April 2008 Issue | JM Wright, MD, PhD Professor, Departments of Medicine & Anesthesiology, Pharmacology & Therapeutics

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Welcome to *Functional Medicine Update* for April 2008. Occasionally we have something happen in biosciences and medicine that is so profound it rocks our world. Such is the case for this edition of *Functional Medicine Update*. This was unexpected and unplanned, but this particular issue is so important. I hope you can clear some space in your thinking because the information contained within it is quite profound. The source of this information is Dr. James Wright, a professor of medicine at the Department of Anesthesiology, Pharmacology, and Therapeutics at the Medical School, University of British Columbia, and his colleague, Jay Abramson, at Harvard Medical School

Dr. Wright and Dr. Abramson came to my attention through the paper they wrote in *The Lancet* in 2007.[1] This article was titled "Are Lipid-Lowering Guidelines Evidence-Based?" In this article, it is stated that between 13 and 36 million Americans are now in candidate status for statin use as a preventive agent for coronary heart disease. Guidelines for the use of statins have come out of seven randomized clinical trials. And yet, says Dr. Wright, none of the studies actually provides evidence that statins should be used as they are in medicine today.

Should Statins be Used in Primary Prevention?

For adults aged between 30 and 80 years old who already have occlusive vascular disease, statins can confer a benefit in total cardiovascular mortality. The controversy doesn't involve secondary prevention, but rather primary prevention (that is, people without occlusive vascular disease). Should people without occlusive vascular disease receive statins? With about three quarters of those who presently take statins in the category of primary prevention in the United States, the answer has huge economic and health implications. In formulating recommendations for primary prevention, why do authors of guidelines not rely on the data that already exists from the primary prevention trials? asks Dr. Wright.

Dr. Wright and Dr. Abramson pooled data from all eight randomized trials that compared statins with placebo in primary prevention populations at increased risk. The analysis isn't perfect because these trials were not solely primary prevention, with 8.5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of patients having occlusive vascular disease at baseline in these trials. They use two outcomes to estimate overall benefit (benefit minus harm): total mortality and total serious adverse events. Total mortality was not reduced by statins in these primary prevention trials. In the two trials that reported total significant adverse events, such events were not reduced by statins.

The frequency of cardiovascular events, a less encompassing outcome, has been reduced by statins, however the absolute risk reduction of 1.5 percent is small and means that 67 people have to be treated

for five years to one such cardiovascular event, so the NTT is above 50, which Dr. Wright says is basically a "crapshoot" (meaning it is not a very good drug). Statins did not reduce total coronary heart disease events in 10,990 women in these primary prevention trials. Similarly, in 3239 men and women older than 69 years, statins did not reduce total cardiovascular events. The analysis of Dr. Wright and Dr. Abramson, therefore, suggests that lipid-lowering statins should not be prescribed for true primary prevention in women of any age, or for men older than 69 years. High-risk men (30 to 69 years) should be advised about the fact that it takes more than 50 patients, treated for five years, to prevent one event, and there is such a very high level of adverse events from statins.

Dr. Wright and Dr. Abramson say that if you start looking at adverse effects, you will find that statins aren't even used in athletes because of the very serious myopathy that can occur. In fact, there is now evidence to suggest that myopathic events are much more prevalent than would be seen from the previous clinical trials when they are applied in clinical practice. In another article Dr. Wright wrote for *The Lancet*, he goes on to say that the hypothesis that statin benefits might be disappointing because people stop taking them due to myopathy deserves more testing.[2] We now recognize that in individuals who use statins, often the more they exercise the more myopathy they get, which then reduces their incentive to exercise and increases sedentary lifestyle and relative risk (an unbeknownst potential adverse side effect of statins).

With that as the context for this issue of *Functional Medicine Update*, let's hear from Dr. Wright himself about his view of this extraordinary analysis.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
JM Wright, MD, PhD
Professor, Departments of Medicine & Anesthesiology, Pharmacology & Therapeutics
University of British Columbia
2176 Health Sciences Mall
Vancouver, BC V6T 1Z3
CANADA

I'm very fortunate today to be able to introduce you to Dr. JM Wright, MD, PhD, Professor at the Department of Anesthesiology, Pharmacology, and Therapeutics, University of British Columbia Health Sciences and Medical School in Vancouver, British Columbia-a local Northwesterner, and we are always very pleased when we have the chance talk with a luminary from our Pacific Northwest. Dr. Wright's work has a direct relationship to the whole of functional medicine and the primary prevention of chronic, age-related diseases.

Dr. Wright has authored some remarkable papers about the field of primary prevention. One article that I was quite interested in appeared in the Canadian Medical Association Journal in 2005 and was titled "Are the Benefits of Statins a Class Effect?"3 The place where we have most recently had a chance to hear about Dr. Wright's thinking was in BusinessWeek magazine in, January 2008.4 This article features a wonderful discussion about Dr. Wright as both a Professor at the University of British Columbia and also as a clinician in practice, one of his patients (Mr. Winn, who had been on Lipitor as part of his therapeutic for lowering cholesterol), and Dr. Wright's evaluation of the success of the class of statin drugs (which

represents about 28 billion dollars in annual sales in America).

I would like to welcome you, Dr. Wright, to Functional Medicine Update. Could tell us a little bit about the history of your interest in doing this kind of evaluation (looking at outcome-related studies and the difference between primary and secondary prevention)? I think it will help us to understand the context of your work a little bit better.

Taking a Closer Look at the Data

JMW: Thank you. It is a pleasure to be here. The real issue is that statins originally came on the stage when they were found to have some effectiveness in secondary prevention, so the big trials were in people who had already had a heart attack. In that setting, I would say that statins have some modest effectiveness. I don't think it is as striking as a lot of people think, but we accept that there is some effectiveness and we recommend statins be offered to people who have had a heart attack.

What I also realized was that most of the people who were being offered the drug and who were taking the drug were actually people who had never had a heart attack, or a stroke, or had peripheral vascular disease. They were basically healthy people, and they were deemed to be at risk because they had had their cholesterol measured (or other things) and then were being told that they should be taking statins. We got involved in really looking at the evidence of the effectiveness of statins in that setting. When we really got into the data, we were quite surprised at how trivial the benefit is and that in most of those kinds of populations there really isn't any overall benefit. When you look at all serious adverse events and all hospitalizations, there is really no reduction in the people taking statins. That was initially quite surprising to us, but it convinced us that for most of the people who are basically healthy, there is no net health benefit.

