NCEP Guidelines in Action

**Dr Kwiterovich:** The new NCEP [National Cholesterol Education Program] guidelines were introduced more than a year ago. Have these guidelines changed the way physicians think about preventing coronary artery disease?

**Dr McKenney:** Yes, I believe we’ve seen a fundamental change in how physicians approach treatment. The overall prevention approach embodied in ATP [Adult Treatment Panel] I and II emphasized a “know your number” cholesterol strategy to determine the appropriate treatment. The new ATP III guideline now emphasizes a “know your risk” philosophy, and the treatment is now apportioned based on the amount of patient risk.

**Dr Kwiterovich:** As a reminder, what specific changes in management were advocated in the new NCEP guidelines?

**Dr McKenney:** The primary change involved the concept of “risk equivalents” in which the guidelines identify certain patients who have a future risk of coronary artery disease events equivalent to that of patients with clinical evidence of atherosclerotic disease. These risk equivalents included patients with carotid or peripheral vessel disease, who had been previously identified in ATP II, as well as all diabetic patients regardless of age and all patients with an estimated 10-year CHD [coronary heart disease] event risk of greater than 20% as determined by the ATP III Framingham-based assessment.

The second substantial change involved more refined risk stratification for patients without CHD or CHD risk equivalents but with 2 risk factors. The guidelines call for using the ATP III Framingham chart to identify patients at the highest level of risk and, therefore, in need of the most aggressive drug therapy in addition to lifestyle modification.

**Dr Kwiterovich:** On a practical level, have primary care physicians and internists been able to implement risk screening?

**Dr McKenney:** It is an extra hurdle because those physicians must change their office routine and go through the algorithm, but I believe it will become more intuitive over time.

**Dr Kwiterovich:** What about the new guidelines related to non-HDL [high-density lipoprotein] risk?
Dr McKenney: The guidelines also focus on triglycerides as a major risk factor. First, they recommend a bedside algorithm for identifying patients with the metabolic syndrome. These are patients at very high risk because of an atherogenic dyslipidemic pattern and multiple risk factors including obesity, glucose intolerance, and hypertension. In addition, to help identify and treat patients who don’t fit the exact metabolic syndrome profile, the guidelines call for treating residual hypertriglyceridemia after the LDL [low-density lipoprotein] is treated to goal levels. These goals are defined as “non-HDL cholesterol” and are meant to identify the remnant particles associated with risk. The non-HDL goal is 30 points higher than the LDL goal.

Dr Feldman: The concept of residual risk beyond LDL has helped physicians educate patients. Physicians who have already been very aggressive in lowering high-risk patient’s LDL below 100 [mg/dL] can tell these patients ‘Now that we have your LDL where we want it, we’re not done. We still need to raise your HDL and lower your triglycerides.’ This often translates into higher doses of statins, use of higher-potency statins, or combination therapy such as statins with nicotinic acid or statins with bile acid sequestrants and/or fibric acid.

Dr Greathouse: The concept of the metabolic syndrome is important, but I’m not seeing this concept gain acceptance among generalists. Certainly not like the concept that diabetes carries risk equivalent to that of a previous myocardial infarction. Why not? Do we lack the clinical evidence?

Dr McKenney: No, the NCEP guidelines include a substantial review of the evidence related to triglycerides, including, for example, critical literature from Austin, Krauss, Hodis, Sacks, and Brown. While the definition of metabolic syndrome in the clinic is always difficult, the guidelines do provide evidence-based information to guide treatment.

Dr Zhao: Our group will soon publish information from our HATS Study showing that patients with metabolic syndrome, even those with average LDL levels, had coronary disease progression at triple the rate of patients without metabolic syndrome. The rate of coronary events was more than doubled. This provides further evidence that metabolic syndrome is linked to more rapid atherosclerosis progression and worse outcome.

Dr Kwiterovich: Are the current cholesterol treatment goals realistic?

