TREATING PATIENTS WITH GLUCOSE INTOLERANCE: LIFESTYLE INTERVENTION VERSUS PHARMACOTHERAPY

Dr Maciejko: Are there cases of glucose intolerance and fasting blood sugar levels between 110 and 125 in which you would consider using a pharmacologic agent, such as an insulin sensitizer (eg, rosiglitazone) or a blocker of gluconeogenesis in the liver (eg, metformin) as opposed to just hygienic intervention?

Dr Golden: I think that lifestyle modification should be attempted first. Recently published data from the Diabetes Prevention Program have shown lifestyle modification to be superior to pharmacologic therapy with metformin in preventing type 2 diabetes in individuals with impaired glucose tolerance (IGT). There are no specific recommendations regarding when to institute pharmacologic therapy in IGT because the data are just being published; however, with my patients who already have diabetes, I usually give them 3 months in which to try lifestyle modification. If that is not effective, I will quickly progress to pharmacologic therapy.

We may start doing this for impaired glucose tolerance as well, but there are not data yet to really direct us as to what we should do. However, I think because the lifestyle intervention arm showed such a significant benefit, everyone is going to recommend trying that first. The question will be how long should we wait after trying therapeutic lifestyle changes before we progress to pharmacologic intervention.

Most of the patients that have come to me with just impaired glucose tolerance have responded to weight loss interventions. However, for many of them, I end up doing a 2-hour glucose tolerance test just to confirm their diagnosis and I'd say the majority of them ended up having type 2 diabetes, based on the results of the oral glucose tolerance test. So then I end up using a pharmacologic intervention if the hemoglobin A1C is above the [American Diabetes Association] ADA target of 7%.

Dr Robertson: The whole metabolic syndrome has been legitimized to the extent that there is an [International Classification of Diseases, ninth revision] ICD-9 code now, 277.7 for that, and so that will allow us to place patients under therapy and actually provide medical supervision for that therapy, be it lifestyle intervention or a pharmaceutical intervention. So I think that has been a big step forward in recognizing that opportunity, but again it's a patient-by-patient decision.
TREATING DIABETIC PATIENTS TO ATP III GOALS

Dr Blumenthal: Is it more difficult to treat the diabetic patient to NCEP [National Cholesterol Education Program] ATP III [Adult Treatment Panel III] goal, compared with the general population?

Dr Golden: There are no data to suggest that treating the LDL [low-density lipoprotein], to a target less than 100 is more difficult in diabetics; they seem to respond equally well. I think what I've found to be more difficult is reaching the triglyceride and HDL-C [high-density lipoprotein cholesterol] goals, primarily because poor glycemic control is frequently contributing to hypertriglyceridemia and low HDL. But even with improvement in glycemic control, because the patients are still insulin resistant at baseline, it's very difficult to get the triglycerides under 150 mg/dL and the HDL above 40 mg/dL. So it usually requires multiple interventions to try to achieve that goal.

Dr Robertson: My greatest concern in LDL-C is whether or not it's an adequate predictor of treatment success. If you have a patient with a total cholesterol of 190 mg/dL and triglycerides of 340 mg/dL, obviously, their LDL-C will be below 100. But has that patient been adequately treated? In most cases the patient has not. The question is how do we best define our treatment goals for patients with diabetes—the calculated LDL-C level may be a misleading number.

Dr Blumenthal: Such patients will often have increased numbers of small, dense LDL particles. I think it will be interesting to see, now that there are more methods available to assess LDL particle density, whether that will begin to be taken into consideration more frequently. The LDL-C could be 90 or 100 or 110 mg/dL, and the number of small, dense LDL particles markedly increased, and so clinical management is a challenge. I think we need to correct all the players, the small dense LDL, the triglycerides, and the HDL-C, and try to get them all as perfect as we can.

One thing I might add is that the late Trudy Bush and I did an analysis looking at non-HDL cholesterol in comparison to LDL-C as a predictor of long-term events, published in the Archives of Internal Medicine in June 2001. One of the things Dr Golden mentioned was that the new guidelines say that when triglycerides are greater than 200, the non-HDL target should be 30 points higher than the LDL-C target. What we found, especially in women, is that non-HDL is a better predictor of cardiovascular and total mortality than LDL-C. I think the reason is the perfect example David gave, namely a person whose triglycerides are high and the calculated LDL is somewhat lower. Once you get triglycerides above 200, I think especially in the 300 range, the accuracy of the calculated LDL-C does diminish. Looking at non-HDL, which is a measure of very low-density lipoprotein VLDL, [intermediate density lipoprotein] IDL, and LDL—at least in our 19-year follow-up of the Lipid Research Clinic study where we had 4500 subjects—non-HDL was a significantly better predictor than LDL-C, particularly in women.

Dr Robertson: Well, of course, the non-HDL is extraordinarily cost effective in terms of its utilization. Your analysis, and others before that, have pushed me towards looking at that number in any patient with either metabolic syndrome or diabetes. I think that it is an easy check to make sure that we're on track with our treatment plan.