Accuracy of Pharmaceutical Advertising

JB: Obviously this is considered by many to be quite a remarkable observation because we have been told-in fact, even as recently as picking up the Journal of the American Medical Association just last week and looking at the advertisements for Lipitor with the graphic of a heart with a sentence that says "I love second chances" and it talks, in bold, about 41{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} risk reduction-and I think people have this view that we have these large-scale, multi-center, clinical trials that have demonstrated unequivocally very dramatic effects in primary prevention, something like a 30{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}-plus reduction in the relative risk to heart attack. It begs the question: How can these advertisements and how can this information be distributed so widely to people who are making decisions with their patients?

JMW: They have to be accurate to some degree. What it means (when they talk about relative risk reduction and primary prevention populations) is that they are only looking at cardiovascular serious adverse events, and they are talking about a reduction in those events of from 3{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} to 2{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}, which is approximately a one-third reduction. But in reality, that is only a 1{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} reduction in absolute terms, and that means that you have to treat a hundred patients for five years to prevent one cardiovascular serious adverse event. Our analyses show that when you look at total serious adverse

events (or total hospitalizations), they are not reduced. The data also suggest that there is some harm occurring and that the net benefit isn't even 1{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}. Do you follow that?

Number to Treat Data

JB: Yes, I certainly do. That leads to this concept (which for most of us we probably don't think about) of the number to treat to get a successful outcome. The number you just gave is 100 to treat to get one successful reduction of a heart attack (or a vascular event) in a primary prevention trial. In the article in which you are quoted in BusinessWeek, it says anything with a number to treat above 50 is not a really great drug (I think the term that was used was "crapshoot," which is a pretty strong vernacular). If 100 is the number, and 50 and above is not so good, it suggests that we are spending a lot of money on a crapshoot.

JMW: That's right. I would say that for most primary prevention situations, that's what you are looking at-you are looking a number needed to treat somewhere between 50 and 100. Some of my patients say, "Well, I really think I should take this," and they are quite anxious and they are willing to potentially take it-then I present that information to them in those terms and I take some time to make sure that they understand what that means. In my experience, most people (when they really do understand how small the benefit is) change their minds and say, "Well maybe it is not such a good idea."

JB: In your experience, in patients using statins in primary prevention (and I know I'm talking here across a wide variety of different products in that class), are side effects (things like neuromuscular issues or myopathies occurring? What percent would be considered a reasonable percent of adverse side effects?

Statins and Adverse Side Effects

JMW: That's the other big issue with the statins. We know of some adverse effects, but the number is growing as we are learning more. Initially it was said that the only serious side effect is muscle damage and that it is a very rare event. That is true-in the randomized trials it was a rare event-but we do know that it occurs. I think most doctors know people who have had severe muscle damage with the statins, so it is not as rare as it might seem. But there are other adverse events that we are starting to recognize and one of them is peripheral neuropathy. That is occurring in a fairly small percentage of people (it is hard to know how many). It has also been shown now that interstitial pneumonitis is clearly an adverse effect of statins. One of the recent trials called the SPARKLE trial has demonstrated that in the statin group there was an increase in hemorrhagic strokes and that appears to be caused by the statins. And then there are these rare people who are having these unusual cognitive effects, which I think is quite concerning because it is not easy to appreciate how that might be happening, but it is certainly something that could be subtle and could be occurring in more people than we think.

JB: I have also heard, clinically, of reports in males about changes in libido, which may have something to do with altering androgen levels. Is that something you have observed clinically?

JMW: Not personally, but I have certainly heard of that as well. That is another potential adverse effect.

JB: If one was to sum all of this up, are we talking about relative percentage in normal dose of 1{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}, 5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36},

10{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}--what would you estimate?

JMW: When you add them all up, I think it is in the range of 1{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} to 2{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} over five years, and that is really what the benefit is as well. That's where I think that the harms are equal to the benefit. I think it is possible that that is the case. That's really, I think, what we need to be doing more trials on and really looking more carefully at. For people who are healthy and in this primary prevention setting who are being considered for statins basically because they have risk factors, I think it makes much more sense for them to look at their risk factors and see how those could be modified by changing their lifestyle, changing their diet, increasing their amount of exercise, etc. That makes much more sense than hoping that taking the drug will resolve the problem for them when the potential benefit is so small and there are potential risks (some of which are unknown) , I think.

JB: I was recently at a conference on vascular medicine where Dr. James Liao was the principal presenter from the vascular medicine research unit at the Brigham and Women's Hospital and Harvard Medical School. He was going over the kind of intervention trials with statins that had been done and supposedly demonstrate positive outcome, like the Scandinavian Simvastatin Survival Study and the Cholesterol and Recurrent Events (or CURE) Study, and the Long-Term Intervention with Prevastatin in Ischemic Disease (or the LIPID) Study, or the West Scotland Coronary Prevention Study, or the Air Force Texas Coronary Atherosclerosis Prevention Study, or the Heart Protection Study-and when he reviewed all of these in combination (there was a big graph of these-a spreadsheet in which he was showing the data), he was saying that they all demonstrate (as a cumulative--several thousands of patients) positive outcome and very marked reduction of cardiovascular risk. And so it is those kinds of seminars that are presented to medical personnel who are making decisions for their patients that leads them to believe that these must be the most highly studied, efficacious medications that have ever come to pass. Clearly, the reputations of the presenters are good, coming from reputable institutions. How do we get into this situation where these issues that you are raising haven't been considered fully?

JMW: I think that it is a flaw in the way that it is presented. What you have described there is, I think, exactly the situation. All of those trials that you described there, except the West Scotland trial and the Air Force trial, are secondary prevention trials. When you combine the secondary prevention trials with the primary prevention trials, the number of events occurring in the secondary prevention trials is so much greater than in the primary prevention trials that it swamps the data from the primary prevention trials and you can't see it. I think it is just wrong.

