impact of oxidative stress and mitochondrial function in health, aging, and disease. Branches of these interests have included (among others) treatment/exposure risk-benefit balance; cholesterol and statin drugs; impact of conflict of interest on medical information and recommendations; placebos; chocolate (and other aspects of diet); metabolic syndrome; amyotrophic lateral sclerosis; autism; and Gulf War illness.*

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It has been stated many times that the most prescribed class of drugs in the last decade was statins. The widespread belief that statins represent an effective preventative measure for patients with elevated cholesterol levels in the belief that this would reduce their risk factors for CVD has proliferated to such a degree that the question has been posed: "Should everyone on the planet—including the possibility of children—be taking statins?"

Resistance to this hypothesis has been building, and while there is clear evidence that statin use is indicated in specific circumstances, current interpretation of the literature may not support such liberal application of this class of pharmaceuticals. To further the discourse, *Alternative Therapies* convened a panel of prominent physicians for a roundtable discussion focusing on the appropriate use of statins in practice.

The discussion was led by *Alternative Therapies* Editor in Chief, Andrew Campbell, MD, and also included statin researcher Beatrice Golomb, MD, PhD; neurologist David Perlmutter, MD; and cardiologist Stephen Sinatra, MD. The discussion was conducted in conversational style, so not every point was addressed by all the participants. And although our panel did not always agree on every item; the discussion of literature regarding the use of statins did reveal some interesting common ground: that there are significant risks of adverse reactions to statins, that there is little proof that statins are effective in reducing cardiovascular mortality with the exception of a narrowly defined population, and that statins remain a valuable, necessary indication for a particular segment of the population.

The discussion that follows includes many references to the body of literature regarding statins. As a convenience to the reader, *Alternative Therapies* has inserted references to these articles upon the first mention of each. (*Altern Ther Health Med.* 2013;19(suppl 1):14-25.)

Dr Campbell: I'd like to begin by reviewing the conditions in which you feel statin use is indicated.

Dr Golomb: I think statins are indicated in the settings in which evidence clearly shows that benefits exceed risk based on outcomes that objectively balance the two: namely all-cause mortality. This condition is true for middle-aged men who have clearly diagnosed heart disease, particularly a myocardial infarction (MI), a history of coronary artery bypass graft (CABG)—men under the age of 70 with those conditions—and who have not had an adverse effect on statins. The further condition in which statins are warranted is acute coronary syndrome.

Dr Sinatra: I wholeheartedly agree with that. And with this recent data in diabetics showing calcification of the coronaries (Veterans Affairs Diabetes Trial[1]), I might even limit statin indication to nondiabetic men with everything Dr Golomb said—coronary disease, stent, angioplasty, bypass, or MI.

I like statins, particularly, in middle-aged men who really have the greatest to gain and the least to lose. I would add the population with low concentration of high-density lipoprotein (HDL) as well. I would give it to a middle-aged male with a normal HDL and coronary disease, but again, with a low HDL—because of the pleiotropic effects of statins, particularly on blood rheology and net surface charge. The ideal candidate would be a middle-aged male less than 70 years old who has coronary disease with an event such as MI, a stent, a bypass, or an angioplasty, and especially those with low HDL.

Dr Golomb: I would possibly differ on the low-HDL criterion, and more generally people who have metabolic syndrome factors. Those with low HDL may be among the groups who are more likely to have predominant pro-oxidant relative to antioxidant effects on statins. The antioxidant effects of statins underlie many of their pleiotropic benefits, including plaque stabilization; antithrombotic, antiplatelet, and a range of anti-inflammatory effects; and a range of their other effects. In the absence of direct evidence to show that group would benefit, I would anticipate that men with low HDL and metabolic-syndrome factors would experience relatively less benefit—recall that diabetes is also characterized by low HDL. In fact, for outcomes like renal problems manifested by proteinuria, evidence showed that the low-HDL group did not reap the benefit that is seen in the higher HDL groups. In our blood pressure data, the blood pressure benefits, which also are tied to the antioxidant effects and benefits to endothelial function, were expressed more strongly in the high-HDL group.

Dr Sinatra: That's fine—I would just say, clinically, that what I've seen is low HDLs have greater blood viscosity and statins ...

Dr Golomb: Many of the metabolic syndrome factors signify more risk of heart disease, and so the need for something that would be beneficial is greater, but unfortunately, the adverse effects of statins are greater in those metabolic syndrome groups as well. Oxidative stress may contribute to low HDL, and also to cell death, which triggers coagulation activation; so where there is oxidative stress, like smoking, and statins effects are net antioxidant—expected to be true for many smokers without metabolic factors—statins would reduce coagulation activation. The question is: is the group in question one expected to have a favorable or unfavorable pro-oxidant to antioxidant balance? Where HDL is a strictly a proxy for smoking the balance may be favorable. But often it is a proxy for metabolic dysfunction—including in the case of diabetes—where the balance may be unfavorable.

Dr Sinatra: Not specifically … I'm just speaking of those men with the low HDL. I'm sure you read the West of Scotland Study[2] where the researchers really believe that the statins were actually affecting the blood viscosity of those patients. The patients who had the lowest HDLs had thicker blood. So there was something about statins that changed the shape of red blood cells (RBCs) going through the spleen where they had an effect on blood rheology, which those researchers clearly thought was an advantage.

Dr Golomb: When you have a randomized controlled trial and see an effect, you can't really say to which of the many effects that is due. My own interpretation of that trial is the comparatively larger trend to mortality benefit is due to the fact that it is the study that had the highest faction of smokers, by far, of any of the randomized controlled trials.

Smoking is one of the settings where we have a risk factor that we know leads to pro-oxidant stress that is not due to or tied specifically to mitochondrial impairments. Low HDL, on average extending outside the setting of smoking, is statistically linked to other metabolic syndrome elements,

and these are linked to more likelihood that statins may have pro-oxidant effects. The benefits of the antioxidant effect of statins, when they occur, are greater in smokers, since they have more oxidative stress to protect against, and since smoking is a condition that is not tied to net pro-oxidant effects of statins. I think that the issue there is that West of Scotland is a high-smoking population. In our own randomized trial we had a relatively small number of smokers. When we have analyzed them—where there looked like there are unfavorable effects in the broader sample—the trends have often looked favorable in the smoking group or, more specifically, among smokers without other metabolic factors.