Dr Feldman: A goal of 100 mg/dL is approachable in a large segment of the population. In fact, I hoped for an even higher HDL goal and lower triglyceride goal, but I also realize it’s hard enough for patients to attain the current numbers. For those of us treating high-risk CHD patients, the lower the better for LDL — and the guidelines now support our efforts. To achieve these goals, however, we often require more than the starting doses of baseline statins; for example, we often need intermediate-to-high doses of statins, higher-potency statins, or the addition of bile acid resins and/or nicotinic acid. Beyond LDL, the general physician may have more difficulty in prescribing and maintaining treatment to achieve all 3 lipid goals. In this setting, the need for combination therapy is greater and compliance becomes an issue.

Dr Kwiterovich: So how can physicians do a better job of achieving the new lipid goals?

Dr Greathouse: We all need to rethink the concept of ‘1 risk factor equals 1 therapy.’ Physicians have expected too many results from statins used as monotherapy and that explains why so many patients are still not at goal levels. Also, patients are reluctant to go beyond the starting dose of statins because of fears of systemic toxicity. The fears may be well founded but in general they’re also overblown. Nevertheless, the physician then must explore combination therapy to meet LDL goals and to meet goals for the entire fasting lipid profile parameters. There are many tools available—fibrates, nicotinic acid, resin therapy — and we must be more willing to use more than 1 drug.

Nonstatin First-Line Therapy

Dr Kwiterovich: Patient conditions or special needs often determine the therapy choice for lipid treatment. What are the main considerations in choosing first-line therapy? For example, which patients should not receive a statin first?

Dr Feldman: Here’s a situation where statins probably should not be used first: a young woman in her 20s with extremely high cholesterol but with an otherwise low global risk assessment. Her cumulative lifetime risk may be high, but her absolute risk over the next 10 years is not. I would not prescribe a statin for this 20-year-old woman. I might consider lifestyle changes and/or resin therapy for her. Then, only if her numbers stay high as
she approaches perimenopause, I might consider low-dose statin therapy with an added resin.

**Dr Greathouse:** In the realm of primary prevention, any tools used to lower LDL cholesterol are appropriate—and if patients don’t want to be exposed to the risk of statins, then nonstatin options are valuable. On the other hand, in terms of secondary prevention, the overwhelming evidence of clinical benefit seen in large statin trials plus the evidence of pleotropic benefit with statins indicates to me that a statin—if it can be tolerated—must be at least the first building block of any combination therapy.

**Dr McKenney:** The guidelines recognize the statins as the workhorse, but the primary consideration is getting the LDL to goal levels. Any of the agents available to us, depending on the patient’s baseline level, are quite acceptable in that regard. Beyond LDL, other concepts and opportunities open up. Niacin, for example, can be used in a patient with a somewhat low HDL. A bile acid resin may be used in a patient with moderate LDL levels, someone not requiring a potent statin.

**Dr Zhao:** Also, a small percentage of the population has poor or no tolerance for a statin. Some patients will be symptomatic with muscle ache, but without elevated CPK [creatine phosphokinase], and the symptoms will often disappear if use of the statin is discontinued. So, alternative treatments should be explored for patients with poor tolerance of statins.

**Dr Greathouse:** This intolerance is not rare. Reports run from 10% to 30% of patients with suggestive myalgias affecting their ability to comply with statins. It’s a large number of patients. Of course, subjects treated with placebo in statin trials also have a high prevalence of myalgias.

**Dr Kwiterovich:** There are other reasons patients may not respond well to initial statin therapy, for example, interactions with other drugs. And what about the patients who don’t achieve target on initial therapy? Will the new NCEP targets only increase the size of this population?

**Dr Feldman:** Yes. By increasing the number of CHD-risk-equivalent patients who now have a target LDL of below 100 [mg/dL], we have naturally increased the number of people not at goal level. On an individual basis, of course, any of us here could manage such a patient aggressively with appropriate therapy and get them to goal level. But that’s not happening; aggressive treatment is not being incorporated into our practices.

**Dr McKenney:** And the Lipid Treatment Assessment Project [L-TAP] data show why it’s not happening. It’s because we’re not using potent statins, we’re not titrating statins sufficiently, and we’re not using combination therapy. These are the issues we need to address.