As clinicians, we can easily recognize in our patients the ones who have had an event versus the ones who haven't had an event and that's really the clinically important distinction. That's why we have been pushing forward and saying we really need to look at the primary prevention data separately and present that information to patients in that setting. When you do that, that is when you are surprised at how small the potential benefit is and the fact that there is really no proven reduction in mortality. When you look at total serious adverse events they are not reduced, so that certainly suggests that there is no overall health benefit for those people.

JB: I think that is a really remarkable discovery/observation for all of us. That begs an interesting question because we do know that a patient who has hypercholesterolemia and goes onto statins for

primary prevention will see a reduction (normally) of between 15 and 20{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} in their cholesterol and their supposed atherogenic LDL cholesterol. Does this beg a question about the validity of the cholesterol hypothesis of atherogenesis as being the dominant or principal or only biomarker for the condition?

JMW: I think, yes, there are some major questions about that as well. A lot of the statin trial data suggests that the reduction in the LDL isn't the reason that the statins are beneficial. There is quite a bit of evidence suggesting that it isn't as simple as just the cholesterol and the LDL cholesterol. When the person is taking the drug and their measures are better that doesn't necessarily mean that they should be feeling "Oh well, I'm good now and I don't have anything to be concerned about." We don't know for sure that that is the complete answer. There is this recent study... are you familiar with this ENHANCE study?
JB: Oh, yes. Please tell us...

JMW: That study showed that if you take a statin plus ezetimibe (I've forgotten the trade name right now...), you get a significant reduction in LDL cholesterol. But that study also shows that you get no reduction in the measure that they were looking at (a measure of atherosclerosis in the vessels). There was no reduction, and in fact there was increase in that associated with the reduction in the bad cholesterol. So that is certainly is part of the evidence against this whole cholesterol hypothesis.

JB: I think the trade name is Vytorin?

JMW: Yes, that is right. That is the combination pill with simvastatin, I think.

JB: When you look at all of this, it seems very persuasive--or at least highly suggestive--that the only documented, real positive outcome data we have on primary prevention goes back to what you were saying earlier: diet, lifestyle, and exercise intervention. It looks like the data there is stronger than that which we have been led to believe about statins.

JMW: Yes. The trials are maybe not quite as big or as good as some of the statin trials, but the magnitude of the benefit of diet and exercise appears to be more, and I don't think you have to be too concerned about a downside to improving your diet and getting some regular exercise. It certainly makes much more sense (and stopping smoking... all the things that we do know have a benefit).

Risk Factors versus Pathonemonic Factors

JB: It begs one last question, which I think is--from the clinical/medical perspective-an interesting point, and that has to do with the differentiation between a risk factor and a pathonemonic factor. I think for most clinicians, they probably associate a risk factor with an actual contributor to the mechanism of the etiology of that disease. One could have a surrogate risk factor (in this case it may be cholesterol) that only indirectly connects (or let's say, even tangentially connects) to the etiology of the disease or is a component of the disease. It is the difference between the smoke and the fire analogy. By lifestyle, diet, and exercise intervention what one gets is a multiple-factored influence on multiple etiological agents giving an outcome. Even though we might look at one risk factor, it is only a part of the whole puzzle, and statins are molecules that relate to some piece of that puzzle, but not the whole. Is that... am I saying something that sounds reasonable?

JMW: I think so. I think what we are measuring is very rudimentary in terms of knowing what is really

happening. I personally believe that measuring total cholesterol and LDL and HDL is something that we are doing right now, but I doubt we will be doing that in the future when we have a better measure of what the really important measures are. I think they are really going overboard in terms of looking at these things. Healthy people probably shouldn't have their cholesterol measured because it can lead to anxiety and illness when someone is told that their cholesterol is high. Often when an individual is told their number is high, it is really just the average for the population. It is quite a surprising situation that we are in in terms of the way we are managing and measuring cholesterol. I don't know if I've explained that very well...

JB: No, I think you have explained it very well. Since most of the people who are hearing this are clinicians, they may be a little shaken by this discussion because of what they have been told or what they have read about the value, in primary prevention, of statins. You obviously are not only involved with the research, but you are a clinician as well. I guess my final question is what recommendation do you have for how to manage this information gap with patients?

JMW: When I present this to physicians I always start off by telling them that it is going to cause them some cognitive dissonance. I sort of warn them and that probably helps them when they start to see the information. In terms of your patients, I think when we are dealing with healthy patients we should be talking to them about modifiable risk factors in terms of diet and exercise, and stopping smoking, and not worrying about measuring the surrogates and getting them concerned about their cholesterol. I actually wouldn't measure cholesterol if a person hasn't had it done already. If they have had it done, then I think you need to then look at that. In many cases, the patient with high cholesterol also has a high HDL. Again, I think that those people (healthy patients) really are not at significant risk at all and we certainly shouldn't be considering trying to lower their cholesterol with drugs. I think we need to get away from this whole focus on measuring cholesterol. If we did, we would also do something about the line at the labs-I notice that every morning when I go by the lab there is a big line of people who are going in for their fasting lipid profiles and I think it is the wrong way to go at the present time.

JB: I said I asked the last question, but I actually have another. Given the controversial nature of this, have you had any discussions with people who feel you are being irresponsible, or that you have no business saying this, or that it puts physicians at risk or patients at risk? What have you been confronted with?

JMW: I have had people who have argued the opposite and said, "Well, it doesn't matter whether it is primary or secondary prevention, we need to measure their risk factors and if they have an elevated risk factor we should be treating them." And they don't worry about the fact that the data doesn't show any benefit in women... I just bring them back to the data and say, "Well, this is what the data shows." I personally think it is irresponsible to be treating people based on risk factors that haven't been studied in randomized trials and haven't been demonstrated to really identify the people who need to be treated. I just tell people that they should be not treating people until doing further randomized trials to see whether the approach they are taking actually is rational. If they did that, they would find that it probably isn't rational.

JB: Have you had anyone that you feel has mounted a successful argument against your very intelligent and thoughtful argument about the lack of demonstrated low numbers to treat in these primary prevention trials when you split them out, or has everyone come up kind of dry when confronted with your

observations?