Dr Sinatra: Smoking's effect on HDL in your experience is …?

Dr Golomb: Smoking is well known to lower HDL, but it is the smoking not the low HDL per se that I believe is the issue. Or, more generally, oxidative stress in a setting that is not tied to metabolic risk. Again, recall diabetes is also characterized by lower HDL, and as you noted, is a setting in which outcomes on statins are less favorable.

Dr Sinatra: Okay.

Dr Perlmutter: I think a couple of very good points have been raised. What I am hearing is a lot of attention being paid to the covariables—the cofactors that obviously tend to exacerbate the risk for coronary artery disease and events, as well as lipid profiles. Therefore, this seems to be what the other doctors are talking about in terms of their decision to treat versus not treat. The classic way that medical science pursues these decision-making trees is to look retrospectively at who has had what benefit from what intervention, along with identifying which are those unique populations who seem to benefit versus those who seem not to benefit. It is a general rule in my practice: I'm far more reluctant to prescribe a statin medication for a female compared to a male, all other things being equal.

That said, I need to see established coronary artery disease by one of multiple criteria, whether it's a stress test or calcium index score, in a female before I would consider a statin medication with almost any parameter being presented to me with reference to lipid profile.

I think the idea of metabolic syndrome or full-blown type 2 diabetes being looked upon as a helpful marker in the decision-making tree is absolutely fundamental. Both Dr Golomb and Dr Sinatra have mentioned the fact that what is really happening here ultimately deals with inflammation, and more importantly oxidative stress.

The fact that oxidative distress as brought on by glycation of proteins—as brought on by glycation of LDL, specifically, and oxidation of LDL, specifically—in my practice seems to be something far more important and far more meaningful in terms of that decision, and in terms of the emphasis of where we are going in the treatment of that individual patient. I, for one, don't like to make generalizations about categories of patients who should or should not get statin drugs.

Dr Golomb: And yet you just did within your group of women: you said that if women have these characteristics, then that is the group you would consider treating, although there are no randomized trial data showing mortality benefit in any group of women with heart disease.

Dr Perlmutter: I have just been painting the broad strokes here. However, coming down to the individual patient, there are so many more variables that have to be taken into consideration. As a broad and general rule, I am far more reluctant to prescribe statin drugs for women, compared to men, based upon the data that I have reviewed in terms of their long-term benefit from statin medication.

That said, I think it has got to be individualized. I'm not in the habit of creating these categories based upon LDL particle size or even levels of oxidative stress. I think these all are factors and, at the end of the day, it's really a bit of art that tells you—based upon their coronary screening profile—who might benefit and who would not.

Dr Golomb: Let me say that I do agree with the idea that the direction of statins' effect on oxidative stress will ultimately prove to be a far more important factor in defining who benefits and who does not. But it is not just because of the issue of who is at risk of heart disease, but also who is at risk of adverse effects on statins.

Dr Perlmutter: Well said.

Dr Golomb: For people with conditions that are linked to mitochondrial dysfunction—including diabetes, hypertension, and every one of the metabolic syndrome factors—use of statins, and the resulting withdrawal of coenzyme Q10, leads to unmasking of mitochondrial-induced free radicals, which actually contribute to the greater likelihood that those groups have adverse muscle effects. These effects are known to be tied to a greater likelihood of pro-oxidant predominance.

I think there has been a tendency in the current guidelines and general thinking to view the need for statins strictly on the grounds of the risk of heart disease—but that only looks at the benefit side of the equation. The other side of the equation is the harm. You need to know what the risk factors are for harm, as well as the risk factors for benefit, in order to make the right decision. The existing evidence has shown that even people who are at high risk of heart disease—if it is by indices that are tied to metabolic syndrome factors—have generally not demonstrated net benefit from statins.

Trials focused on hypertensive individuals who also have high cholesterol and other factors have not shown any hint of mortality benefit with statin therapy. Trials that have high fractions of patients with other metabolic syndrome

factors seem in general to be the same.

The two non-heart-disease studies that have shown mortality benefit or near-significant mortality benefit are the West of Scotland Study, which is distinctive, first, by including only men, but also by including—by far—the highest fraction of smokers. The other is the Jupiter Trial,[3] which selected people on grounds of inflammatory indices not expressly tied to metabolic-syndrome factors. In addition, the Jupiter Trial excluded people with higher LDL. This exclusion might actually have turned out in that study's favor because LDL may actually be driven up in settings of oxidative stress, for the antioxidant transport capabilities of LDL. So they may have—whether by design or not—selected the group that would be less likely to have problems associated with use of statins among the high C-reactive protein group. On top of which, of course, the net mortality benefit was very, very small.

Dr Campbell: What are the thoughts of this group regarding arterial plaques and calcifications? The first is in *Atherosclerosis*[4] where observation of 6673 patients showed that statins had a 52% increase in prevalence and extent of calcified coronary plaques compared to nonusers. The second, published in *Diabetes Care*,[1] showed that type 2 diabetics with advanced atherosclerosis who used statins have significantly higher amounts of coronary artery calcifications compared to those who use it less or don't use it at all.

Dr Sinatra: To me it was a shock because I really thought that statins would be very useful in delaying coronary calcification. I have been using EBT (electron beam computed tomography) scans for the last 20 years, and several of my patients had higher calcium scores. I was using Vitamin K_2 for the last 5 years and trying to reverse some calcification. We have had some great anecdotal cases where coronary calcification was reduced on subsequent scans.