**Combination therapy**

**Dr Kwiterovich:** In terms of achieving LDL goals, is there evidence to help us decide between increasing the statin dose and adding a drug such as a bile acid sequestrant or niacin?

**Dr Feldman:** In medical school not long ago, physicians using combination therapy for hypertension were not considered higher-end academic physicians. And then, interestingly, JNC-6 [6th Joint National Committee Report] was published and showed us that low-dose fixed-combination therapy increased efficacy by physiologic synergy and reduced adverse effects. Then the diabetic world recognized that combination therapy makes sense synergistically. And now finally in the lipid world we’re seeing that most patients are not reaching goal levels on low-dose statins, so we’re adding a new drug like colesevelam, which has been shown to work nicely in combination with a low-dose statin. So the combination strategy of hypertension and diabetes is now working in lipid therapy for similar reasons: physiologic synergy and an ability to achieve goals with reduced overall adverse effects. The only downside might be increased costs as opposed to fixed-dose monotherapy.

**Dr McKenney:** One of the Seven Habits of Highly Successful People [by Stephen Covey, Simon & Schuster, NY] is to begin with the end in mind. I see more people trying to apply this habit in lipid therapy by selecting the starting dose that is most likely to achieve the goal—and not necessarily the established starting dose. Using a low-dose combination for initial treatment is another strategy. I think primary care physicians are moving in this direction.

**Dr Greathouse:** I agree were moving in that direction, but I’m not sure we have the data on how best to combine therapies. I think the general population would be most comfortable starting with a very low-dose statin, maybe even 10 mg or 20 mg, and combining this with a resin or less than 3 grams of nicotinic acid. But we don’t have any large studies yet.
In the HATS study, the average daily dose was 13 mg for simvastatin and 2 grams for niacin. The LDL was lowered from 130 mg/dL to 75 mg/dL, the HDL was increased from 31 mg/dL to 40 mg/dL, and there was a 30% triglyceride reduction as well. The rationale for combination therapy is to avoid each medication’s dose-related adverse effects and to take advantage of the different mechanisms of action.

Dr Feldman: I agree that with the new guidelines there are compelling reasons to consider combination therapy earlier in therapy, but we are limited to a degree by our package inserts and by the FDA, which has cautioned us in a variety of ways about combination therapy. Most physicians have received a phone call from the patient whose pharmacist told them that a statin and fibric acid combination was ‘very dangerous.’ True, we do have some combination approvals, such as low-dose simvastatin plus nicotinic acid, and we can use statins plus bile acid agents. But if we’re going to close this treatment gap with combination therapy, we must remove the regulatory restrictions and the related physician’s medicolegal concerns. For this, we need industry to present more data.

Dr McKenney: The concerns are mostly about the statin and fibrate combination.

Dr Feldman: That’s correct, but for many doctors, pharmacists, and patients the issue of combination therapy is complex, and they worry about any combination of lipid-lowering agents that might increase the risk of hepatitis, myositis, and rhabdomyolysis.

Dr McKenney: So we must clarify which combinations are safe. I think we also must educate our colleagues about the reproducibility of these additive effects. For example, with colesevelam or niacin you can expect a 10% to 15% reduction on top of the statin. On the other hand, doubling the dose of the statin will lead to a 6% or 7% further reduction. This is the type of information that will help physicians manage patients effectively.

Dr Kwiterovich: That’s an important point, because with the new guidelines more people should be treated more aggressively with LDL-lowering drugs, and there is a perception — and a small reality — that increasing the dose of a statin will increase the risk of adverse effects. An alternative concept for limiting the adverse effect potential is to combine a bile acid sequestrant with a low dose of statin. There is a synergistic lowering of LDL, with 1 drug working by bile acid absorption and the other working by limiting endogenous hepatic production and uptake of LDL cholesterol.

Dr Feldman: A recent Atherosclerosis publication reported on the pairing of colesevelam hydrochloride with atorvastatin. This study compared treatment with atorvastatin 80 mg, a high dose of one of the most potent statins, with 10 mg of atorvastatin plus 3.8 grams of colesevelam. To summarize, the researchers found the combination therapy produced results equivalent to those found with the high-dose statin monotherapy. So, in a way, you can convert 10 mg atorvastatin into 80 mg atorvastatin by using it in combination with colesevelam.