JMW: They haven't, and I have challenged them to come up and show us that serious adverse events and total hospitalizations are decreased in primary prevention trials and they haven't come up with the information. Not all of that information is in the public domain, so I think if in the trials (where it hasn't been published) it was showing a positive effect then it would have come forward already. I am confident that there really isn't any evidence out there that our approach is wrong.

JB: Lastly (I know I keep saying "lastly" but you beg another important question), I presume that this is a class effect, whether it is atorvastatin or Zocor or Crestor or Prevacol, we are talking about something that cuts across all of the members that reside within the statin class?

JMW: Right. I think there is pretty good evidence that the benefits are class effect. There is also pretty good evidence that the adverse effects are dose-related, and therefore the higher the dose and the more potent the statin that you are using, the more likely you are to have adverse events. I personally think patients should be taking the lowest dose that has been studied in trials. I think treating to targets has never been proven in randomized trials and so again, I think that whole concept is not a good approach to take because it hasn't been studied.

JB: In Japan, I know the cardiology community does not agree with the higher-dose statin therapy we use in the United States and their statin doses are much lower. They feel that regulating to lower dose is the preferable way of treatment. It seems that your concept is consistent with what they are doing in Japan.

JMW: Yes, that's so. Even in secondary prevention, I think (except in some rare circumstances) we should be using the lower doses that have been shown to be beneficial. In the trials there are not big differences in terms of the benefit (there are not big differences in the trials where they used less potent and lower dose statins as compared to the more potent and high dose statins). That is being borne out in some of the newer trials where they are using high doses.

Genomics and Statins

JB: I noticed in October of last year that the NIH in the United States released into the public domain the data on some 30,000 patients from the Framingham Study who had had full genome scans (some 500,000 SNPs, or single nucleotide polymorphisms, were evaluated in this database), which is supposedly going to lead to a new era of cardiovascular research where we'll start to individualize treatment based upon unique patterns of unique genetic and epigenetic expression. Do you feel the genomic component of medicine that is emerging will help us to better understand, in a primary prevention perspective, what patients might be most likely to benefit from statins versus those that won't?

JMW: I personally don't think it is likely to have a big effect, and it is going to be a long ways down the road before we know. I would advise that we be very careful. If some of these things appear to be identified in patients then we should test that and do a randomized trial to find out whether that bears out; we shouldn't just jump onto the bandwagon and start identifying people and treating them blind based on that data. In every case, it needs to be, I think, tested in a randomized trial. If they did, say, identify a subgroup and did a randomized trial and demonstrated a benefit with a number needed to treat of 10 to 20, I would be the first one to say that this is something that we should be recommending for our patients, but at the present time that is not the case and so I think that is the message to patients. It is unfortunate,

but the drugs just aren't as effective as they are touted to be.

JB: Once again, I think the message that you are communicating to us is so important. I mean, it has implications not just for statins, but really about how we evaluate the efficacy of all drugs used in primary prevention (where a patient is going to be taking them for long periods of time throughout their life). I think this really raises some questions that probably most of us were not sensitive to. I want to thank you.

JMW: I agree with that completely. It is not specific to statins and we need to be thinking about it in terms of antihypertensive therapy as well as a lot of the things we do, for sure.

JB: It seems like we are treating numbers now as the blood pressure recommendations have come down. It is more and more reasons to use ACE inhibitors or ERBs or whatever the class of antihypertensives are. The question is, do we have the long-term outcome studies demonstrating that we've reduced morbidity and mortality? Are we just changing numbers or are we really changing outcome? I think you've raised that question so eloquently in your analysis. This is going to be an interesting chapter in medicine that you have helped to open for us.

JMW: Thank you. That is completely the case. All of these ideas we need to test properly in trials before we start doing them widely.

JB: Thank you once again. We really appreciate you spending the time with us and, of course, your advocacy. Sometimes it's not easy to speak out against what everybody assumes to be the facts. Sometimes the facts are in the moment of interpretation and you have shed some extraordinary new light on this whole important topic for us.

JMW: Thank you. I have enjoyed talking with you.

How is it that statins appear to be the most commonly used family of medications (29 billion dollars worth of them used a year), and yet an investigator from the University of British Columbia with a good academic background and solid publication record questions the assumed usefulness of statins as agents for primary prevention? When we look at advertisements that appear for statins in the top-line medical journals, or for statin-containing drugs like the new drug, Caduet, which is a combination of Norvasc and Lipitor, the advertisements are saying there is a 45{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} reduction in myocardial infarction risk. These publications of statistical benefit in supposed primary prevention are dramatic--41{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} risk reduction for Lipitor in an advertisement that appeared in The New England Journal of Medicine and the Journal of the American Medical Association. One has to wonder how this data came about. It is not lies; the Food and Drug Administration has approved these claims. What is going on?

As Dr. Wright has pointed out, it has to do with how you manicure and evaluate statistics. If you reduce the relative incidence from 2{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} to 1{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}, that's a 50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} reduction. The patient may not know that that means one out of one hundred less incidents; what they see is the number

50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} reduction. Dr. Wright points out that the problem is going from a statistical base to an individual base in trying to make an assessment of value. As he says in a BusinessWeek article titled "Do Cholesterol Drugs Do Any Good?" the number to treat (or NTT) for many of these statins, in primary prevention, is upwards of a hundred, meaning that you have to treat a hundred patients for five years or more to get one demonstrable reduction of an incident in cardiovascular disease.

How does the NTT for statins contrast to a family of drugs that we know have very high therapeutic value, like antibiotics for a bacterial infection? With antibiotics, for every 11 patients you get 10 who benefit, so antibiotics have a very low number to treat (a number more like 10, not a number like 100).

When you get to number-to-treat data sets on agents for therapeutics above 50, it is pretty much a statistical game, not an individual therapeutic efficacy game. Yet we see statins being used with extraordinary frequency as primary prevention agents, and treating the number (which is the cholesterol number) rather than treating the condition (i.e. the pathophysiology-the functional disturbance). So these are very, very interesting philosophical questions.

As we examine blood cholesterol levels in contrast to their cerebrovascular disease (even Alzheimer's disease) in older-age individuals, we find people from 80 years of age and older who have higher cholesterol have lower incidence of vascular disease and vascular dementia. People with very low cholesterols have increasing relative risk. So cholesterol, in and of itself is not a direct univariate relationship to vascular disease.

