

NEWS FROM THE AMERICAN HEART ASSOCIATION'S (AHA) SCIENTIFIC SESSIONS 2009

NOVEMBER 14 TO 18
ORLANDO, FLA.

In Statin Patients, Raising HDL With Niacin, But Not Reducing LDL With Ezetimibe, Decreased Plaque

In combination with statins, adding a medication that raises high-density lipoprotein cholesterol (HDL-C) was more effective in reversing artery wall plaque build-up and in reducing heart disease risk than adding a drug that lowers low-density lipoprotein cholesterol (LDL-C) researchers reported here.

According to an AHA news release, the study ARBITER 6-HALTS (Effect of Extended-release Niacin or Ezetimibe Added to Chronic Statin Therapy On Carotid Intima Media Thickness) found:

- Adding niacin to a statin improved HDL-C levels and significantly reduced arterial plaque build-up within 8 months, with further improvement seen at the end of the study (14 months).
- A second approach, adding ezetimibe (Zetia, Merck/Schering-Plough) to a statin, lowered LDL-C to a greater extent, but did not raise HDL-C. No overall effect on arterial build-up in the carotid arteries was observed.
- With ezetimibe, greater reductions in LDL-C paradoxically were associated with more arterial build-up, a result opposite to that expected.
- The incidence of major cardiovascular events such as fatal and nonfatal myocardial infarction (MI) was higher in the ezetimibe group versus the niacin group (5% vs 1%).

HALTS (HDL and LDL Treatment Strategies) was a prospective, randomized, parallel group, open-label, blinded endpoint study conducted at Walter Reed Army Medical Center in Washington, DC, and Washington Adventist Hospital in Tacoma Park, Md. It included 363 adults (80% male, average age 68 years) with or at high risk for atherosclerotic cardiovascular disease (CVD). All participants were on statin agents and their LDL-C was at the treatment goal of <100 mg/dL. HDL-C was <50 mg/dL for men and 55 mg/dL for women.

"These findings for ezetimibe are counter to the prevailing understanding of LDL-C—that lowering LDL results in slowing of the atherosclerotic process as has been convincingly shown for other classes of lipid modifying drugs, such as statins and bile acid resins," said Allen J. Taylor, MD, FAHA, in a news release. He is principal investigator of the study and director of Advanced Cardiovascular Imaging and the Lipid/Prevention Clinic in the Department of Medicine (Cardiology) at Washington Hospital Center in Washington, DC.

Earlier studies demonstrating the protective effects of

statins found strong associations between LDL reduction and the prevention of CVD. Consequently, many experts view LDL reduction as a way to measure whether a treatment will be useful. But HALTS researchers' findings "challenge the use of LDL reduction as a guaranteed surrogate for clinical performance, particularly for new clinical compounds, and in this particular case, ezetimibe," Dr. Taylor said.

Some Obese Individuals Perceive Body Size as OK, Dismiss Need to Lose Weight

Some obese people misperceive that their body size is normal and think they don't need to lose weight, according to research presented here. In the Dallas Heart Study of 5,893 people, researchers found that 8% of the 2,056 who were obese said they were satisfied with their body size or felt they could gain weight.

"Almost one in 10 obese individuals are satisfied with their body size and didn't perceive that they need to lose weight," said Tiffany Powell, MD, in an AHA news release. She is lead author of the study and a cardiology fellow at the University of Texas Southwestern Medical Center in Dallas. "That is a sizeable percentage who don't understand they are overweight and believe they are healthy."

According to the news release, participants included about 50% blacks, 20% Hispanics, and 30% whites, similar to other urban populations, Dr. Powell said. About half were women. African Americans (14%) and Hispanics (11%) were significantly more likely than whites (2%) to be satisfied with their body size and believe that they did not need to lose weight.

Those with a misperception of body size believed they were healthy. But 35% of them had hypertension, 15% had hypercholesterolemia, 14% had diabetes, and 27% were current smokers. These risk factors are similar to obese individuals who acknowledged they had a weight problem and needed to lose weight, Dr. Powell said. Overall, 2% to 3% of the study population perceived an above-normal body size as ideal. Compared with individuals who perceived their ideal body size as normal, those who perceived ideal body size to be above normal were more likely to be women, African American, and had higher body mass index, blood pressure and higher insulin resistance.