Dr Greathouse: This was a nice study not only because it showed how you can limit the exposure of certain patients, for example those with diabetes, to the highest doses of statins, but also because it provides a solid base for further combination therapy. From a regulatory and labeling standpoint, this is important because you want to remain at a very low dose of atorvastin or simvastatin if you’re eventually going to consider adding a fibrate or nicotinic acid. In other words, the colesevelam-statin combination allows you to keep the statin dose low, which gives you more leeway to consider a third-line drug to affect triglycerides or HDL levels. The low-dose colesevelam-statin combination allows for further steps, and that is a good way to keep building the system.

Dr Kwiterovich: How did the combination of bile acid sequestrant and statin affect the HDL and apolipoproteins?

Dr Feldman: In patients receiving the combination, HDL went up by 11% as compared to a 6% increase in the high-dose statin monotherapy group. The apolipoprotein A-1 [apo A-1] levels increased by 9% in patients receiving the low-dose combination, as compared to a 3% reduction in the high-dose atorvastatin group. Thus, the combination of colesevelam and low-dose statin yields an equivalent LDL reduction and greater increases in both HDL and apo A-1, as compared to high-dose statin. If the results are confirmed in larger trials, it could be recommended that combination therapy should be used instead of the high-dose fixed-dose statin to move all the lipid parameters in the proper direction.

Dr Greathouse: It’s also important to note that colesevelam in this study did not have the adverse effects on triglycerides that have been traditionally associated with resins. This suggests that colesevelam is
a unique product within the class. This lack of effect on triglycerides is a huge step forward, particularly for the diabetic population.

**The Inpatient Opportunity**

**Dr Kwiterovich:** The new NCEP guidelines call for immediate postdischarge cholesterol-lowering treatment for patients with coronary artery disease. Are hospitals achieving this goal?

**Dr Greathouse:** I can’t imagine any institution in 2002 not including statin therapy on the day of admission for any patient with acute coronary syndrome. With the Reduction of Cholesterol in Ischemia and Function of the Endothelium [RECIFE] trial and other studies we have objective evidence that such treatment can improve surrogate markers for endothelial function and vasodilatory effects and reduce recurrence within 6 weeks of discharge. All the information we have about this treatment strategy is positive.

**Dr Feldman:** I agree, and with the Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) trial we’ll have even more data. But now we need to incorporate this strategy into our continuing quality improvement processes. Just as we’re rigorous about quality standards for our surgeons and interventional physicians, we need to become rigorous about our primary care physicians and clinical cardiologists sending patients home with the appropriate medicines. Last year, Greg Fonarow published information on a thrombolytic registry evaluating TPA [tissue plasminogen activator] use and showed that only 31% of 131,000 patients with myocardial infarction were prescribed statins at time of discharge. Similarly, the Cardiac Swedish Intensive Care Unit Study showed that only about 5000 of 20,000 patients were prescribed statins at discharge—and that there was a dramatic reduction in mortality in patients treated with statins.

So we must short-circuit the excuses our colleagues use to avoid starting therapy at the time of discharge. We also must implement systematic instructional ways to prevent patients from ‘falling through the cracks’ because the interventional physician thinks the primary care doctor is prescribing the statin and the primary care doctor says ‘The clinical cardiologist didn’t prescribe statins.’ The American Heart Association program called “Get with the Guidelines” is an attempt to remedy the treatment gap. [www.americanheart.org/getwiththeguidelines/]

In our institution we have converted the AHA/ACC Guidelines into a 1-page form that takes about 15 minutes to complete. We’ve taken a more aggressive treatment approach with the approximately 130,000 inpatients and outpatients we see every year.

**Dr McKenney:** Are the new guidelines reaching beyond the cardiology departments of institutions? For example, is the neurologist who is managing the stroke patient aware of the postdischarge recommendation? What about the emergency department doctor?

**Dr Zhao:** That is exactly what the AHA “Get with the Guidelines” program is trying to achieve: to go beyond cardiology.