When I saw that data on the diabetics it did disturb me. I really thought statins would have a positive effect, at least delaying or holding calcification stable because of their pleiotropic effect. That is why I am now thinking about whether statins would be a good idea for middle-aged men with coronary disease who are diabetic. If you look at that—and even in a cataract study,[5] where they showed the increase in cataracts on statin users—again, it could be the same mechanism, but it did disturb me.

Dr Golomb: I think that one of the reasons that women may fare less well on statins, including women with heart disease, is this: if you look in the same trial that showed the greatest mortality benefit—the 4S Trial (Scandinavian Simvastatin Survival Study),[6] which showed a 30% mortality benefit in the overall sample in a group of people with previous MIs—in women, there was a 12% increase in overall mortality. I have long thought that part of the reason for this difference is that women, relative to men, who have heart disease are far more likely to have diabetes or other metabolic-syndrome factors and also older age. And again, these are groups in whom there is a greater likelihood of net pro-oxidant effects—reflected also in the fact that women have higher rates of adverse effects on statins.

Again, my focus is not on intermediate markers, whether they are LDL or calcification. I like to look at outcomes that objectively and equitably balance risk and benefit to heart outcomes for the *patient*, such as all-cause mortality. Again, diabetics and people with other mitochondria-linked metabolic problems have generally not fared as well as individuals who don't have those conditions, and they have generally not shown mortality benefit.

Dr Perlmutter: I would say that I was not totally surprised by the result of the study last month in *Atherosclerosis*, indicating that statin users actually had higher risks for development of plaque. This creates a situation where, indeed, despite these so-called antioxidant effects in statin medications, when you do deplete important cofactors like coenzyme Q10 you effect phase 1, level 1 of oxidative phosphorylation and compromise mitochondrial function and increase free-radial production. You end up in a situation where otherwise helpful, productive LDL and cholesterol, which are so beneficial for life and beneficial for health in every cell in our bodies, become modified in such a way that they create problems like the deposition—or the creation, rather—of immunogenicity because of their modified morphology and their presentation to the immune system.

These studies are consistent with myopathic reports, with encephalopathy reports, and with neuropathy reports—with all the other issues that actually are predicated on mitochondrial dysfunction—that actual process itself, of plaque formation, is ultimately a free-radical mediated immune response.

Dr Sinatra, these reports you mentioned about cataracts, as well, are not surprising. It goes the opposite way, as well, for individuals using statin medications. This was demonstrated—for women, at least—when the *Archives of Internal Medicine* reported a 71% increase in risk of type 2 diabetes,[7] which is in and of itself a powerful pro-oxidative and proinflammatory situation.

We have gotten into the mindset that becoming a diabetic is a bad thing because of all the complications of type 2 diabetes. In my business, becoming a type 2 diabetic doubles a person's risk, for example, of developing an untreatable disease called Alzheimer's. But somehow or another, I think it is important to get across the message that being simply prediabetic—or even early insulin resistant—is a powerful risk factor in and of itself. It's not like everything is totally cool with a fasting blood sugar of 125, but all hell breaks loose at 126. It's not a binary kind of thing. It absolutely takes place early on.

Ideally now, we're seeing blood sugars, at least from a neurological perspective, as being related to brain atrophy at levels that generally labs and physicians would consider normal, like 105. A new report just came out showing

evidence of ongoing brain atrophy, even at that level. Wonderful reports demonstrate very specific correlation of hemoglobin A_{1c} with the degree of hippocampal atrophy.[8,9] Prominent hippocampal atrophy is going on at hemoglobin A_{1c} level of 5.6, which most doctors would say is a wonderful level: "Your blood sugars are under great control." That perspective is considered acceptable just because an A_{1c} of 5.6 is not outside of one standard deviation away from the mean. We have got to come to the understanding that this is the cornerstone of coronary artery disease. It is the oxidative damage to these fats, to the carrier proteins, that is really leading to the immunogenicity of the whole process, which is what is narrowing arteries and causing problems peripherally throughout the body. This approach of focusing on cholesterol, which brain function is so desperately dependent on, is profoundly narrow-minded and myopic.

Dr Sinatra: Well said, Dr Perlmutter.

Dr Golomb: We should add, though, that glucose is being adaptively upregulated, and that the glucose is also vitally important for the brain. Although the brain is about 2% to 4% of body weight, it uses 50% of the glucose.

We haven't published the findings yet, but we will be presenting something for the American Heart Association meeting in March [2013]. But let me share that there is a lot of evidence that glucose elevations serve adaptive functions, and just as we shouldn't demonize high cholesterol, the body upregulates glucose when there is need for more energy. Certainly depleting cholesterol, with its proenergetic functions and its antioxidant transport functions, which also help in energy production, provides a reason for the body to seek to recover energy sources. As has been pointed out, this both *reflects* a body state that is at higher risk of a lot of problems like Alzheimer's, etc, and may itself through glycation end products *contribute* to those adverse outcomes.

Dr Perlmutter: Let's be really specific here and relate these two wonderful topics that you have just brought forward. Glycation of proteins plays a pivotal role with reference to cholesterol and brain function. It is absolutely the glycation of the LDL carrier of cholesterol into the astrocyte that compromises the astrocyte's ability to receive cholesterol and therefore deliver it to the neuron, which is one of the functions of the astrocyte. So you hit the nail on the head.

However, the brain functions best when it is burning fat, not glucose. It will preferentially burn glucose as that fuel is available, but the ideal fuel for the brain (1) from a mitochondrial perspective; (2) from an ATP production perspective; (3) from an efficiency perspective; (4) from an upregulation of mitochondrial biogenesis perspective; (5) from an upregulation of brain-derived neurotrophic factor perspective; (6) and from a reduction of NF-κB perspective, in terms of reducing inflammation, is in fact β-hydroxybutyrate, a ketone product derived through the mobilization of fat through the liver.