"Understanding and countering this misconception may be a novel and perhaps vitally important target for obesity prevention and treatment. Because many of these individuals believe they are healthier than they really are, they do not go to the doctor and thus community interventions will be needed," she said in the release. Dr. Powell also emphasized that her findings show that physicians need to talk with their obese patients about exercise and weight loss.

"The onus falls on us as physicians to determine who this population is and how to talk with them."

Secondhand Smoke Worse for Toddlers, Obese Children

Toddlers and obese children suffer more than other youth when exposed to secondhand smoke, according to research presented here.

“Secondhand smoke in children is not just bad for respiratory issues, as has been previously described by other researchers,” said John Anthony Bauer, PhD, the study’s senior co-author and principal investigator at Nationwide Children’s Hospital & Research Institute at Ohio State University in Columbus. “Our data support the view that cardiovascular effects of secondhand smoke in children are important, particularly for the very young and those who are obese. We had not investigated the impact of obesity in previous studies.”

According to an AHA news release, Dr. Bauer and colleagues recruited American boys and girls, including 52 toddlers (aged 2 to 5 years) and 107 adolescents (aged 9 to 18 years). The study included black, white and Hispanic children, including obese toddlers and adolescents. The researchers found:

- There was a link between the amount of secondhand smoke exposure and a marker of vascular injury in toddlers. This link was two times greater in toddlers who were obese.
- Obese adolescents exposed to secondhand smoke had two times the evidence of vascular injury compared to normal-weight adolescents.
- Toddlers had a four times greater risk of secondhand smoke exposure when compared to adolescents, despite having similar reported home exposures.
- Toddlers exposed to secondhand smoke had a 30% reduction in circulating vascular endothelial progenitor cells.

“The changes we detected in these groups of children are similar to changes that are well recognized risks for heart disease in adults,” Dr. Bauer said in the news release. “This suggests that some aspects of adult heart disease may be initiated in early childhood, where prevention strategies may have great long-term impact.”

NEWS FROM THE INTERNATIONAL DIABETES FEDERATION (IDF) 20TH WORLD DIABETES CONGRESS
OCTOBER 18 TO 22
MONTREAL

IDF President Calls for Concerted Action to Stop Diabetes Epidemic

Newly published data from the IDF show that the number of people with diabetes continues to grow unchecked. The figures reveal that, if action is not taken to change the path of the epidemic, the numbers of people with diabetes will be close to 440 million by 2030. At a press conference held at the close of IDF’s 20th World Diabetes Congress,

President Jean Claude Mbanya of Cameroon voiced his concern at the figures.

“We have just released the dismal news that some 285 million people live with diabetes today. Our data show that the low- and middle-income countries, where four out of every five people with diabetes will soon to be found, are bearing the brunt of the disease. The men and women most affected are of working age—the breadwinners of their families. Diabetes is now a development issue that threatens to undermine economies.”

Dr. Mbanya said that two burning issues in diabetes care will define his term of office. First, the need to ensure that people with diabetes receive the quality of care and informed instruction they need to best manage their disease and avoid its complications and, second, the need to stop people from developing diabetes in the first place.

The IDF President stressed the need to increase access to diabetes education so that people living with the disease can play an informed and central role in their own care, according to a news release.

“From the global perspective, many people with diabetes can find themselves alone on a path that can lead them towards complications, depression and early death. We will need to increase awareness and deliver health education to make sure that diabetes is detected early and to make sure that the newly diagnosed are guided along a path of treatment and informed self-care that empowers them to avoid or delay the potentially devastating consequences of the disease.”