**Dr Feldman:** But we have a long way to go in risk-equivalent groups. Some neurologists now recognize that statins make sense, for example, but the comfort level is not high. It’s similar to cardiologists learning to prescribe antiepileptic drugs. The AHA program is aimed at this type of department-by-department education, reviewing the evidence and then taking responsibility for all the guidelines. It’s a long-term process to improve utilization of proven life-saving therapies such as aspirin, statins, beta-blockers, and ACE [angiotensin-converting enzyme] inhibitors. But that’s exactly the goal for what the AHA has called the ‘Decade of Prevention.’

**Elderly Patients**

**Dr Kwiterovich:** Results from the Heart Protection Study [HPS] were recently presented at the AHA meeting. This important study included about 20,000 English patients who ranged in age from 40 years to 80 years with cholesterol levels from 135 mg/dL to 270 mg/dL. Fifty percent of the patients received simvastatin 40 mg/day and 50% received a placebo; all patients were observed for approximately 5 years. Are there any comments on the potential clinical significance of this study?

**Dr Feldman:** This was an extraordinary prospective study in terms of subgroup analysis. There were approximately 13,000 patients with CHD, about 9000 patients with peripheral vascular disease, and more than 6000 diabetic patients—obviously, there was some overlap.

**Dr Kwiterovich:** What did the study show for the approximately 4000 elderly patients? Was there a treatment benefit?
Dr Greathouse: Yes, just as we saw in the Pravastatin Pooling Project and other large meta-analyses, the results of HPS showed that elderly patients have a benefit at least equal to that seen in younger patients. The numbers even suggest a larger benefit in the elderly group. As our population ages and as older people become more vital, this message is important. We can no longer withhold preventive therapy based on age.

Now, practically speaking, older patients do not tolerate higher doses of lipid-lowering drugs—particularly the statins. Therefore to obtain the clinical benefit that is clearly established, these older patients are prime candidates for low-dose combination therapy.

Dr Feldman: Several studies show that elderly patients do benefit more from lower-dose statins than they do from higher doses, particularly with the longer-acting statins. This relates not only to the general reduction in hepatic and renal function in elderly patients but also to the higher potential for drug-drug interactions due to the frequency of multiple medications in this age group. Thus, the low-dose fixed combinations may eventually prove to be particularly appropriate for elderly patients. Such a combination might allow us to be aggressive in treatment and yet avoid the higher doses of statins that are potentially problematic. However, we currently lack data for the elderly group.

Dr McKenney: The results of HPS are consistent with those of other clinical trials of lipid-lowering therapy. Prior studies documented the clinical benefit of lipid treatment in patients younger than 80 years; now the HPS has pushed the upper age where we have evidence of benefit to 85 years. This consistency of evidence is important because of the emphasis that the new guidelines place on age-related risk. My colleagues who are consultant pharmacists in retirement centers and nursing homes have already begun to respond to this challenge by recommending consideration of treatment for their patients, who have a mean age of 82 years. Keep in mind that many of these patients, including many who are institutionalized, are living active lives and appear to have good prognoses. For these patients, CHD risk assessment and consideration for treatment are warranted.

Dr Feldman: Yes, many of the elderly patients who are referred to us for complex coronary interventions have highly functioning brains, kidneys, and livers. These patients are vibrant and active members of the community and have grandchildren and great grandchildren. It's ludicrous to think that these patients, based on age alone, should not go home with a long-term risk modification plan and, perhaps, lipid-lowering medication. If they're young enough for coronary intervention, they're certainly young enough to receive appropriate medical therapy.

The more challenging case is the 75-year-old or 80-year-old patient (who will, based on actuarial tables, live to age 90) who has no coronary or vascular disease, no CHD risk equivalent, and lipid numbers that are above normal. How aggressive are we with that population?

Dr McKenney: Elderly patients with comorbidities that already affect quality of life present an additional challenge. In all these cases, medical judgement is required. One thing is clear: we are not treating this elderly population today. All the studies tell us that patients older than 80 years are at higher risk of having a CHD event and can benefit from cholesterol-reduction interventions—but these patients are not being treated.

