Using the 2013 ACC/AHA Cholesterol Guideline in Caring for People with Diabetes.

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Matthew Clark:

My name is Dr. Matthew Clark. I'm board certified in Internal Medicine and Pediatrics. I'm the Clinical Director at the Ute Mountain Ute Health Center in Towaoc, Colorado. I've been serving with the Indian Health Service in Southwestern Colorado for about 13 years. I'm also the Albuquerque Area Indian Health Service representative to the National Pharmacy & Therapeutics Committee.

I wanted to express my thanks to Dr. Ann Bullock for inviting me to present this webinar regarding the 2013 American College of Cardiology and American Heart Association Cholesterol Treatment Guidelines. I would be happy to take any questions at the end of the presentation today. So, let's get started.

I'll briefly discuss the epidemiology of dyslipidemia and atherosclerotic cardiovascular disease. And then, the presentation will focus on the review of the statin drug class in the context of the American College of Cardiology and American Heart Association Guideline which was released in November 2013. Lastly, I will compare and contrast the AHA/ACC guideline with the American Diabetes Association 2014 Clinical Practice Recommendations regarding lipid management.

The National Health and Nutrition Examination Survey data indicate a decline in the prevalence of elevated total cholesterol over the past two decades felt due to the treatment of hyperlipidemia. It is well-known that there is a log-linear relationship between lipid levels and atherosclerotic cardiovascular disease. While there are many lipid sub-fractions, the 2013 Guideline focuses specifically on LDL cholesterol and the risk for atherosclerotic cardiovascular disease.

This graph represents the log-linear relationship between LDL cholesterol and the relative risk for coronary heart disease. Data suggests that for every 30 milligrams per deciliter change in LDL cholesterol, the relative risk for coronary heart disease is proportionately increased by about 30% with the relative risk set at one for LDL cholesterol of 40.

Now, I'd like to discuss the epidemiology and the impact of cardiovascular disease in the US population, including cardiovascular-related health disparities for the American Indian and Alaska Native population. According to recent data from the National Heart, Lung, and Blood Institute, heart disease is the second leading cause of death in the American Indian and Alaska Native population, second only to cancer. Note that stroke is the seventh leading cause of death in our service population.

Coronary heart disease death rates decreased among American Indians from 1999 to 2008 but remained stable or increased during 2009 through 2010. Stroke death rates similarly decreased among American Indians from '99 through 2008 but also remained stable or increased during 2009 through 2010. This is a concerning trend.

Now, we are going to transition to a brief review of statins as a drug class. There are multiple agents in the statin class with varying degrees of potency and varying pharmacokinetics, as we

shall see later. All statins inhibit the rate-limiting step in cholesterol biosynthesis by competitive blockade of the enzyme HMG-CoA reductase. This produces various beneficial effects on lipid metabolism.

In addition, there are several other proposed statin benefits over and above their effects on cholesterol biosynthesis. These include regression of atherosclerotic plaques, reduced progression and stabilization of plaques, reduced inflammation independent of lipid lowering effects, reduced endothelial dysfunction, reduced thrombogenicity, and reduced ventricular arrhythmia and cardiac death.

There are a number of reported adverse effects from statin therapy. As regards hepatic dysfunction, a low rate of liver enzyme elevations has been reported, on the order of a half to three percent, and usually in the first few months of therapy. In a study of 23,000 statin-treated patients enrolled with Kaiser Health in Colorado, only a tiny fraction of statin-treated patients were found to have elevated liver enzymes and nearly all of these were associated with drug interactions. As a result of this and other similar studies, the FDA revised statin labeling in 2012 to deemphasize monitoring of liver enzymes.

Despite common perceptions, statin therapy, particularly solo therapy, has rarely been associated with muscle injury including myalgia, myositis and rhabdomyolysis, at least in the clinical trials. However, when other risk factors are present such as advanced age, preexisting muscle disease or drug interactions, statin-induced myopathy can occur. A MEDLINE search published in Circulation in 2006 found no statistically significant increase in myopathy among over 74,000 study participants on statin monotherapy. It should be noted that higher rates of muscle pain have been reported in clinical practice.

Of particular interest in the Indian Health Service is the association of statin therapy with the development of Type 2 diabetes mellitus. In the 2008 JUPITER trial, a modest increased rate of physician-diagnosed Type 2 diabetes mellitus was noted in the rosuvastatin treatment group compared with placebo.