We have never really lived on carbohydrate until just the past 10 000 years. We do manufacture, through gluconeogenesis, carbohydrate as needed, but the notion that we need our four to six servings of fruit, pure carbohydrates, glucose, and fructose each day and three to six servings of whole grains, including bread, is absolutely ludicrous. We have got to start participating in the conversation with individuals indicating that a hemoglobin A_{1c} around 5.2 to 5.3 is ideal and that 5.6 to 5.8 as a marker, not just of glucose regulation but of the global process of protein glycation, that you mentioned, is really fundamentally germane. Just as hemoglobin A_{1c} is a marker of glycation of hemoglobin, it is also a marker that we are glycating other proteins—including low-density lipid proteins and other proteins in the brain and throughout body that are enhancing radical formation as much as 50-fold.

To me this is front and center. The whole notion that somehow people need to be on a low-fat diet because it is good for their hearts, it is good for their brain, and it will lower their cholesterol, doesn't sit squarely in any way, shape, or form with current science.

Dr Golomb: I agree with the statement that there is not evidence to support superiority of low fat diets or cholesterol-lowering diets. But on a prior point, I merely stated the brain uses a greatly disproportionate fraction of glucose and oxygen. The brain needs energy and one key source that assumes increased importance in settings of energy deficit is glucose. I said nothing about carbohydrates as a class, nor about fruit, but I should point out that fruit generally serves as an insulin sensitizer and higher fruit consumption has been epidemiologically linked to markedly *lower* incidence of diabetic-related deaths, as well as cardiovascular and all-cause mortality.

Dr Sinatra: The oxidation of fat in mitochondria provides 60% to 70% of the energy for the heart. So again, as a cardiologist, when people throw out the baby with the bathwater and go on these no-fat diets, to me this is disturbing. It is the β-oxidation of fat in mitochondria in the heart cells that is really the predominant fuel for the heart.

Dr Perlmutter: Absolutely. This demonization of cholesterol that has happened since the early Framingham work is so off base. Twenty-five percent of the body's cholesterol is in the brain, where it is performing desperately important tasks of, as you mentioned, antioxidation. The brain actually manufactures vitamin D from cholesterol, in and of itself, and is not necessarily fully dependent on what it gets from the serum. Need I say, cholesterol is important as the precursor to the sex hormones as well. This idea of lowering cholesterol because cholesterol is bad—that is just not sitting well with current science.

Dr Sinatra: It is absolutely the wrong marker for heart

disease. I think we all agree about that. We chose the wrong marker to follow cardiovascular disease deterioration, progress, or whatever. It's just the wrong marker, period.

Dr Golomb: I think we should be cautious. Markers refer to things that are predictors. There is a separate issue of whether something is a target for therapy. There, I would actually say that there are similar issues with glucose as with cholesterol. Statements were made, supposedly in contrast to what I said—such as what the "best" substrate is for brain energy—on which I never made comment. What I commented was that 50% of glucose utilization is by the brain; in contrast, 20% to 25% of oxygen utilization is by the brain.

The brain is heavily energy dependent and relatively even more heavily glucose-using than other organs are. It is still the case that when there are energy deficits from things like mitochondrial dysfunction, the body relies more on secondary energy sources. Just as when you speak pejoratively about settings in which one reduces cholesterol because it is a predictor of heart disease, but it may actually also be serving adaptive functions, the same is true with glucose. I did actually say, as was followed up on, that the elevated glucose itself can then induce problems. But, it is essential that we not fall into the same trap with glucose that we criticize others for falling into with cholesterol. It's not the case with cholesterol—everybody here would agree—that the lower the better.

I would also say that I think most of us here would also agree that it is not the case for glucose. Too low a glucose level is bad—dangerous or indeed fatal. The point that I'm trying to make is that just as cholesterol is adaptively regulated and may be higher in some people for a reason, the same is true of glucose—that it may be higher in some people for a reason. If you reduce glucose by lifestyle factors that support cell-energy function and remove the need for the adaptive upregulation, that is on average going to be good for the person. But, if you pharmacologically reduce glucose fully to "normal levels" without addressing the reason that glucose was adaptively upregulated, you may create more problems than you solve—similar kinds of problems to the ones that the worst patients experience, in terms of adverse effects with cholesterol-lowering drugs.

Dr Perlmutter: Along those lines, when the FDA in February of this year indicated that a warning for cholesterol medications should now include cognitive dysfunction and memory dysfunction, why was that a surprise when the neurology literature, dating back to 2005 at least, has clearly demonstrated that higher total cholesterol levels later in life are protective with respect to dementia? That was published in the journal *Neurology* 2005, volume 64, "Serum Cholesterol: How Does It Relate to Cognitive Performance?"[10] Data taken from the Framingham Study, published in *Psychosomatic Medicine*, volume 67, also in 2005,[11] demonstrated that higher cholesterol later in life is a predictor of better cognitive performance and resistance to dementia, not to mention the *Lancet* report that showed that longevity—risk of living longer—is better with higher cholesterol versus lower cholesterol.[12,13]

Dr Golomb: Right, there are many, many studies that show that the sort of positive relationship of cholesterol to all-cause-mortality that is present in middle-aged men flattens in studies that are focused on people over the age of about 70 with the age cutoff varying. Then it actually reverses and higher cholesterol becomes a strong predictor of longer survival in the older elderly.

Dr Perlmutter: Absolutely, but we're swimming upstream with this type of conversation. I think when this is published it is obviously going to raise some eyebrows, but at the end of the day—I am going to go to this place now that I think we have to go to it—there is a huge, powerful lobby involved in perpetuating the myth of the demon of cholesterol, and how—no matter what we do—we have got to lower it to levels that are almost immeasurable with the use of these potentially toxic medications. That needs to change.

Dr Golomb: Recognizing that people will be resistant, I think we also need to include the caveat: in those studies of older-elderly, those are observational studies. One of the things that is commonly stated in that setting is, "It's all due to confounding. People can have existing medical problems, like cancer and so forth, that can lower cholesterol and can also lead to enhanced mortality." That is true. But it can't be *Presumed* to be the full explanation. Indeed, the PROSPER trial provides experimental evidence consistent with the epidemiology, for the early part of this aging process, with the flattening in mortality risk for high-risk persons prior to the reversal. This was presumed in studies in younger ages that showed that lower cholesterol is linked to higher mortality from cancer—particularly in certain groups like smokers and those with low socioeconomic status. Not incidentally, these are groups who are expected to have more oxidative stress and need for antioxidant transport. But the findings held even if the first number of years of deaths—5 or even 10—were excluded from analysis, precluding the interpretation that "existing disease" was exclusively responsible for the low cholesterol association.