Dr Greathouse: I agree that we're not aggressive enough in offering the therapy now. Even for the patient with comorbidities, it's incumbent upon us to offer lipid therapy. But older patients know what they want out of their last 5 years or 10 years of life, so this is a treatment decision which I believe can be handled best within the physician-patient relationship.

Dr Feldman: As shown by HPS, another reason for treating elderly patients was the dramatic reduction in stroke potential. Most people fear having a stroke even more than a heart attack. Also, in terms of limiting disability, institutionalization, and costs to society, stroke prevention is another major reason to treat elderly patients.

WOMEN

Dr Kwiterovich: The HPS also provides data on the single largest group of women observed prospectively in a study to date. The results confirm what we saw in the large statin trials from the previous decade: women receive the same benefit from lipid reduction as do men, and in some cases they receive more benefit. Note that the study, paralleling the new ATP philosophy, did not focus on lipid profiles as the endpoint in treating risk. In postmenopausal women with coronary disease, statins
now appear to be the treatment of choice versus hormone replacement therapy (HRT) for prevention. Based on the recent studies, is there a risk that HRT actually contributes to coronary disease?

**Dr Greathouse:** Based on results from trials such as the Women's Health Initiative, the WEST [Women's Estrogen for Stroke Trial], and to a lesser degree the HERS trial, it's clear that the estrogen-based protocols we've used traditionally for vascular health are absolute failures.14-16 These protocols are prothrombotic and produce many other adverse reactions. The new NCEP guidelines suggest that we should no longer use estrogen-based protocols for vascular health. Of course, estrogen therapy for symptomatic menopause or osteoporosis is a different matter, but estrogen should no longer be advocated for prevention of vascular disease.

**Dr Feldman:** More women die of heart disease than do men. In fact, it's by far the most common cause of death in women. The rewarding element of the HPS data is that as we continue to educate women, especially elderly women, about their cardiovascular risk, we finally have something to offer them in terms of cardiovascular protection.

**Dr Zhao:** But the message that postmenopausal women are at extremely high risk from heart disease is not being emphasized to female patients. Women are undertreated for cholesterol, which may be because we often compare a 50-year-old man to a 50-year-old woman. Biologically we should not make that comparison because we know that coronary disease accelerates in women during postmenopause and actually catches up in terms of risk to that of men.

**Dr Greathouse:** The additional challenge in treating some women is their desire to bear children later in life. This is an arena in which the idea that statins are the only valid therapy must be changed. It's a situation where nonsystemic therapy may be needed.

**Dr Kwiterovich:** Why do women have greater mortality rates from cardiovascular disease as compared to men?

**Dr Zhao:** Atherosclerosis enters a very rapid phase during the postmenopausal period. Women are also more prone to the metabolic syndrome.

**Dr Feldman:** Women also tend to be diagnosed later, often resulting in more comorbidities at the time of diagnosis. Why are they diagnosed later? First, because early in life women benefit from estrogen protection. Second, physicians still tend not to take women as seriously as they do men. For example, women undergo catheterization and intervention less frequently. And from an interventional perspective, women may be at greater risk because their arteries are smaller. From a pure geometric standpoint, smaller arteries with plaque have a worse prognosis.

**Dr Greathouse:** To a certain degree, the lateness of the diagnosis also represents a failing of our public health education on cardiovascular risk. While the American Cancer Society has done a wonderful job of raising awareness of reproductive carcinoma, many women remain unaware of their cardiovascular risk and don't bring their problems to the healthcare system early.

**Dr Feldman:** I spoke at an international women's day conference recently and asked the audience 'Which disease are you most at risk of dying from?' Over 200 of the 300 women in the audience said breast cancer. Only 60 women said heart disease. So awareness is definitely a key problem in getting women into medical facilities earlier. But when women are seen at a medical facility, the treatment is appropriate.

**Dr Kwiterovich:** Is it inherently more difficult to diagnose coronary disease in women?

**Dr Greathouse:** It can be more difficult because most women's hearts are smaller in size, and it's harder to discern ischemia in smaller hearts. If our imaging tests can be improved, this problem may become a thing of the past.