IDF Releases Guidelines Seeking to Improve Diabetes Treatment Worldwide

The *IDF Global Guideline on Pregnancy and Diabetes* aims to set a global standard for the care of gestational diabetes and people with diabetes who become pregnant. Gestational diabetes is common and, like obesity and type 2 diabetes, is increasing in frequency throughout the world. The risk of developing diabetes after gestational diabetes is very high.¹

“This is the first [IDF] guideline on pregnancy. It is an important issue for IDF to address because of the growing number of women this now affects worldwide,” said Stephen Colagiuri, MD, Chair of the IDF Task Force on Clinical Guidelines and professor of metabolic health at the Institute of Obesity, Nutrition and Exercise at the University of Sydney in Australia.

IDF also released new *Guidelines on Self-Monitoring of Blood Glucose in Non-Insulin Treated Type 2 Diabetes* and *Oral Health for People With Diabetes Guideline*. “Both these guidelines cover important but often neglected areas of diabetes care,” said Dr. Colagiuri.

The *IDF Oral Health for People With Diabetes Guideline* rec-

ommends a focus on clinical care for people with diabetes, integrating not only diabetes, but oral health professionals. Poor oral health can negatively impact the lives of people living with diabetes and they need to be educated on how to not only manage their diabetes but their oral health. The guideline joins a list of IDF guidelines addressing core needs in diabetes.

The IDF *Guidelines on Self-Monitoring of Blood Glucose in Non-Insulin Treated Type 2 Diabetes* provides recommendations for people with diabetes and their health care professionals. Type 2 diabetes is responsible for 85% to 95% of all diabetes, and this guideline recommends that self-monitoring of blood glucose (SMBG) should be considered an ongoing part of diabetes self-management education. Another of its key recommendations is that SMBG protocols should be individualized to address each individual's specific educational/behavioral/clinical requirements and provider requirements for data on glycemic patterns and to monitor impact of therapeutic decision-making.

NEWS FROM THE 45TH EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES (EASD) ANNUAL MEETING

SEPTEMBER 29 TO OCTOBER 2, 2009
VIENNA

Glucose Targets and Diabetes Treatment

For patients with type 1 diabetes, who are generally very young at the time of diagnosis, there is clear evidence of a positive effect when blood glucose is lowered to a near-normal range. In contrast, the evidence for most type 2 diabetic patients is much less clear, wrote Andrea Siebenhofer-Kroitzsch, MD, from the Medical University Graz, Austria, in a press statement. Epidemiological studies in type 2 diabetes have shown an association between higher blood glucose values and higher incidence of severe diabetes related complications.¹⁻⁵ Even if this association is true, however, it does not guarantee that strict glucose lowering benefits patients with type 2 diabetes. Adherence to this strict regimen is demanding and often burdensome. Most patients would have to take a combination of two or more antidiabetic drugs and would need to prick their fingers several times a day to check their blood glucose and need multiple injections. And there is a risk that an overly intensive therapy might do more harm than good, Dr. Siebenhofer-Kroitzsch wrote.

Clinical relevance of strict glucose control: benefits and harm. Treating patients with type 2 diabetes to near-normal range means aiming to treat them to a level as close as possible to that of a nondiabetic patient. To date, seven large, long-term randomized controlled studies have tested whether more intensive glucose lowering strategies lead to

fewer complications in comparison to a treatment strategy with standard glucose therapy.⁶⁻¹⁴ When all available studies are combined into a meta-analysis, the results are as follows: The only benefit of a more intensive treatment was a reduction of nonfatal MIs, Dr. Siebenhofer-Kroitzsch wrote. Apart from that, the number of deaths could not be reduced by treating patients more intensively; one of the seven trials even had to be terminated early due to an increased death rate in the intensively treated group. No benefit was seen for any further patient relevant endpoint such as stroke, blindness, renal failure, amputation or quality of life.

So the benefit is not very great, Dr. Siebenhofer-Kroitzsch wrote. One can estimate that some 100 type 2 diabetic patients would have to be treated very strictly for several years to save one patient from an MI. And it comes with a price: one would have to accept a higher risk for hypoglycemia, which was at least doubled for patients in the intensively treated group. In addition, patients in the strictly controlled group put on more weight. It so far remains unproven that lowering blood glucose to approximate the normal range of a nondiabetic individual has an advantage over standard care. When the studies were examined in further detail, it could be seen that the best results were found for newly diagnosed and young type 2 diabetic patients without any severe complications. The intensity of blood glucose treatment should very much depend on the age of the patient, whereby younger patients might have greater benefits from strict blood glucose control. In contrast, for older patients less stringent values might be appropriate, Dr. Siebenhofer-Kroitzsch stated.