There is, however, an issue of concern for discussion. The American Diabetes Association stepped forward, along with the American Heart Association, several years ahead of the NCEP in recommending LDL below 100 mg/dL for patients with diabetes. At this juncture, the American Diabetes Association had stepped forward and said that an HDL goal is also a screening tool for recognizing high-risk patients, and also a therapeutic intervention target, which is not what ATP III suggests. So I think there are a lot of physicians out there very confused about whether we treat HDL or we diagnose with HDL.

FENOFIBRATE VERSUS GEMFIBROZIL

Dr Blumenthal: I had a question that maybe some of the other people on the panel are better equipped to answer. My impression is that fenofibrate seems to lower LDL-C more than gemfibrozil.

Dr Kwiterovich: There are some data from the European literature that indicate in a person who has high LDL-C, whether it's a type 2A or type 2B, that fenofibrate may be more effective. However, in patients who don't have high LDL-C, who may have primarily hypertriglyceridemia with low HDL-C, then I think that there probably isn't much of a difference between the 2 agents.

Dr Blumenthal: Dr Kwiterovich, do you have experience in following [apolipoprotein] apo B levels—not patterns, but levels—on the 2 agents?
Because I think that’s probably a more accurate way to follow fibrate therapy than the calculated LDL-C.

Dr Kwiterovich: I don’t follow the Apo B that much after I use it for diagnostic purposes. I think it would be interesting in the future to compare the non-HDL-C with an assessment of the mass of the small, dense LDL particles.

I know that one study used NMR [nuclear magnetic resonance] spectroscopy in over 4000 people from Framingham. Of course, they will also have the data available for the non-HDL cholesterol. Of interest, the investigators found that at the 80th percentile, or higher, for the level of small, dense LDL, one half of such patients would not be treated using NCEP guidelines. We certainly need additional research in this area, to make sure that we are adequately treating high-risk patients, particularly diabetics, who frequently have small, dense LDL particles. It is critical to distinguish between just the presence of small, dense LDL particles and increased numbers of small, dense LDL particles because it is the combination, of an increased number, of small, dense LDL particles that is particularly atherogenic.

Dr Maciejko: My impression regarding the efficacy of gemfibrozil versus fenofibrate for reducing triglycerides is that they are similar, and the issue with LDL concentration has to do more with the baseline level of triglycerides. When treating higher triglyceride levels, I do see a rise in the LDL-C concentration. Whether that reflects an increased number of LDL particles or an enrichment of the LDL particles with cholesterol ester is not clear at this point.

However, there is another important issue concerning the selection of a fibrate. The FDA [US Food and Drug Administration] brought this to my attention several weeks ago. In discussions about the cerivastatin withdrawal, due to excess deaths from rhabdomyolysis in individuals taking cerivastatin, many, but not all, of those patients were also taking gemfibrozil concurrently. Since the statins have become available, there have been over 750 cases of rhabdomyolysis reported to the FDA. Many of those cases have been in patients taking a statin with gemfibrozil. About 400 of those cases were in individuals taking cerivastatin with gemfibrozil.

I believe that the FDA feels that there is something unique to cerivastatin—particularly when used in combination with gemfibrozil—that is responsible for the high incidence of skeletal muscle side effects. It is my impression that the FDA will recommend that gemfibrozil not be used in combination with a statin. That would only leave fenofibrate to be used in combination with statins.

I know that fenofibrate and gemfibrozil pharmacokinetically rely on predominately the 3A4 isoenzyme of the cytochrome P-450 system, yet I think that the chemical structure of gemfibrozil, particularly when used with statins, predisposes individuals to higher risk of muscle side effects. Therefore, I think when selecting a fibrate for triglyceride reduction in a patient taking a statin, fenofibrate should be considered first. Also, I do not recommend using any more than the starting dose of a statin with fenofibrate.

Dr Blumenthal: That raises a question as to whether there may be interaction of gemfibrozil with other statins in patients that may have a certain genetic makeup, and that we don’t realize this because we haven’t looked for it. Perhaps in some patients, when we used gemfibrozil with another statin, it elevated the levels of those statins just as gemfibrozil did with cerivastatin. They found that gemfibrozil increased the levels of cerivastatin to a greater extent and it seemed to be contributing to the rhabdomyolysis. But perhaps it also happens in other patients using one of the different statins.

Dr Blumenthal: Dr Little, would you review the difference in the extent of coronary disease within diabetics versus nondiabetics. Some reports suggest there may be a greater incidence of plaque erosion in diabetics, as well as plaque rupture.

The bottom line is that patients with diabetes get premature coronary disease, they get extensive coronary disease, they have higher complications from their coronary disease, and they’re not as well treated with our procedural revascularization. So it’s a particularly high-risk, most difficult-to-treat group.