**Dr Feldman:** A recent study compared risk identification in women based on NCEP guidelines versus risk identification based on electron beam computerized tomography and calcification scoring. These investigators found no correlation between risk factors and the method of detection, so our guidelines for predicting risk in women may not be as effective as they are for predicting risk in men. We also know that the plain exercise test in women generates a high incidence of false positives and is no better than flipping a coin. So, we still have much to learn about the relative roles of the coronary lumen and the heart wall itself in predicting disease.

**Dr Kwiterovich:** Certainly, there is much we don't understand. But just as certainly we now have several large medical trials showing that cholesterol-lowering treatment benefits women as well as men. So our knowledge gaps should not be a reason for not treating women vigorously. Are there any special considerations in choosing the appropriate pharmacotherapy for women?
Dr Feldman: I remind the group that for premenopausal women of reproductive years, the statins are category X—not because the statins have ever been shown to be mutagenic or teratogenic, but only because we lack sufficient data. Thus, it’s prudent to be extremely cautious in this group. For example, in high-risk women you should ensure the adequacy of birth control. If a patient is planning on becoming pregnant, you should probably discontinue the statin therapy several months in advance of the pregnancy.

**Diabetic Patients**

Dr Kwiterovich: What data support the new NCEP inclusion of diabetes as a risk equivalent to coronary heart disease history?

Dr Feldman: The key study was done several years ago by Stephen Haffner who compared the rates of coronary events over a 7-year period in 2 patient groups: 1 group had a known history of coronary artery disease, and the other group had a history of diabetes but no coronary disease. It turns out that the risk of future cardiac-related events was equivalent in these 2 groups. This finding caused the American Diabetes Association to call for more aggressive cardiovascular prevention in patients with diabetes. And now we see the same recommendation in the NCEP guidelines.

Dr Kwiterovich: In these patients with diabetes, should prevention focus on the LDL or on the HDL?

Dr Zhao: I believe the LDL, HDL, and triglycerides should be addressed equally in the diabetic population. We know these patients typically do not have high LDL, but they do tend to have small dense LDL, low HDL, and high triglycerides. So lowering LDL is a good start, but diabetic patients will benefit most from the new NCEP emphasis on lowering triglycerides and increasing HDL.

Dr Kwiterovich: The LDL cholesterol reading can be misleading in many diabetic patients because of the presence of atherogenic small dense LDL particles. Sometimes the patient will have LDL cholesterol of 90 mg/dL and the apo B is still at 115, so they have more atherogenic LDL particles than meets the eye. Perhaps in the future, apo [apolipoprotein] B levels will provide a better marker of risk in these patients.

Dr Greathouse: I agree that the number of particles is very important in these diabetic patients. This may be 1 population where the expense of looking beyond LDL, whether it’s apo B or using the NMR [nuclear magnetic resonance] method to identify abnormal lipoprotein subclasses, will add a true medical benefit.

Dr Kwiterovich: In terms of treatment, the HPS seems to indicate that starting with a statin and then adding a second agent to get the HDL higher is appropriate.

Dr Feldman: The American Diabetes Association guidelines are similar.

Dr Zhao: That’s why we need studies that start with statins as the standard baseline therapy and then compare different combinations with the statins to see which produces the greater benefit in terms of HDL and triglycerides.

Dr Kwiterovich: Is there anything inherently more difficult about selecting lipid therapy for patients with diabetes?

Dr Feldman: Given that many of these patients are already on multiple drugs for diabetes and hypertension, the polypharmacy issue is always a huge potential problem. Some of these patients may already be taking 5 or 6 drugs each day. The cost and compliance issues can make treatment difficult.

Dr Kwiterovich: Are you saying it is more the sheer number or drugs being taken, and not the potential for interactions between the drugs, that is the problem?