A 2011 meta-analysis published in the Journal of the American Medical Association also noted an increased incidence of Type 2 diabetes mellitus with intensive statin therapy compared with moderate statin therapy. This accounted for two additional cases per 1,000 patient-years. However, the same meta-analysis showed six and a half fewer cardiovascular disease-related deaths per thousand patient-years. Taken together, the cardiovascular disease benefit from statin therapy appears to exceed the risk of diabetes. A host of other potential statin-associated adverse effects have been proposed.

Let's discuss the November 2013 American Heart Association and American College of Cardiology cholesterol treatment guideline. First, I'd like to review a few caveats. The systematic review generally did not consider evidence beyond 2011. However, the expert panels discussed major randomized controlled trials and meta-analyses that were published through July 2013. They plan to begin updating the guideline this year. Recommendations were derived from randomized trials, meta-analyses, and observational studies; and only when sufficient evidence was available to make a recommendation.

The expert panel assigned grading according to the level of evidence and the class of recommendation. Among studies reviewed by the panel, exclusion criteria included patients with secondary causes of elevated lipids and those with triglyceride levels in excess of 500. The panel emphasized that guidelines are not intended to replace clinical judgment.

The scope of this guideline offers a departure from the ATP model that we're all familiar with. It focuses on the primary and secondary prevention of atherosclerotic cardiovascular disease in adults and is not intended to be a comprehensive approach to lipid management.

In a statement accompanying the guideline, the expert panel points out that the focus on statins represents a significant departure from current strategies and changes a long-standing paradigm. Specifically, it was determined that a treatment strategy of fixed-dose statin therapy to reduce risk of atherosclerotic cardiovascular disease was supported by multiple randomized clinical trials. No evidence was found to support other popular strategies including "treat to target," "lower is better," or even risk-based treatment approaches.

In an overview of treatment recommendations, it was determined that statins consistently reduce atherosclerotic cardiovascular disease events in both primary and secondary prevention populations, with the exception of hemodialysis patients and those with moderate or advanced heart failure. Lifestyle modification was recommended as background therapy, both prior to and during statin therapy for all patients that were treated. Finally, it was determined that additional lipid therapy to further lower non-HDL cholesterol did not further reduce cardiovascular disease events.

Regarding dose, the panel felt that evidence supports that an appropriate intensity of statin therapy should be used. We will discuss this a little bit later in the presentation. No evidence from randomized clinical trials was found to support dose titration to achieve specific LDL or HDL goals. I think this is an important point to bring out. These guidelines were based on a review of studies that encompassed nearly 200,000 study participants. They really found no evidence that dose titration was beneficial because in general, the studies that they reviewed did not follow a dose titration methodology.

Now, let's review a few definitions used in the guideline. The term "clinical atherosclerotic cardiovascular disease" which is based on randomized control trial inclusion criteria is intended to represent the secondary prevention population. It includes those with a history of acute coronary syndromes, myocardial infarction, stable or unstable angina, coronary or arterial revascularization procedures, stroke, transient ischemic attack, or peripheral artery disease presumed due to cardiovascular disease based on randomized control trial inclusion criteria.

The term "atherosclerotic cardiovascular disease risk" is intended to represent the primary prevention population and pertains to those with history of non-fatal MI, coronary heart disease death, non-fatal and fatal stroke; note that the inclusion of stroke differentiates this primary prevention risk group from other prior guidelines which focused on so-called "hard coronary heart disease risk".

Based on pooled cohort data from multiple selected randomized clinical trials representing over a 150,000 study participants, the expert panel generally found that events from atherosclerotic cardiovascular disease decreased across a spectrum from a baseline LDL cholesterol of 70 or above, that there was a consistent relative risk reduction for all clinical subgroups including diabetic patients, and that primary and secondary prevention of cardiovascular disease events was reduced consistently. There was an absolute reduction in events proportional to absolute cardiovascular disease risk.

Based on these findings, the panel defined four major statin benefit groups in whom the statin benefit was felt to, in their term, clearly outweigh the risks of adverse events. These were patients with known clinical atherosclerotic cardiovascular disease; those with a primary elevation of LDL cholesterol greater than or equal to 190; those with diabetes mellitus of any type and an LDL cholesterol from 70 to 189 without atherosclerotic cardiovascular disease if the estimated 10-year cardiovascular disease risk was equal to or greater than seven-and-a-half percent; and the primary prevention subgroup of those with an LDL cholesterol 70 to 189 without either diabetes or known cardiovascular disease if their estimated 10-year risk of cardiovascular disease events was greater than or equal to 7.5 percent. This latter group is the group that accounted for much of the controversy following the publication of these guidelines. We'll discuss that briefly as time permits.