Similarly, we can't assume that the findings in older-elderly are due to confounding from existing disease. In fact, there is strong evidence that the functions cholesterol serves, such as energy support and antioxidant transport, assume markedly heightened importance in older age.

Dr Campbell: Let me expand on something that was just brought up here—very eloquently, I might add. What does this roundtable discussion bring to the average doctor who is going to read it? What message can we give to the average physician who hears the big roar out there that cholesterol needs to be treated and that it needs to be lowered? "Here are all of these wonderful medications and you need to use them

in your patients." These doctors are getting this message all the time. It is obvious that the message is flawed. How do we help these physicians so that, once this is published, they can apply this in their practice that day?

Dr Sinatra: Dr Campbell, you've hit the nail on the head. That is the big question. There is such a tidal wave of information out there, to the point where cardiologists actually believe that lowering cholesterol is really beneficial to health. The proof in the pudding is that a third of all cardiologists take statin drugs themselves. This belief—or this conspiracy, whatever you want to call it—goes miles deep. It's hard to really get to the hearts of these doctors. When I talk to fellow cardiologists, they cite all of these studies.

By the way, look at the statin studies before 2005. Celebrex and Vioxx truths were exposed, the FDA pharmaceutical companies under a microscope. Michel de Lorgeril, MD, the author of the Lyon Diet Heart Study report focusing on the Mediterranean Diet,[14] wants a reappraisal[15] of those studies because he feels that those studies were improperly reported. Why is it that the studies before 2005 showed a remarkable increase in longevity and decrease in cardiovascular events, yet, the studies in 2005 and beyond have shown no really significant improvement in patients taking statin medications?

Dr Golomb: Let me qualify that. The first large statin trial was the EXCEL Trial,[16] in which all-cause-mortality was threefold increased in the statin group relative to the placebo group. That is a trial that everybody chooses to forget about. The excuse for omitting consideration of this trial, initially, was that the follow-up period was, on average, less than 1 year. A lot of meta-analyses then say "We will exclude any study that had follow-up of less than a year." The argument at the time was that it takes longer than a year to reduce plaque buildup.

Subsequently, trials actually showed the statin benefits, when in settings where they occur, are clearly evident by 6 months. In fact, the studies that look in the acute-coronary-syndrome setting show that statin benefits precede, basically, the time course of lipid-lowering effects and have a time course compatible with their antioxidant effects ...

Dr Perlmutter: ... and anti-inflammatory effects.

Dr Golomb: It is not actually the case that all of the major, early trials were favorable. In the very first of them—again, EXCEL—with over 8000 people in the trial, the trend was actually unfavorable. This was in a low-risk population so, even though the deaths were threefold elevated, that wasn't statistically significant—but clearly not a trend in the right direction. What does distinguish some of the early trials is the characteristics of the patients who were enrolled.

Dr Perlmutter: Right.

Dr Golomb: The 4S Trial—one thing that may tilt perception a little bit is to remind people just exactly what the magnitude of benefit was. One of the most tragic things is that we get a lot of patients with adverse effects contacting our group, sometimes with really crippling adverse effects, who have contacted their physician to no avail. One recent example was a lawyer who said that his cognitive function had deteriorated to the point that if clients asked him a question he would respond by asking them, "What do *you* think?" because he really couldn't reason for himself anymore. He wrote a letter to his esteemed academic cardiologist about this issue and was told "We followed the cognitive issue and, despite the FDA warning, we think that all those people who get cognitive problems have other reasons for having cognitive problems; and you need to stay on the drug." Here is a person who has plausibly had an incredibly serious, career-threatening event that may very well be an adverse effect of his drug, and his cardiologists are telling him he needs to stay on the medication—with no trial off the drug, or any steps to exclude statins as the cause.

Let's suppose for a minute that he was in the group that would have the greatest expected mortality benefit. Let's forget for the moment the fact that for people who have adverse effects, cognitive problems may be the marker for a net pro-oxidant effect, which may mean they're not even reaping the cardiac benefits and possibly might even be having the opposite effect. Suppose he really was going to get the full magnitude of benefits shown in the very most favorable trial, which was the 4S Trial. How big was that benefit?

The rate of death over 5-point-something-year average follow-up in the statin group was 12%, and in the placebo group it was 8%. Now that is not a trivial difference: it is characterized as a 30%, or one-third, difference, but in absolute terms it's a 4% difference. Both groups were within 2% of 10% of them dying through 5-year follow-up. This also means that most of the people in that "very high risk group" would not have died over that follow-up period; obviously, we will all die eventually and most of the ones who would have died off the statin also died on the statin—two-thirds of them.

One of the important things to bear in mind, particularly when people present with an adverse effect, is exactly how big the magnitude of benefit is in the best-case scenario. And to remember that it is not the case that, as we hear patients telling us their doctors told them, "If you don't take this drug you'll die." This act presents the situation as a binary issue: take the drug, live; fail to take the drug, die.

That is one of the messages that it would be helpful to disseminate—in the very best case, the most favorable prevention trial, the mortality benefit was a 4% absolute mortality benefit. Of course, in that same trial women showed a 12% increase in mortality on statins, relative to placebo—relative, not absolute, risk—so it compares to the 33% reduction overall. Not statistically significant, but clearly not even in the favorable direction. I think that is one of the

messages I would like to get out to physicians.

I don't know if any of this will help, because a lot of physicians get performance pay for the fraction of their patients that meet lipid targets, and that basically pits the physician's self interest against the patient's interest.