Dr Feldman: Yes. The other clinical issue related to this population is how to define and manage the patient who is insulin resistant. How aggressive should we be in treating patients who do not fall into the metabolic syndrome category but who have a predominant amount of insulin resistance, glucose intolerance (blood sugars between 110 mg/dL and 126 mg/dL), and borderline lipid levels? Is this patient a CHD risk equivalent? I tend to treat these patients as such, but I haven’t seen much evidence-based medicine in this area.

Dr Greathouse: I believe that by using the current ATP guidelines you can tease out 1 or 2 major risk factors from this population and use the information to treat the patients aggressively.

Dr Feldman: Fortunately, the ATP III guidelines do allow for clinical decision making in determining the optimal target for patients. I now tend to consider the patient who is insulin resistant and doesn’t meet all the criteria for metabolic syndrome as a high-risk CHD equivalent.
CHILDREN AND ADOLESCENTS

Dr Kwiterovich: In considering heart risk in children and adolescents, let me remind the group that we may be missing an opportunity to identify high-risk individuals by evaluating the offspring of patients with coronary heart disease, myocardial infarction, angioplasty, and stents. If these offspring are in their 40s, 50s, or 60s, they should be screened—but this also raises the question of how early to begin screening and treatment.

Dr Feldman: What are the cutoffs for children and adolescents?

Dr Kwiterovich: High total cholesterol is defined as 200 mg/dL or higher; 170 mg/dL - 199 mg/dL is borderline. For LDL, 130 mg/dL or above is high and 110-129 mg/dL is borderline. Of course, if children have a family history of early coronary disease, then they definitely should be treated.

Dr Feldman: For those children requiring treatment, at what point do you consider switching from diet and exercise therapy to drug therapy?

Dr Kwiterovich: The NCEP pediatric panel recommends that in 2 situations medical therapy can be considered after 6 months to 12 months of diet therapy in a child older than 10 years: If LDL is 190 mg/dL or higher in a healthy child with no positive family history (more than 99.9% of children are below this level), or if LDL is 160 mg/dL or higher (represents the 99th percentile for this group) in a child with a positive family history of early coronary disease, or 2 or more other cardiovascular disease risk factors.

Dr Feldman: And what are the medication choices for children and adolescents?

Dr Kwiterovich: When the pediatric panel met in 1992 we lacked data on statins, so we recommended that only the bile acid sequestrants should be used. Since 1992 we have gathered some experience with statins, but there still is some concern about using statins in adolescents, particularly in female adolescents. Nevertheless, the FDA has approved lovastatin for use in both male and female adolescents with familial hypercholesterolemia. Also, the only bile acid sequestrants available in the early 1990s (cholestyramine and colestipol) were associated with significant constipation and flatulence, so compliance was a major issue. The new data with colesevelam hydrochloride indicate there are very few gastrointestinal adverse effects. This is encouraging, and it will be interesting to gather the needed efficacy and tolerability data on this new bile acid sequestrant in this young population.

Dr Greathouse: At what point should a patient younger than 18 years be referred to a center for lipid treatment? Can family practitioners treat these younger patients? Should they treat just to a certain point, for example with nonsystemic agents?

Dr Kwiterovich: It depends on the physician. Some practitioners will not feel comfortable using medications—particularly the statins—in children and adolescents, so this physician will obviously refer the patient. But if practitioners are interested and experienced in this area of lipid treatment, then they may do a very good job.

Dr Feldman: Based on my family’s history of dyslipidemia, I can tell you that I am experiencing what you are describing. Both my parents were hyperlipidemic and hypertensive, and yet my dad will soon be 86 years old and my mom will be 80 years old. You don’t have to die prematurely of cardiovascular disease. All the preventive measures can make a difference if you’re aggressive and compliant and under good medical care. And so when 1 of my sons, at age 10, had elevated cholesterol, we did all the nonpharmacologic points recommended in the guidelines: restricted television use, computer use, and video game use and encouraged him to be more active. Now, with a little added help from puberty, he’s not in the high-risk group.

Dr Kwiterovich: A drop of LDL levels of 15% to 20% during adolescence is not uncommon. Thanks for sharing your personal experience, which makes an excellent point about the value of aggressive and appropriate therapy for specific patient types. Thanks to the whole panel for your valuable input today.

REFERENCES

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