For secondary prevention, a high level of evidence was found to support use of statins to reduce total mortality risk in persons with prior cardiovascular disease events. For primary prevention, a moderate level of evidence was found to support reduction of total mortality in persons felt to be at increased risk based on certain specific defined parameters.

Now I'd like to summarize the recommendations of the expert panel. Each recommendation is presented based upon the supporting level of clinical evidence. In some instances where data is lacking, either expert opinion is used to support a recommendation or no recommendation is made. As previously noted, the panel felt that there was insufficient evidence for a recommendation for or against LDL cholesterol or non-HDL cholesterol targets for either the primary or secondary prevention of atherosclerotic cardiovascular disease. This is in contrast to prior recommendations and represents a true shift in the approach to cholesterol management which needs to be communicated to our providers. Note that in the slides that follow, you'll see reference to statin intensity and the calculation of the 10-year risk of atherosclerotic cardiovascular disease, which I will discuss in some detail later in the presentation.

For secondary prevention among patients under 75 years of age with clinical atherosclerotic cardiovascular disease, the guidelines committee found strong evidence to support high-intensity statin therapy or alternately moderate-intensity statin therapy if there was either poor tolerance, contraindications to high-intensity therapy or risks associated with that. They also recommended initiation of high-intensity statin therapy or increased intensity as tolerated if a patient is already on low or moderate-intensity statin therapy.

For patients older than 75 with a known history of cardiovascular disease, expert opinion is to weigh risk-reduction benefits versus adverse effects and patient preference when considering higher or moderate-intensity statin therapy, based on the observation that there is no clear evidence of additional risk reduction with high-intensity versus moderate-intensity statin therapy in this particular group, and that moderate-intensity statin therapy did reduce cardiovascular disease events compared to control. They also recommended considering moderate-intensity statin therapy or continuation of statin therapy if it's already being tolerated at a certain level.

Now, let's talk about statin recommendations for the primary prevention of atherosclerotic cardiovascular disease. Among adults age 21 or older with LDL cholesterol greater than or equal to 190, the expert panel found moderate evidence to support high-intensity statin therapy or maximum statin therapy tolerated if the LDL cholesterol is greater than or equal to 190, or triglycerides greater than or equal to 500. In this particular situation, they recommended evaluating for secondary causes of hyperlipidemia. Evidence shows that for every roughly 30 to 40 milligram per deciliter reduction in LDL cholesterol, there's a 20% to 30% reduction in cardiovascular disease risk.

Regarding treatment endpoints among the same group, expert opinion favors for untreated LDL cholesterol greater than or equal to 190, that statin therapy should be intensified to achieve a 50% LDL cholesterol reduction. After maximum-intensity statin therapy is achieved, consider adding a non-statin drug to further lower LDL cholesterol. Again, for these particular points, this was based on expert opinion. They didn't find specific study or clinical trial evidence to support these particular recommendations.

In the primary prevention subgroup of diabetic patients with LDL cholesterol between 70 and 189, the panel found strong evidence to support moderate-intensity statin therapy for persons between the ages of 40 and 75. In the same subgroup, expert opinion supports consideration of high-intensity statin therapy when the calculated ten-year risk of atherosclerotic cardiovascular disease exceeds seven-and-a-half percent unless contraindicated. For either younger or older diabetic patients with LDL cholesterol of 70 to 189, expert opinion supports considering moderate-intensity

statin therapy after weighing risk-reduction benefits versus the risk of adverse effects, as well as patient preference.

Now, let's get into some of the controversial elements of the guideline. Among non-diabetic patients with LDL cholesterol between 70 and 189, for the primary prevention with statins of atherosclerotic cardiovascular disease, expert opinion supports the use of new so-called "pooled cohort equations" for the estimation of 10-year risk.

First, let's consider the recommendations of the screening work group regarding who should be screened and appropriate screening intervals, and then we'll talk about the pooled cohort equations and the controversy.

The work group concluded that all persons aged 20 to 79 should undergo a measurement of cardiovascular risk factors every four to six years, including total and HDL cholesterol, blood pressure, diabetes mellitus status and current smoking status. Based upon screening for these risk factor variables, the work group recommended calculating 10-year risk of atherosclerotic cardiovascular disease in persons aged 40 to 79 using the newly formulated pooled cohort equations for the purpose of determining potential statin benefit.