Dr Sinatra: From the perspective of a cardiologist, because I speak to my colleagues and I argue with my colleagues all the time, cardiologists really believe in their own hearts that statins are miracle drugs. I don't know whether it is the detailing with those earlier studies as most of the studies before 2005 did show benefit. This is what these cardiologists are still working from. They're working from this data that came out on statins in the late 1980s, early 1990s, and all the way up to 2005. The problem we have here, and this is what Dr Campbell is addressing, is how do we get the establishment—the conventional medical establishment, board-certified cardiologists—to look at this as a possible myth? That's the problem for us.

Dr Perlmutter: This is the point that you're making, Dr Sinatra—and I think to be fair let's go toe-to-toe—I'm hopeful that this report/roundtable discussion allows physicians to answer the question: "What are we supposed to do with this information?" I think you did a yeoman's job along with Dr Bowden in writing *The Great Cholesterol Myth*[17] from the perspective of supporting each of your statements through peer-reviewed literature. If the playing field is going to be, "what does the peer-reviewed literature say?" let's use that as the rule and then indicate to people: "Let's look at the data." That is exactly what you did. I think that people tend to want to read into these statistics, such as that there is a 30% lower risk of cardiac-related deaths. But when you really look at the whole picture, it is just how the statistics were spun.

That said, I would also indicate that we have to look at our patients in a global way. Above all: do no harm. Let's just say for argument's sake that there is some reduction in cardiac risk by using a statin drug. The side effects, like those for the attorney with cognitive dysfunction, number one, are not trivial; number two, they are not infrequent; and number three, they are oftentimes irreversible.

When we look at these miniscule or even significant benefits from this medication, I think what the public is currently not aware of is the very significant risk associated with using this potentially damaging drug. We've seen books written, for example, about transient global amnesia. But the fact that the FDA has recognized it and now requires information in the literature given with these medications about the cognitive issues that are happening is a wonderful development. It is something we have been observing for 15 to 20 years. There are wonderful mechanisms that explain it including coenzyme Q10 and the fact that cholesterol is actually very important for brain function—this isn't news, but people don't want to look at that. A cardiologist would say: "You're not having angina anymore. Obviously the statin drug is working. Oh, you're having a side effect; obviously that has nothing to do with the statin drugs." They really want to see things through those rose-colored glasses.

My hope is that when this is published, that the readers understand that it is time to do some diligence and review the peer-reviewed—that is our standard—data and draw their own conclusions. I think it's just a travesty—what has been perpetrated on the public about the dangers of high cholesterol and the efficacy of statin medications in terms of the big picture, overall, for health.

Dr Sinatra: Again, hypercholesterolemia is a fabricated disease in this country. How many patients have you seen in the office, Dr Perlmutter, who come in with high cholesterol and they are dreadfully afraid that they are going to have an event, a cardiovascular event, whether a stroke or a heart attack?

Dr Perlmutter: Actually, less and less. I saw probably 22 patients today and many of them had cholesterol in the mid 250s with LDLs probably at 120. But what I am focused on—maybe I'm a little narrow minded—is the fact that the hemoglobin A_{1c} is elevated, and that their fasting-insulin levels might be 22, and that their antioxidant profiles, their T-bar levels, and their serum lipid-peroxide levels are elevated. Maybe even gluten sensitive, which may perpetrate an additive event. These are very easily controllable cofactors. To focus myopically on just lowering the cholesterol and deprive the brain, in my business, of what it desperately needs is doing more harm than good. The bottom line needs to be: above all, do no harm.

Dr Sinatra: Right, so our plea to physicians is: instead of focusing on cholesterol, let's focus on other factors that cause inflammation and oxidative stress in the body that then lead to illness, whether it is cardiovascular disease, neurological, or even cancer.

Dr Perlmutter: Absolutely. That is where we are going. That is what this decade has in store for us—to get that message out.

Dr Golomb: I would say that I am interested in focusing on the other factors, but if they're pharmacological, I hold them to the same standard to which I hold statins. I want randomized controlled trial evidence in people similar to the patient. For example, if they are female or elderly, those are very important cofactors requiring separate documentation to show that benefit exceeds harm based on objective indices that balance risks and benefit, like all-cause-mortality. Otherwise I don't care if it addresses inflammation or any of these other factors. It still fails to meet my criterion for an acceptable preventive medication.

Dr Perlmutter: Here is the problem with comparing benefit to harm: it is not quantifiable.

Dr Golomb: In all-cause-mortality, it is quantifiable.

Dr Perlmutter: In all-cause-mortality, yes. I am talking about benefit to harm in terms of morbidity.

Dr Golomb: Right. In order to inflict a drug on a patient and recommend it as a "preventive medication," where you are not mitigating suffering but acting for the purpose of protecting the patients, then my minimum standard is that evidence show that benefit exceeds risk by these objective indices. This is different if your patient takes medications other than preventive medications, as that is a different category.

The older definition of *serious adverse events* functioned as a definition of serious all-cause-morbidity, but wherever that was looked at with all-cause-mortality, if all-cause-mortality was neutral with statins, so was the old definition of serious adverse events.

The definition of *serious adverse events*—which basically used to mean anything that causes a prolonged hospitalization, is disabling, or is life-threatening—has now been modified so that the investigator gets to count it as a serious adverse event only if it is unexpected, which presupposes the outcome, and if it is believed to be related to the drug, which again presupposes the outcome.

Because of this, serious adverse events have now morphed into a useless index. It used to function as an acceptable—not a perfect, but an acceptable—index of serious all-cause-morbidity and tracked—for statins—with all-cause-mortality. Because that erstwhile definition is no longer available, what we are left with is all-cause-mortality. And that is why my minimum standard is that evidence be present to show benefit to all-cause-mortality before a pharmacological intervention is recommended to the patient for prevention—versus for mitigating suffering.

If an intervention is a "lifestyle intervention" that comports with what most of us can agree evolution expected, that is a different matter. If you are recommending that people generally get regular exercise, consume adequate amounts of micronutrient-rich foods, or avoid pro-oxidant "fake" foods, all of these are recommendations I can stand behind, without this high standard of evidence. You'll never be able to do randomized controlled trials—or they will be complicated, costly, and highly flawed—and I could actually accept it as not necessary, based on the current evidence.