There is a paper that appeared in the International Journal of Cardiology in 2007 in which the investigators talk about cholesterol in the blood really being a marker of nutritional status in mild to moderate heart failure.5 As people have low cholesterol, it is associated with low levels of microalbumin, meaning, basically, their pre-albumin levels are low, suggesting they are nutritionally compromised and they have low cholesterol because of a nutritional compromise (lowered anabolic function, lowered physiological nutritional status). So low cholesterol may be a risk factor, just as high cholesterol is, that is indicative (in this case, in an older-age population) of poor nutritional status with poor pre-albumin levels.

Beyond Statins: A General Lack of Data for Primary Prevention of Many Conditions. Is a Systems Biology Approach the Answer?

I think we are starting to look at this cholesterol story (the statin story) and drugs in primary prevention for chronic disease in an entirely different way. As you heard Dr. Wright point out, it is not just statins alone that are cause for concern. This model translates into other drugs used for primary prevention for which we don't have good outcome data to examine whether they really do anything other than to lower a biomarker-whether they really affect outcome related to mortality or morbidity over the long term. This would be things ranging from whole families of antihypertension agents, fibrates, insulin-stimulating drugs, and anti-inflammatories. What are the real outcome variables that relate to the effectiveness of these drugs other than them just altering a biomarker? A number?

This obviously speaks to a different philosophical approach to medicine, moving away from disease as a *sine qua non*, to looking at function. Those of you who have been listening to*Functional Medicine*

Update for some time probably knew I was going to go here at some point in this discussion because it once again points to the importance of looking at an emerging view of medical philosophy-a view based less on the pathophysiology (the end disease) and more on the path that goes there (the functional processes that resulted in disturbances that warped or altered the physiological web in such a way as to ultimately lead down a trajectory towards the disease).

I was reminded of this emerging view when I read an interesting paper that came from some investigators at the Department of Medicine, Brigham and Women's Hospital, Harvard Medical School that was titled "Human Disease Classification in the Postgenomic Era: A Complex Systems Approach to Human Pathobiology."[6] This paper appeared in the journal*Molecular Systems Biology* in 2007 and I think it frames the whole basis upon which the functional medicine model has been built. The authors say that contemporary classification of human disease derives from observational correlation between pathologic analysis and clinical syndromes. Characterizing disease in this way establishes a nosology that has served clinicians well to the current time in which acute disease was the major focus. It depends on observational skills and simple laboratory skills to define the diagnosis using the presenting phenotype The *sine qua non* for many of us in our training was to become good diagnosticians. Yet this time-honored diagnostic strategy has significant shortcomings as we have moved into an era when chronic disease has become the dominant disease type because it reflects both a lack of sensitivity in identifying preclinical disease and a lack of specificity in defining disease unequivocally. The focus, then, is on viewing disease as a reflection of different clinical presentations and starting to look at the underlying causes of disease rather than just what we call them (this variable phenotypic expression), and of excessive reliance on kind of a reductionistic view in establishing diagnosis. The purpose, then, is to provide a logical basis for classifying human dysfunction that uses conventional reductionism, but also incorporates the nonreduction approach, which is a systems biology approach in medicine. It is this systems approach that I think is very important.

Controversy over Homocysteine as a Biomarker

One of the examples that we could use to describe this concept is the recent controversy concerning homocysteine as a biomarker for cardiovascular disease. Homocysteine has come under some challenge recently as to whether it really does represent a true risk factor to atherothrombosis. Some papers have been published that indicate that the homocysteine hypothesis of heart disease doesn't hold up. Some trials have actually been completed which yield negative results (while homocysteine levels were reduced with vitamin B12 and folate therapy, the event rates were unchanged compared with a population treated with placebo in these studies). I think these studies have received a lot of attention in the media, so you may be familiar with them. The suggestion is that atherosclerosis is not a result of hyperhomocysteinemia.

Another way of looking at the data from these studies is to examine homocysteine as a biomarker that reflects distortions in the physiologic web beyond that of just being a risk factor to cardiovascular disease. The homocysteine connection is not exclusively owned by cardiology. We recognize that the modulation of homocysteine by B12 and folate supplementation not only lowers homocysteine related to potential vascular and toxic injury, but also promotes DNA synthesis (thereby supporting cell proliferation), enhances methylation potential, increases the formation of S-adenosylmethionine (or SAM), and lowers S-adenosylhomocysteine, which can alter gene expression by modulating the methylation status of certain DNA promoter regions. There are many different functions that derive out of the alteration of the folate cycle, which is seen by a surrogate marker called homocysteine. Homocysteine is not just connected to

cardiology; it is connected to neurology, oncology, endocrinology, obstetrics/gynecology, developmental biology, and pediatrics. All of these fields have some connection to that marker, homocysteine, which is reflective in the way it expresses itself in the web of interaction (the connection between genes and environment in that individual).

In a traditional diagnostic view, we would say that hyperhomocystemia has to be strongly connected with a disease to be seen as real. In this new model of systems biology we would say that hyperhomocystemia is an indication of a distortion in the web of physiology modulated through the folate cycle that can express itself based on genetic uniqueness in a variety of different clinical entities depending upon that individual's own susceptibility or their own physiological status. It might be seen as a neurologic, or it might be seen as an immunologic, or it might be seen as a cardiologic, or even as an obstetrical complication in some individuals.

When we apply a systems biology approach to looking at dysfunction it is different from always tying one indicator to one disease type. This organizational network-this disease network concept-is a very, very important emerging underpinning that differentiates a functional medicine model (which is built on systems biology precepts) from that of a *sine qua non*, pathonemonic disease nomenclature model in which each disease is seen as independent and isolated, one from the other, and it is not connected across different disciplines. I believe that we can apply that back to this discussion we have had with Dr. Wright concerning statins and cardiovascular disease, but in order to understand how we need to do a quick bit of background work on the history of the cholesterol hypothesis for atherogenesis. Let's quickly review how this all fits together.