By far, the most controversial aspect of the new guideline are the pooled cohort equations which are intended as a new assessment tool for the calculation of 10-year risk of atherosclerotic cardiovascular disease. For purposes of these equations, the expert panel defined risk in the broader terms of the first occurrence of both non-fatal and fatal MI and stroke instead of the usual hard coronary heart disease risk. Note that this is a global assessment of risk rather than risk factor counting or assessment by risk factor inclusion criteria from the randomized control trials.

As regard to generalizability, it is important to note that this risk calculation tool is intended for the prediction of stroke and coronary heart disease events in specifically non-Hispanic Caucasian and African-American women and men aged 40 to 79 years with or without diabetes and an LDL cholesterol of 70 to 189. The reason why the pooled cohort equations are specifically intended for use in this fairly narrowly-defined group is that that was the group that they developed the equations from; those were the cohorts that they looked at.

You might say, "Well, we treat an American Indian and Alaska Native service population that doesn't fit into this group." I'll discuss some of that controversy as well. But suffice it to say that the data that exists currently does not permit this expert panel to develop equations around our particular service population because the studies that they were looking at were not powered for that service population. There weren't enough individuals who were enrolled in those studies in order to make a determination.

The pooled cohort equation risk calculator can be accessed at the American Heart Association website at the web address listed here, and you will have access to these slides after the presentation.

The risk assessment work group reviewed a variety of pooled cohorts comprised of only African-American or White participants with at least 12 years of follow up. The work group concluded that there was insufficient data for other racial and ethnic groups. However, the work group did note that the 10-year risk of atherosclerotic cardiovascular disease in the American Indian and Alaska Native population can be substantially higher. The variables deemed to be of "statistical merit" for the four-pooled cohort equations were age, total and HDL cholesterol; systolic blood pressure, treated or untreated; diabetes mellitus status, and current smoking status. These are the variables that you have to plug into the equations in order to come up with a risk assessment.

Let's talk a little bit about the risk calculation controversy. Remember, this applies almost exclusively to the primary prevention groups and not to individuals with known cardiovascular

disease. Soon after the release of the guideline, a commentary was published in the journal, The Lancet, by Dr. Paul Ridker and a statistician, Nancy Cook, both from Harvard Medical School. They argued that the risk calculations based on the epidemiologic models have several shortcomings, including a lack of calibration resulting in an overestimation of risk by about double. They also pointed out that the risk calculators did not use randomized control trial inclusion criteria and were also not externally validated for contemporary populations. They felt that the risk calculations might not account for persons with high cardiovascular risk who may not benefit from statin therapy. Finally, they pointed out that smoking and hypertension, of which are the major drivers of global risk, would be better treated directly rather than indirectly by statin therapy.

This resulted in a controversy regarding the primary prevention recommendations. When applied to the cohorts from the Women's Heath Study, the Physician's Health Study, and the Women's Health Initiative Observational Study, it was determined that the pooled cohort equations overestimate cardiovascular disease risk by about double. Taking into account those deemed to have greater than 5% 10-year risk, an estimated 45 million Americans or roughly one in every three adults would require statin therapy based on this new guideline. This was a concern for these folks.

As we move forward into the primary prevention subgroups, it assumes that you accept that the pooled cohort equations are appropriate. And remember that the use of the pooled cohort equations was based on expert opinion.

But assuming you accept that, then the expert panel felt that there was strong evidence to support moderate or high-intensity statin therapy for non-diabetic patients aged 40 to 75 with an LDL cholesterol level of 70 to 189 and a calculated 10-year risk of atherosclerotic cardiovascular disease of over seven-and-half percent regardless of gender, race, or ethnicity.

The panel felt that there was also weak evidence to support moderate intensity statin therapy in similar patients with the calculated risk of five-to seven-and-a-half percent. However, it was felt that the adverse event rate is felt to possibly outweigh the risk-reduction benefit for high-intensity statins in this particular group.

Forming the basis for these primary prevention recommendations among non-diabetics with LDL cholesterol of 70 to 189 were three exclusively primary prevention randomized control trials. When the excess cardiovascular event rates were compared between the statin-treated groups and placebo, a risk-reduction benefit from moderate or high-intensity statin therapy was observed and was felt to exceed the risk of adverse events.