For pharmacological intervention, I hold statins to the same standards to which I hold other preventive medications and preventive treatments.

Dr Campbell: Talking about the physician who is going to, hopefully, read this and apply it, it seems to me that there is a diagnostic code for hypercholesterolemia, and physicians have been ingrained with this. You tell them that hypercholesterolemia is a myth and they look at you like there is something wrong.

Dr Perlmutter: There is something wrong; there is plenty wrong. The whole perpetration of a diagnostic code for hypercholesterolemia is predicated on it being looked upon as a disease for which there is a treatment. Just the fact that the manufacturers of these medications have allowed this or actually pushed to make this happen does take your breath away.

Dr Campbell: It is looking at authority being the truth rather than truth being the authority.

Dr Perlmutter: Absolutely, well said.

Dr Campbell: Looking at these studies—yes, you should look—I cannot agree more. Look at the peer-reviewed literature. Read and apply it. We have all been taught and trained to do that.

Dr Perlmutter: In and of itself, pure elevated total cholesterol in my humble opinion is not really a risk factor for anything in and of itself—anything.

Dr Campbell: Dr Perlmutter, looking at this from a neurological standpoint, in your own experience, what have you noted? Since these statin drugs came on the market, you must have seen a trend—you must have noticed patients, especially since so many—basically one in four Americans over the age of 45—now take a statin drug. Besides what we have already discussed, what have you noted neurologically?

Dr Perlmutter: Aside from the cognitive issues, which I think are rampant—I think fully underrecognized—we have seen issues obviously with myopathic pain; inflammatory myopathy, either with or without elevation of the CPK, which is more common in women than men; peripheral neuropathy as described in the journal *Archives of Neurology*[18] many, many years ago—we have seen that and that could be very recalcitrant to any therapeutic intervention including cessation of the medication; headaches; generalized fatigue—these are probably the big things.

I see mostly neurologic patients during the course of my day; again it gets back to this issue of weighing morbidity of these drugs versus their utility, and I think it is very difficult to weigh a person with cognitive dysfunction as clearly a consequence of medications versus some supposed advantage in terms of coronary artery disease.

Again, what is a physician to do reading this? I think to be fair, review very carefully: what are these peer-reviewed trials actually saying? Then, draw your own conclusions—aside from those that you might read in the advertising.

Jerry Avorn, MD, from Harvard published a report in the mid-1980s, actually in the journal *Consumer Reports,* if I can quote that, where he stated that 78% of the information that doctors glean from reading medical journals is coming from the advertiser. That is a very, very powerful intervention in terms of a doctor's decision-making tree. The advertisements

pervert statistics in such a way that you would think you were foolish not to prescribe a statin medication to any patient that would walk into your office.

Dr Golomb: You don't need the advertisements to do that. You are probably aware that essentially every time there has been litigation against drug companies, in the discovery process—and this has been shown across multiple if not all major drug companies—evidence emerges of rampant ghostwriting by industry or MECCs. These are medical education communication companies, which are for-profit companies, funded essentially exclusively by Pharma, in which they create advertising parading as scientific literature and find willing physicians and pharmacists—preferably academics—to be listed as the authors. Review articles typically have one or two authors, who are academics, and in analysis of one of these instances from discovery it was found that only half the time—for review articles—was there any disclosure of any industry or MECC involvement in those papers.

Dr Perlmutter: Even if there is disclosure it doesn't matter.

Dr Golomb: It is correct that disclosure does not suffice to solve the problem, but the point is that half the time there is not any. These review articles *are* advertising—so doctors don't need to be reading a glossy ad to be reading advertising. Even for randomized trials, they often solicit academics and then list them as the first and second authors even though it was the journal that wrote the paper. For the ghostwritten review articles, they often give honoraria to physicians for participating.

In the Darwinian world that is academic medicine, where the currency is the number of publications and also money you bring into universities, it is also evident in this disclosure process that drug companies financially favor physicians who say things favorable to their drug and give them grants and honoraria. In addition, instead of having the costs associated with doing work and publishing a paper, they can actually get paid and not have the work associated with doing it.

Dr Perlmutter: Let me tell you what I tell my patients about this. I say, "Where do you think your high cholesterol is coming from?" Generally they will say, "Maybe I ate too many eggs, or I ate too much meat," and I of course correct them and let them know that probably 80% of the total cholesterol that you are reading on the test has been manufactured by your liver.

Now why would your liver that evolved, in terms of its metabolic processes, at least over the past 2.6 million years, be suddenly making such a terrible mistake and creating a chemical that is bad for your body? Does that make any sense at all? And they take pause, and they understand that, gee, maybe there is a reason their bodies are producing cholesterol. Then I inform them, "Do you know how important vitamin D is for your body? How do you make vitamin D? Well you go out in the sun. What is it made from? It is made from cholesterol ... who knew?" When you're out in the sun you're not going to make vitamin D unless you have adequate amounts of cholesterol, its precursor.

So, my argument is the upside of cholesterol. I think when, as we talked about earlier, people are confronted by this sudden dichotomy of realities that yes, cholesterol is something that is good and we should favor it. I think that kind of argument oftentimes has a little bit of cachet when they realize their body is desperately trying to put itself into position to allow longevity and health span. This is one of the key players. Rather than really coming out strongly with an argument against statin drugs and lowering cholesterol, I think the other side of the message is to get people to fully understand how powerfully important this wonderful chemical is for the physiology.

Dr Sinatra: Look at AIDS patients. When AIDS patients' cholesterol levels drop below 100 they're headed for death. Look at patients with chronic respiratory disease or gastrointestinal disease or infection of the respiratory tract or gastrointestinal tract. The higher your cholesterol, the more protection you have against those conditions. Look at MRSA in children, another factor. You are protected with cholesterol.