The History of Statins: Context for Dr. Wright's Research

The early history of statins and cholesterol was built on the interpretive history of this cholesterol controversy. It goes back to Anitschkov, the Russian physiologist who did work with white rabbits, feeding them a diet enriched with cholesterol. This was in 1913, while he was working at the Military Medical Academy in St. Petersburg. Feeding these white rabbits cholesterol dissolved in sunflower oil induced vascular lesions resembling those of human atherosclerosis, both grossly and microscopically.

Dr. Anitschkov's work had been based upon the research of one of his previous Russian colleagues (Igor Ignatowsky), who had been looking at the relationship between protein in the diet and atherosclerosis and actually making an assumption that high protein diets were atherogenic. When he used the high proteins diets in animals, he was actually using diets that had a lot of animal products in them that brought cholesterol and saturated fat as well as protein. Igor Ignatowsky was the first, then, to actually demonstrate that these diets would induce atherosclerosis in animals, and that then led Anitschkov (later) to use more purified materials in demonstrating the cholesterol hypothesis in rabbits.

Interestingly, just to make a full circle of this, Ignatowsky actually took his work from a previous Nobel Prize-winning microbiologist whose name we are very familiar with and that is Elie Metchnikoff. Metchnikoff (who took over the Pasteur Institute after Dr. Louis Pasteur passed away, and was given the Nobel Prize in Medicine and Physiology for his discovery of aspects of the immune system) proposed that an excess of protein in the diet was toxic and somehow accelerated the aging process. By the way, he is also the person who talked about the use of yogurt installation through the rectum for the management of hospitalized patients and suggested that bacteria in the gut were very important in producing disease or

health. A lot of the probiotic concepts were built on the immune strengthening properties that Dr. Metchnikoff observed in animals and later in humans at the Pasteur Institute. It is interesting how this whole history kind of fits together-Metchnikoff, Ignatowsky, Anitschkov-and the cholesterol model that emerged.

From there, this lipid hypothesis model was considerably advanced by work that allowed for the differentiation of the way that cholesterol was packaged in the blood (work by Dr. E.H. Ahrens showing the impact of diet on blood cholesterol levels and how that ultimately resulted in atherogenesis). Later, the discovery of Dr. John Goffman related to the various lipoproteins led to our recognition that these lipid molecules were packaged in carriers called lipoproteins. At this point the LDL/HDL/VLDL nomenclature started to be developed.

Now we are moving, obviously, into the 1960s. By the late 1960s, many clinicians and investigators were already convinced that hypercholesterolemia was an important factor in atherogenesis. The connection of fat in the blood and atherosclerosis was further promoted and amplified by the work of Dr. Ansel Keys, a pioneer in nutritional research at the University of Minnesota who was convinced that blood cholesterol levels were determined significantly by the amount and the nature of fat in the diet. He started talking about the polyunsaturated fatty acid concept versus saturated fats, so we started to get into this whole lipid domain.

This was the era, by the way, when we left behind the concepts of Rudolph Virchow. Dr. Virchow, recall, was the German pathologist, the so-called "father" of pathology, who had observed in the 19th century that atherosclerosis appeared to be more of an inflammatory disorder. So the Virchow model was kind of left behind and the Anitschkov model (the lipid model) was advanced, and the cholesterol connection became much more important.

Without knowing exactly how or if cholesterol did, in fact, serve as a primary etiological agent for coronary vascular disease, we came to the Framingham Study in Massachusetts (what later became known as the Framingham Heart Study), a pioneering evaluation of relative surrogate markers that associated themselves with increasing incidence of vascular disease as people aged. This led to our traditional association of cardiovascular risk factors with serum cholesterol, particularly bad LDL cholesterol being elevated and good HDL cholesterol being reduced. We start to get into this whole lipoprotein/cholesterol lipid model.

Fortunately, a new technology was developed to make available finger-stick measurements of cholesterol. It could now be done at health fairs and shopping malls and everybody could suddenly know their number (their cholesterol number). This technology advancement was very helpful in making the concept more accessible to all people.

And then, there was the discovery of statins and the connection to the red rice yeast fungal metabolites that were used as culinary agents in Japanese cooking, as well as the chalcones. Japanese chemists were able to lower cholesterol levels in animals when they were fed certain red rice yeast metabolites. That led to the extraction, isolation, purification, and ultimate structure proof of these molecules, and they became antihypercholesterolemic agents, which then got derivatized and modified in structure to make new-to-nature molecules by the drug companies. From Lovastatin and Nevacor was birthed a whole family of new, improved versions of these cholesterol-lowering agents originally derived from natural products

(from the red rice yeast). The history is a pretty fascinating history if we go all the way back to the turn of the last century right up through the development of Lipitor, the blockbuster drug of today for modulating cholesterol *de novo* biosynthesis.

All of the history leads us to lipid research intervention trials and to looking at what happens when you start intervening with these cholesterol-lowering agents. There are two approaches that have been used. One approach is the use of diet, lifestyle, and exercise. There is a huge body of literature that supports the value of this primary therapy, and that becomes the basis of what the National Institutes of Health now calls the first line of therapy, or the therapeutic lifestyle change program (TLC program), which is recommended to physicians for use with patients who have hyperlipidemias prior to the onset of intervention with a lipid-lowering drug. This treatment approach involves dietary modification, exercise, stress management, smoking cessation (obviously), and ideal body weight achievement. This approach has a demonstrated success in primary prevention with limited to no adverse side effects.

The other approach is pharmacotherapy, which is to intervene with a cholesterol-lowering pharmacological agent. Here is where we come full circle back to the comments of Dr. Wright. He says that we jump very quickly into utilizing pharmacology for the management of a surrogate marker (cholesterol) without really knowing if a patient is individually at risk to a disease because not every patient with elevated cholesterol gets heart disease and not every patient with low cholesterol is absent to heart disease. We need to know more about the individual etiology--the functional status of the patient--rather than just go off a biomarker, because the drugs in and of themselves, as he points out, may have a limited benefit in primary prevention when applied in a general way, without knowing the individual risk that a particular person has.

Statins have been made into over-the-counter (OTC) drugs in Britain, and there is even suggestion that they should be made available to children on a regular basis to bring their cholesterol levels down to levels that are considered ideal. These steps are being taken without a full understanding of exactly what we are we doing, what are we treating, what the long-term outcomes are-not just the biomarker change, but the actual health outcomes (morbidity and mortality).