William C. Little, M.D.
**Dr Little:** Diabetics who present with coronary disease certainly have more extensive and diffuse coronary disease, involving the smaller vessels. The outcome in patients with diabetes, when treated with angioplasty or stenting, is not as good as it is in non-diabetic patients. They are more likely to have restenosis and other complications.

The mechanism of MI [myocardial infarction] may also differ. In nondiabetics, most MIs are triggered by plaque rupture and thrombus stimulation, based on a ruptured plaque. In diabetics, instead of rupture of the vulnerable plaque, erosion of atherosclerotic lesions occurs, stimulating thrombus. Some research suggests that is a more frequent pathogenesis of acute coronary syndromes in diabetics than in patients without diabetes.

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**THE IMPORTANCE OF AGE IN FRAMINGHAM RISK SCORING**

**Dr Blumenthal:** Do the Framingham risk scoring and ATP III address all areas that are critical in dealing with risk assessments? Is age so important at one end, so that you might overemphasize older people and underemphasize high-risk younger people?

**Dr Knapp:** The clinician's usual first question is about family history, and of course, that wasn't incorporated with the Framingham database in a way that can be used for risk assessment points. So that is one area that leaves room for improvement in the next iteration of ATP. If we're going to have scoring points for 10-year risk, certainly it's going to be hugely skewed one way or the other by family history; that's a major issue for a lot of us.

**Dr Robertson:** I see the Framingham analysis as an important piece of the puzzle and a step forward in that it allows a much more individualized assessment of patients, but I see the NCEP guidelines in general, only as a starting point. It's a public health policy statement. It's basically the minimum standard of care. It's just like with JNC VI [The sixth report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure], the maximum acceptable blood pressure is 140/90. Does that mean we never lower it below that? Not at all. It's a starting point, and it allows us, as practitioners, to introduce any relevant and additional information that should sway us towards more aggressive therapy, but create a minimum standard for all patients.

But I think the important message to the patients and to the practitioners, in general, is that every patient deserves an individual analysis. The old guidelines really didn't accommodate that.

**Dr Blumenthal:** I agree. Dr Scott Grundy published a paper recently that suggested that quantitative measures of coronary atherosclerosis could modulate the number of points you get for age. What Dr Grundy proposed is that if a 50-year-old man was in the top quartile for age and gender in terms of coronary calcification, the patient would get 10 points as opposed to 6. If that 50-year-old is in the bottom quartile for his age, he would get 2. And I think that's a reasonable way of doing it. Plus 4 points for a high score, and minus 4 for a lower coronary calcium score. Dr Grundy also proposed that if you have a positive stress test, you should probably add several points because your positive stress test may be due to obstructive disease or it may represent exercise-induced vasoconstriction or decreased coronary flow reserve, which also has prognostic value. So I think as we move further along and get more information, some of these more novel risk assessments will modulate the number of points given for age.

**Dr Kwiterovich:** In patients who might have inherited hypercholesterolemia, for example, a 35-year-old male with familial hypercholesterolemia, particularly with a family history, the risk over the next 5 years of having an event will be 25%. If this patient was 40, then the risk over the next 10 years will be 50%. So I think it's really important that physicians understand that there are particular groups of patients with very high LDL-C levels that are at very high risk of coronary disease and they need attention earlier in life. The Framingham risk score really is misleading under such a scenario. We should emphasize that if there are groups of people with inherited cholesterol problems, Framingham risk scoring is not sufficient.

**Dr Maciejko:** In fairness to the authors of the guidelines, this third issuance of ATP gives us the ability to use our clinical judgment more than previous editions. ATP III allows you to make the decision as to whether you want to target the LDL-C to 100 or below 100 in certain high-risk individuals. Another example of change is the therapeutic
lifestyle changes section. There are ranges now for carbohydrate and ranges for nonsaturated fats, which allow us to use our clinical judgment to tailor the diet to the needs of the patient: sugar-sensitive patients versus fat-sensitive patients.

**Dr Robertson:** The primary goal in ATP III is to establish an LDL less than 100 in a wider range of patients than we had previously considered - to stratify those primary prevention patients who don't reach this highest level of risk to additional levels of care. That whole concept, perhaps, is called into question. But we have to consider the fact that on the whole, as a nation, we don't consistently achieve therapeutic goals. As much as we'd like to think we've made great leaps and bounds, I think although this bar has been brought down some, if we are even exceeding 30% achievement of goals, we're generally establishing a high level of care. Within my own practice, patients who have diabetes and who, according to the current guidelines, all need to get their LDL-C below 100, generally still exceed that goal, even following 3 months of intervention. As intervention follows out to 3 and even 5 years, the prevalence of patients who have an LDL-C below 100 is not significantly improving. Approximately 50% of patients have LDL-C below 100, but there's still a substantial number of patients whose LDL-C barely stands under 100, and many who are well above 100. Hemoglobin A1c does gradually improve over time, and averages about 7% in our practice, but, again, where should we be going, and what is optimal care for these patients? That offers fodder for our continuing discussions.