In your specialty, I was blown away by the MRFIT[19] (Multiple Risk Factor Intervention Trial) where they showed that cholesterol of 330 and above in men protected them from hemorrhagic stroke versus cholesterol of 180 and below. Clearly, cholesterol does some good things for the body and again that is the word we have to get out, not only to doctors and cardiologists but also to the public as well.

Dr Golomb: Right. I think then you run into people saying that statins have these pleiotropic effects. That is why I think it is important to focus on outcomes in which the patient is the unit of interest, rather than some intermediate marker, whether cholesterol or anything else.

Dr Campbell: Exactly. And what doctors really have to do, and you said it very clearly when you said "patients," we have to treat patients. But doctors are treating numbers; that is the problem.

Dr Golomb: I do not know about where you practice, but where I see patients, there is performance pay associated with those numbers, and I routinely elect to risk performance pay cuts for blood pressure—particularly in the elderly and for blood cholesterol markers—because they do not reflect the evidence.

But physicians are incentivized to treat, even in groups for whom the evidence does not show any suggestion that benefit exceeds harm and even when the patient then reports adverse effects from the medication.

Dr Campbell: Part of this is because medicine has now evolved into a business, and the business is to keep controlling diseases rather than doing what could be the epitome of medicine or the highest thing a physician can achieve, which is to cure. The cure is no longer sought; it is control.

Dr Golomb: In their defense, I think that some of this arose out of the assumption that we should do "evidence-based medicine." But unfortunately there was a gross misreading of what the evidence is, from which people were hoping to try to standardize "high quality care." Of course, I think all of us here would agree that high quality care is not actually the consequence of this sort of performance pay for things that are not supported by literature, ie primary evidence, but in fact, the practices under discussion are supported by guidelines. For the cholesterol guidelines, if recollection serves, all but one of the members of the guideline-generating committee were found to have had industry conflicts of interest, which were initially not disclosed until outed by an investigative reporter. That kind of involvement by persons with industry conflicts has led to guidelines that skew things tremendously.

Often, even where there is evidence available, the evidence does not encompass all the groups for whom there is effect modification leading to differences in outcomes associated with that intervention.

I think there were good intentions that became associated with performance pay, but the consequence unfortunately, in my opinion, has been highly deleterious to patients.

Dr Sinatra: Again, if you listen to Dr de Lorgeril, he feels that the story before 2005, in most of those studies—if not all of those studies—is that they should be re-evaluated—especially the positive ones.

Dr Golomb: That may be true, but I will also say that other big difference is that a major lesson was learned in the prestatin cholesterol-lowering trials. That major lesson is encapsulated in the meta-analysis by George Davey-Smith.[20] He showed that if you meta-analyze the trials of people at high risk of dying of heart disease—and he defined high-risk ex post facto, after the trials were completed, as the rate of death from heart disease from the placebo group—if you meta-analyze all the prestatin cholesterol-lowering trials in people at very high risk of death from heart disease, which in that study were defined as basically 1 in 4 people dying from heart disease every 5 years, there was statistically significant benefit with cholesterol-lowering treatment compared to placebo.

If you meta-analyze all the trials of people not at high risk of death from heart disease, in the "low-risk category"—which were people at the time whose risk was fewer than 1 in 20 for dying of heart disease every 5 years—now the numbers would be actually much lower to count as low risk, because a lot of other things have changed. In that group there was a statistically significant increase in all-cause-mortality associated with lipid-lowering therapy compared to placebo. Again this is in meta-analysis of randomized trials.

Then there was the *Medical Journal of Australia* meta-analysis[21] just looking at cardiac deaths in which members of high-risk groups have a much greater absolute mortality benefit and far greater statistical power in meta-analysis to see the benefit.

So then what happened with the statin trials is that they had learned that lesson. If you want to see the benefit, you focus on populations at high risk of heart disease. Other than the EXCEL Trial, the earliest trial was the 4S Trial, which also had the study sample with the highest risk of heart disease, among prevention trials. Then you also had the LIPID[22] Trial and then you had the trial that I consider somewhat aberrant because the population enrolled, which I actually do think has a higher benefit to its population than predicted by heart risk alone, is the high-smoking, West of Scotland group.

I actually think it is not just necessarily when the trials were done, but that those trials included people who were at high risk of death from heart disease that was not due to factors that also put them at high risk of problems with statins. And since then, as people have tried expanding the evidence for statins, they have gone to groups like the PROSPER Trial[23] in the elderly that showed no mortality benefit, trials in people with metabolic syndrome factors, or things like the ACCORD Trial[24] and so forth that failed to show benefit. And that it is not just when the trials were done, but it is the effect modifiers associated with the participants in those trials that determines benefit relative to harm.

Dr Sinatra: I think the greatest travesty in vilifying statins is for the highest-risk population—I think you said it right in the beginning—those experiencing acute coronary syndrome. In other words, we don't want physicians to take away statins when patients are in the hospital experiencing acute coronary syndrome or severe unstable angina.

Dr Golomb: I agree.

Dr Campbell: That is very, very important from a cardiovascular point of view, and consequently we want to take away statins when patients who have had cerebrovascular events bleeding into the brain. Because if you continue a statin on somebody who has bled into the brain, those patients do far, far worse than patients taken off statins.

That is the kind of message we have to give clinicians; in acute coronary syndrome you must give a statin.

Dr Golomb: Again, I would go back to asking if it is a group where mortality benefit is shown. Acute coronary syndrome is such a setting, and men under the age of 70 who have not had problems on statins and who have heart disease, eg, angina, or history of MI or bypass, are another such group. I would add something that I think we have not brought up, which is even in that group—and acute coronary syndrome is the exception—but even in men with stable heart disease, meta-analysis of

head-to-head higher- versus lower-dose statin trials do not show greater mortality benefit, or even trend to greater mortality benefit, with higher statin doses.

Dr Sinatra: Correct.

Dr Golomb: I think the other message is that where statins are used, with the possible exception of acute coronary syndrome, higher doses and use of LDL targets and threshold are not supported by the evidence.

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