The above interpretive history of the cholesterol controversy may give us a little bit better understanding of the context by which Dr. Wright is delivering this information that he shared with us.[7,8,9,10,11]

There is another important and interesting part of this story. As the interpretive history of the cholesterol controversy emerged and statins were discovered and more fully investigated, it has become recognized that they operate, physiologically, in ways that are beyond that which was originally thought. Initially statins were thought to be HMG CoA reductase inhibitors (hydroxymethylglutaryl Co-enzyme A reductase inhibitors), the rate-limiting enzyme for cholesterol biosynthesis. It was thought that these molecules (these statin molecules) worked by lowering cholesterol, specifically by blocking the valonate polymerization to give rise to sterols that ultimately are derivatized into cholesterol itself.

It is true that statins will lower the biosynthesis of cholesterol at the hepatic level. No question. It is also true that they will serve as HMG CoA reductase inhibitors. As such, they will then lower not only cholesterol in and of itself, but the intermediary molecules that are involved in the squalene pathway that are associated with the conversion of mevalonate ultimately into these tetracyclic diterpenoid molecules that we call steroids. So it has to do with sex steroids. It has to do with stress steroids. It has to do with the

whole family of cholesterol and their derivatives that relate to membrane function and steroid synthesis. So there are many, many things that are involved with regulation of brain structure and function. All of these components of the synthesis of long-chained polyenoic molecules that are cyclized into steroids are modulated, modified, or reduced as a consequence of consumption of statins.

It begs the question: what happens to physiological function if you limit all of these molecules in their biosynthesis? Are you influencing things other than just the potential cardiovascular relative risk of an elevated LDL? That is where the state of the art of discussion is now really focusing: to look at how these other things--geranyl pyrophosphate, farnesyl pyrophosphate, the farnesylation of molecules-are modulated or modified by the consumption of statins and what impact they may have over the long term on a person's physiological function.

One role of statins is LDL reduction. But it is interesting to note that if you go back to the story that Dr. Wright was sharing with us concerning Vytorin, (a drug that contains not only a statin, but also contains a cholesterol-binding substance that prevents cholesterol absorption from the diet) in clinical trials this drug was demonstrated to lower cholesterol LDL levels. The clinical outcome of that trial was that patients had an increased thickness of their artery wall and increased filtration of lipid with increased potential atherogenic risk. So even though LDL cholesterol was lowered, which is presumably desirable, the relative risk to atherogenic dysfunction was increased Are we sure we know everything we need to know about LDL cholesterol and atherosclerosis? Obviously the answer is no.

In previous issues of *Functional Medicine Update*, I have reported that in cases where you had patients on aggressive statin therapy (this would be above 80 milligrams a day of atorvastatin), that you could lower their LDL cholesterol below 70 milligrams per deciliter, which is in a low-risk category. But yet if their hsCRP (their high-sensitivity CRP) still stayed elevated above 2, they had an increasing relative risk to a secondary event (this is in secondary prevention trials). So even though aggressive lowering of LDL with statins reduced the LDL below 70, if a patient's hsCRP was above 2 milligrams per liter, they still had a highly significant increased relative risk to a secondary cardiovascular event (meaning it is more than just that of LDL, there is this inflammatory component as well). This relates, then, to a question whether statins might have anti-atherosclerotic effects beyond that of lowering LDL itself. Are they pleiotropic drugs? The answer to that question is emerging to be "yes."

The Pleiotropic Effects of Statins and Other Drugs

With statins (as in the case of probably all medications), as we examine the mechanism of action in more detail we find out there is not just one thing that they do. With statins, it appears as if their effects are pleiotropic (multiple), with one effect being the blocking HMG CoA reductase. Other effects have to do with the influence on the synthesis of isoprenoids and the attachment for intercellular signaling molecules.. These post-translational effects have to do with modulation of GTP-binding proteins (guanosine triphosphate-binding proteins) that are involved with intercellular signal transduction. These are the trans-membrane-binding proteins that translate outside-inside information-the G proteins-that are modulated in their function by post-translational influences (like farnesylation). The connection with these farnesyl residues affect their function (and statins appear to influence this), and therefore might have wide-ranging influences on things other than cholesterol biosynthesis. I am now talking about immunomodulation, neuroprotection, and cellular senescence and inflammation.[12,13,14,15]

Do we really know how statins work in the individual? Maybe there are people who have specific types of high-risk physiological processes for which statins influence (through these pleiotropic mechanisms) function in very desirable way, whereas for other individuals in primary prevention, the alteration of these functions may have deleterious effects. Statins might alter these post-translational modifications of G proteins in such a way as to alter the response of some people and put them at higher risk (like the reduction of neurosteroids that might produce increasing risk to Alzheimer's, which we have seen at least some suggestion of). Statins might increase the risk to altered intercellular replication associated with oncogenesis. They might have influence on immunological function in such a way as to produce deleterious outcome in some individuals. These are the kinds of questions that are now being raised about the altered functional status that statins might produce.

These questions might also help us to understand some of the myopathy that develops with statins. We know blocking the synthesis of coenzyme Q10 (and lowering CoQ10 levels) is one of the adverse effects statins have. This alters mitochondrial oxidative redox function and can increase oxidative stress. Concern is spreading to many different areas.

One emerging topic is the effect of statins on Rho proteins that are involved in G-protein signaling and how they influence expression activity and physiologic function. In 2008 in*Biochemical Pharmacology*, an article was published looking at the effect of lovastatin on Rho isoform expression activity and association with GMP dissociation inhibitors (the relationship to this intercellular signaling processes mitigated by statins).[16] We know that endothelial dysfunction, oxidative stress, and inflammation is influenced in atherosclerosis and that statins could have an influence on that as well through these G-protein signaling events through farnesyl and post-translational modification of these proteins. And statins may ameliorate pulmonary hypertension versus Rho-Rho kinase signaling pathways. It is interesting to note that now statins are being seen to influence specific cellular kinase signaling agents that are involved with these Rho protein post-translational modifications and how they regulate intercellular signal transduction. Understanding the pleiotropic effects of statins (and related pharmacological approaches) is starting to evolve beyond the simple thought that statins were only working as HMG CoA reductase enzyme inhibitors.