Due to the lack of supporting clinical trial data, no recommendation was made regarding statin use in persons with end-stage renal disease or moderate to severe heart failure.

The expert panel acknowledged that there is a higher rate of atherosclerotic cardiovascular disease in American Indians and Alaska Natives compared to Whites. Accepting the lack of specific data among the IHS service population, a recommendation was made that future clinical trials should be powered for subgroup analysis by race and ethnicity. They pointed out the fact that many of these trials that they have accessed information for, came during the era when statins were being tested for marketability and for FDA approval, and that many of these statin drugs have, in the interval, gone off-patent and that some of the motivation for new large trials is fairly low. So it may fall to other individuals with an interest to look specifically at our service population and the applicability of these risk calculators in our particular patient population.

Expert opinion of the risk assessment work group was that the pooled cohort equations may be considered when estimating risk in patients from populations other than African-Americans and non-Hispanic Whites. Basically what they said was, "Look, we think these equations are still useful

and more generalizable to other groups; particularly groups such as the IHS service population where we know there are health disparities and higher rates of cardiovascular disease."

I had a chance to address this issue with the Native American Cardiology Program staff. Specifically, I spoke with their cardiologist who served as a subject-matter expert for the discussion of this topic for the National Pharmacy & Therapeutics Committee. Basically, what the cardiologist said was that based on guidance from their practice, they felt it was reasonable to assume a higher risk for atherosclerotic cardiovascular disease in our service population. And that the Cardiology Program simultaneously did risk calculations using the pooled cohort equations and an older risk calculator from the Strong Heart Study, which as many of you know, was conducted among the IHS service population -- there were differences, but those differences probably do not affect treatment decisions based at least on the new guidelines.

They also felt that the Strong Heart Study data and the population that it applied to may no longer be representative of the current service population. Although there are some new data that is pending release and publication soon that may shed some light on this. In a nutshell, basically, the staff of the Native American Cardiology Program advised me that they do recommend using the pooled cohort equations and risk assessment for the IHS service population.

Regarding the issue of statins and primary prevention, I would like to bring forward the discussion with two additional meta-analyses that were published after the American College of Cardiology and American Heart Association Task Force systematic review. These two studies were published in The Lancet and the Cochrane Database in 2012 and 2013, respectively. Even though they precede the publication of the current guideline that we're discussing, they actually bring forward some additional data that was not specifically reviewed during the systematic review for this guideline.

The Cochrane Database review that was published in 2013 evaluated statins for the primary prevention of cardiovascular disease. It included new trials since the last Cochrane Review of this particular topic, which was published back in 2011. It considered a broad range of outcomes including all-cause mortality, fatal and non-fatal coronary heart disease, stroke, various combined end points, revascularization procedures, total and LDL cholesterol concentrations, adverse statin side effects, quality of life, and total cost. They really looked at the full gamut.

The review which identified four new trials and updated follow up data from three additional trials found benefits from statins, for primary prevention essentially across the full range of outcomes that they were considering. A meta-analysis, which was published in The Lancet in 2012, included data from the Cholesterol Treatment Trialists' Collaboration and it reviewed 27 randomized clinical trials among over 174,000 study participants. So, this was a very robust meta-analysis.

Statins were found to reduce the risk of major vascular events and both vascular and all-cause mortality in all of the primary prevention subgroups. The proportional reduction of risk of major vascular events was at least as high in the low-risk groups as in the higher-risk groups. Statins were deemed highly effective for primary prevention even in relatively low-risk groups.

Expert panel definitions of statin intensity in terms of dosage were based on the average expected response to a specific statin and dose. Note that high-intensity statin therapy is defined as an expected LDL cholesterol reduction of greater than or equal to 50%; moderate-intensity statin therapy is defined as an expected LDL cholesterol reduction of 30% to 50%, and low-intensity statin therapy is defined as an expected reduction of less than 30%. These percent reductions were based on a previous 2010 meta-analysis that was performed by the Cholesterol Treatment Trialists' group, in which statin therapy was shown to reduce atherosclerotic cardiovascular disease events.

Here is a summary of statins and statin doses categorized by intensity, which comes from the guideline. Note that the only statins categorized as high-intensity are atorvastatin, formerly brand name Lipitor, in the 40mg to 80mg strength and rosuvastatin, which is the only statin to my knowledge currently on patent, also known as Crestor, in 20mg to 40mg strength.