Mapping all of this against the comments of Dr. Wright, what does it say about the primary prevention applications of statins? That's a very interesting and somewhat controversial question. Let's follow the kind of precedent of Dr. Wright's discussion and look at what an alternatives there might be to usingstatins for primary prevention in an asymptomatic individual. What about the National Institutes of Health Therapeutic Lifestyle Changes Program, which uses diet, lifestyle, and exercise as primary therapies, and holding statins for secondary prevention? Would this be considered irresponsible? Would it be best to apply these medicines-these statin molecules-with the presumption (in primary prevention) that we are going to forestall some outcome that would be a cardiovascular event? Or would it be best to focus our attention and energy onto really learning how to apply lifestyle, diet, and exercise therapies more effectively?

These questions take us back to conditions that have cardiovascular risk, like cardiometabolic syndrome (the connection between hyperinsulinemia, endothelial dysfunction, and cardiovascular disease). Even in the face of normal blood cholesterol levels, people may carry a conferred, enhanced risk to vascular disease as a consequence of altered lipoprotein transport and hypertriglyceridemia and lowered HDL levels.

A very interesting paper published in *Clinical Pharmacology and Therapeutics* looks at metabolic syndrome and cardiometabolic disease from a global epidemiology perspective to individualized medicine.[17] What the authors point out in this wonderful review article is that in virtually every country that has been examined, as one starts to see increasing waist-to-hip ratio, increasing waist circumference, and increasing fasting triglyceride and low HDL levels, there is an increasing incidence of cardiovascular disease that you cannot tie directly to elevated blood cholesterol levels, but rather it is tied to insulin resistance and hyperinsulinemia. My review of the data seems to say it is consistent across all these countries: Brazil, Equador, Finland, France, Greece, India, Iran, Ireland, Latin America, New Zealand, Turkey, the United States, and Venezuela. This trend includes increasing blood pressure, increasing dyslipidemia, increasing sleep apnea, increasing systemic inflammation, increasing erectile dysfunction in males, increasing central adiposity. All of these things seem to map against increasing prevalence of cardiovascular disease. What is the best way of intervening? We are caught with the same conundrum, aren't we, that we were talking about earlier? What do you do? You talk about the drugs that are used for the primary prevention/intervention related to cardiometabolic syndrome. If you look at the clinical trials that have been published about drugs for the prevention of cardiometabolic syndrome or even surgical intervention in the morbidly obese person, they have limited outcome data available and they all have limited success. Bariatric surgery in the morbidly obese person is probably the most efficacious, but for ambulatory medicine, the drugs have really not been able to demonstrate their success, be it either statins, fibrates, ACE inhibitors, or the other drugs that have been employed in the management of insulin resistance and metabolic syndrome.

Again, what is the best approach? The best approach appears (once again) to be that of diet, lifestyle, and exercise intervention. Katherine Esposito has authored a very eloquent recent paper in *Current Opinions in Lipidology* talking about how the Mediterranean diet really represents the most efficacious, safe, and effective intervention for insulin resistance and cardiometabolic syndrome and the dyslipidemia associated with this condition (which is alteration of apo B to apo A-1 ratio, increasing apo B and a decreasing level of apo A-1, with increasing atherogenesis).[18]

There was a wonderful paper in the journal *Circulation* in 2008, talking about dietary intake and the development of metabolic syndrome and its connection to atherosclerotic risk.[19]Again it showed a complex diet (such as the Mediterranean diet) that is low in refined carbohydrate and high in whole grains, omega-3 and omega-9 fatty acids, and fruits and vegetables that are rich in phytochemicals is-by far and away-the most successful therapy and should be employed before one would even consider pharmacotherapy. By the same token, in the *Journal of the American College of Cardiology*, a very nice paper on dietary strategies for improving postprandial lipids, inflammation, and insulin levels was reported, and it again showed that a high fiber, plant-based diet, rich in vegetables and fruits, whole grains, legumes, and nuts, markedly blunted postprandial hyperinsulinemia and improved lipid dynamics and lipoproteins more effectively than pharmacotherapy intervention.[20]

It seems there are specific treatments for metabolic syndrome emerging. This was described in a recent review paper by Katherine Esposito in the *American Journal of Clinical Nutrition* in 2008.[21] We are seeing first-line therapy (therapeutic lifestyle changes) become the standard of identity that takes us away from relying on intervention with pharmacological agents for which the long-term effects in primary prevention have not been adequately demonstrated, and for which there is adequate information suggesting potential adverse side effects that can occur (at least in sensitive individuals) that can limit the

clinical effectiveness of these agents.

I think we should recognize that the presaging comments of Dr. Wright that you've heard today in this issue of *Functional Medicine Update* are dramatic. They are earth-shaking. They are seismic in their implications. Not everybody aligns themselves behind Dr. Wright's concepts, obviously. We have a lot of vested interest in the status quo. In fact, in the letters to the editor to *The Lancet*, there were some criticisms. How could he be so audacious to call into question the fact that the lipid-lowering therapies using statins weren't effective in primary prevention? Of course, Dr. Wright says the following. "The people who criticize this work use the common excuse: that the primary prevention studies are not powered to detect changes in total mortality. In reality, our evaluation of the eight available trials for primary prevention using statins comprise more than 40,000 individuals of all ages, followed up on an average of five years. These pooled data are certainly powered to detect a reduction in mortality and failed to do so. As a consequence, we know there is an association between LDL cholesterol and coronary artery disease in some populations. However, one cannot assume that predicted benefits from epidemiological data will be achieved in drug intervention trials. The reason for that is that all drugs are double-edged swords and have harms as well as benefits. We must not so quickly forget the lesson from the Women's Health Initiative trial in which a reduction in LDL cholesterol with combined estrogen-progestin therapy caused an increase in coronary heart disease events. We believe, as we explained in our comment, that in some subpopulations statins cause serious, unrecognized harm, which negates the benefit when the benefit is small. In most primary prevention settings, statins have a low therapeutic positive benefit. That is why we are calling for a detailed, subgroup analysis to be made available so that we and others can get a better idea of who is being harmed by primary prevention with statins."

I hope I have left you with some very strong "food for thought." I look forward to visiting with you in May.

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