I'm going to make a few conclusions about the current guideline and then we'll move on to a comparison with the American Diabetes Association recommendations. In conclusion from the American College of Cardiology and American Heart Association Guideline, statins in proper dose appear to be the most effective medications for reducing atherosclerotic cardiovascular disease risk in both primary and secondary prevention groups. Statins are safe with uncommon adverse events and in the view of the expert panel and other experts outside this guideline, monitoring can probably be simplified.

Data do support a simplified treatment strategy of fixed-dose statin therapy instead of statin titration to specific cholesterol targets. High-intensity statin therapy, as tolerated and unless contraindicated, is preferred for secondary cardiovascular disease prevention as well as for certain high-risk primary prevention subgroups. There is a role for moderate and low-intensity statin therapy under certain circumstances.

The new risk calculators, the pooled cohort equations, are controversial and they probably do overestimate risk in the primary prevention population. They were not specifically generalized to the American Indian and Alaska Native population. However, we know that our service population has higher rates of atherosclerotic cardiovascular disease than other subgroups, and expert opinion even from within our own system favors use of the new risk calculators in determining risk and in making statin treatment decisions for primary prevention in our service population.

What about the American Diabetes Association? Let's transition to the 2014 Clinical Practice Guidelines from the ADA. The American Diabetes Association recommends annual screening of fasting lipid profiles for all diabetics except for those who are known to have a low-risk lipid profile. In those folks, they recommend testing every two years. Lifestyle modification, particularly dietary reduction of animal and synthetic trans fats is recommended for all diabetics. The American Diabetes Association supports the use of statins for cardiovascular risk reduction for both primary and secondary prevention among diabetics with other risk factors regardless of their baseline lipid levels. The ADA agrees with the American Heart Association in recommending against the addition of non-statin lipid agents to further reduce the risk of cardiovascular disease.

As with the American Heart Association Guideline, the ADA recommends statin therapy for all diabetics with known cardiovascular disease. This is the secondary prevention group and this is a "Class-A" recommendation. In the January 2014 ADA Guideline, the American Diabetes Association retained its "LDL less than 100" treatment target for diabetics including an alternate target of an LDL of less than 70 for those who have overt cardiovascular disease. In the secondary prevention group, the ADA still supports the LDL target of 70 or less.

The American Diabetes Association defines two diabetic primary prevention subgroups deemed candidates for statin therapy to reduce cardiovascular risk based on age and other factors. The ADA cardiovascular risk factors include both traditional risk factors as well as albuminuria. For diabetics over the age of 40 with one other risk factor as well as for diabetics under age 40 with multiple cardiovascular risk factors including albuminuria, statin therapy is recommended. The ADA has retained the "treat to the LDL target of 100" approach for primary prevention among diabetic patients, and as we mentioned, the alternate "treat to target" approach of an LDL of less than 70 for diabetic patients with known cardiovascular disease.

In comparing the current ADA Guideline with the American Heart Association Guideline for lipid management in our diabetic patients, there appears to be consensus between the two guidelines about the strength of data supporting statin therapy for both primary and secondary prevention of

cardiovascular disease. Both guidelines do agree that non-statin medication therapy provides no additional cardiovascular risk-reduction benefit for diabetic patients.

The guidelines differ in some respects over the treatment strategy. The American Heart Association Guideline advocating a fixed-dose statin approach based on the apparent clinical evidence that has been reviewed in this presentation. The ADA continues to support a "treat to target" approach.

I wanted to save some time at the end of this presentation for the next 10 or 15 minutes to entertain questions which you may have. I realize that there are some outstanding controversies with regard to this new American Heart Association Guideline, both with regard to the development of the new risk calculators for the primary prevention subgroup and also with regard to that so-called "paradigm shift." We're also familiar with the "treat to target" approach, the one that is still advocated by the American Diabetes Association, so the controversy with the new American Heart Association Guideline about sort of shifting from that approach to more of a fixed-dose strategy.

I want to point out that the reasoning that the American College of Cardiology and American Heart Association adopted that stance was that purely based on the science, based on the clinical information that was available from the various studies that were reviewed, the "treat to target" approach was not supported because there was no data to support it. Specifically, the studies that were conducted generally did not evaluate a "treat to target" approach; they evaluated a fixed-dose approach. That was the reasoning given by the expert panel on making that paradigm shift in terms of treatment strategy. So those are kind of the main controversies and I would be happy to entertain questions at this point. I'll ask our presentation moderators to kind of prioritize the questions.

Jan Frederick (moderator):

Dr. Clark, we do have a few questions. The first one came early in your presentation from Dolores from the Tucson area. "Are there current studies looking at populations that are not represented in the recommendation?"

Matthew Clark:

Okay. The question is, "Are there current studies looking at populations that are not represented in the AHA Guideline?" Is that correct?

Jan Frederick:

Yes.

Matthew Clark:

Essentially, the study data that has been reviewed not only by the guideline committee from the American Heart Association and American College of Cardiology, as well as by the Cochrane Database and the Cholesterol Treatment Trialists' meta-analyses which are very current. I mean that's data current through 2013. It generally looks at this population cohort that is largely African-American or Caucasian, middle-aged to elderly. It's not looking at other racial and ethnic groups. At least the expert panel from the American Heart Association pointed out the fact that this is an opportunity for further research.

The Strong Heart Study, which is not a contemporary study in that the data dates back to the '80s and '90s, is an excellent example of how the IHS can undertake to evaluate some of these issues in our specific service population. But unfortunately, even the experts from within IHS are saying that data is pretty dated.

I briefly referenced the fact that there's some data pending publication I didn't have access to because it's quarantined until it's published. It looks at some epidemiologic data within the American Indian and Alaska Native patient population. I'm told that the data may shed a little bit of light on cardiovascular disease-related events, particularly mortality. But it may be difficult to draw a conclusion about risk factors with regard to that mortality data.

Jan Frederick:

Thank you. Dr. Clark, there's another question. This one is from Deedee. She would like you to explain what are considered non-statin treatments that should not be combined with the statin therapy.

Matthew Clark:

Okay, let me talk a little bit about this issue. It's a very good question. I think what I want to make clear is that the new guideline from the American Heart Association specifically looked at statin therapy for the prevention of atherosclerotic cardiovascular disease. This was a departure from the previous Adult Treatment Panel Guidelines I, II, and III, which came from the National Heart, Lung and Blood Institute, which took a more comprehensive approach to lipid management.

That's really the issue when we're talking about non-statin treatments, specifically non-statin drug treatments. So we'd be talking about things like ezetimibe, which is brand named Zetia for instance, or the medications such as fenofibrate or Gemfibrozil, which are commonly used for triglyceride lowering as their primary purpose. Another example would be niacin.

It's not to say that these other medicines don't have a role, but at least from the standpoint of this particular guideline, there was not enough clinical evidence or not any clinical evidence, really, to support that they have a role in further reducing the risk of atherosclerotic cardiovascular disease for patients who are otherwise eligible for statin therapy. Let me kind of rephrase that. If the goal is to prevent heart attack and stroke, statin therapy is where the data lies. That's where the money is, so to speak. Non-statin therapies were not found to provide additional advantage with regard to those particular outcomes.

That's not to say that, for instance, persons with a very high triglyceride level who are at risk of pancreatitis, for instance, would not benefit from these other therapies. But in those instances, the other therapies are being used not to prevent atherosclerotic cardiovascular disease events, but rather to prevent some other clinical syndrome, the example given, pancreatitis. Hopefully, that clarifies that issue. I'd be happy to entertain a follow-up question if it does not.

Jan Frederick:

Thank you, Dr. Clark. There's a question from Darian. "I'm wondering if you know any new guidelines on restricting high lipid food? And then I guess that there's a related question, if you want to cover both of these questions, any good links?" This is from William, "Do you know of any good links on patient-centered education regarding heart-healthy nutrition?"

Matthew Clark:

First of all, I want to point out that the expert panel for the American Heart Association and American College of Cardiology Cholesterol Treatment Guideline made very clear that lifestyle modification, particularly dietary modification, should serve as what they called "background therapy". You can also use the term "foundational therapy" -- for all persons than the primary and secondary prevention subgroups. Even though this guideline for which the primary intent was to

examine the relationship between statin therapy and reducing cardiovascular disease events and adverse outcomes, the expert panel is very clear that lifestyle modification, particularly dietary modification are essential.

With regard to guidelines on that, I'm not aware of any published guidelines. As far as links, I think the best data, although it's mostly observational data, looks at, for instance, the "Mediterranean diet" in terms of lowering the bad fats and focusing on more intake of fruits and vegetables and whole grains, and some intake of Omega-3 fatty acids and so forth. The Mediterranean diet, I think, would be one example of an appropriate approach, and I'm sure there are others.