Properties of certain antidiabetic drugs. In addition, antidiabetic therapies differ in their effects and some of them appear to be more beneficial than others, even when the blood glucose level is decreased to the same extent.^{7,8} It does not suffice for an antidiabetic drug to lower blood glucose; the way it does so makes a difference, Dr. Siebenhofer-Kroitzsch said.

It makes more sense to treat high blood pressure or lipids. Most type 2 diabetes patients are quite old when diabetes is diagnosed and generally suffer from further comorbidities and have risk factors such as high blood pressure and high lipids as well. The main therapeutic aim of the treatment of type 2 diabetes is to reduce the rates of deaths and diabetes related complications like MI, blindness, renal failure or amputation. Dr. Siebenhofer-Kroitzsch wrote that a comparison of the potential effects that can be obtained by increasing the intensity of blood pressure and lipid therapy with statins shows that these treatments—easy to perform with a few side effects—are at least 50% more effective than a very complicated blood glucose treatment.

Self-management might be the key. Nevertheless there is good news: when patients participate in training courses

and practice self-management, severe hypoglycemic episodes can be minimized.¹⁵ Instead of paying more and more money for glucose related drug treatment, more emphasis should be placed on patient education to overcome the notorious problem of noncompliance with prescribed therapies, Dr. Siebenhofer-Kroitzsch wrote. Informed patients define their treatment goals themselves, choose their therapeutic strategies and are prepared to weigh risk and benefit of more or less tight glucose control on their own.

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977–986.
2. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med.* 2005;353:2643–2653.
3. Khaw KT, Wareham N, Bingham S et al. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med.* 2004;141:413–420.
4. Port SG, Boyle NG, Hsueh WA, et al. The predictive role of blood glucose for mortality in subjects with cardiovascular disease. *Am J Epidemiol.* 2006;163:342–351.
5. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2003;321:405–412.
6. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VIII. Evaluation of insulin therapy: final report. *Diabetes.* 1982;31:1–81.
7. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet.* 1998;352:854–865. [see comment][erratum appears in *Lancet* 1998 Nov 7;352(9139):1558].
8. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352: 837–853. [see comment][erratum appears in *Lancet* 1999 Aug 14;354(9178):602].
9. Abraira C, Colwell J, Nuttall F, et al. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. *Arch Intern Med.* 1997;157:181–188
10. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med.* 2009;360:129–139.
11. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358:2545–2559.
12. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study.[see comment]. *Diabetes Res Clin Pract.* 1995;28:103–117.
13. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358:2560–2572.
14. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care.* 2000;23:B21–29.
15. Samann A, Muhlhauser I, Bender R, et al. Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study. *Diabetologia.* 2005;48:1965–1970.

New Insights: Pathogenesis of Type 1 and 2 Diabetes

Type 1 diabetes is an autoimmune disease that develops against insulin-secreting pancreatic beta-cells. Lymphocytes invade the islet of Langerhans along the disease process; anti-beta-cell autoantibodies and T lymphocytes are detected in patient with type 1; and the disease only occurs in individuals carrying a restricted set of human leukocyte antigen genes and a long list of other gene variant modulating immune responses or beta-cell function.

Writing in an EASD press statement, Prof. Christian Boitard, Vice-President, EASD, said that proinsulin is a major autoantigen in the disease process, but other autoantigens are likely involved. Type 1 diabetes is a health challenge due to high incidence in northern countries and steadily increasing incidence in all countries under observation, disease onset at an age that is progressively decreasing, and the

absence of treatment other than palliative in the form of multiple daily insulin injections. Despite major advances in understanding immune mechanisms involved in type 1 diabetes, critical issues remain unanswered.

- What are the initial events triggering type 1 diabetes?
- How do viral infections and other environmental factors initiate or modulate the development of diabetes?
- Are defects in key regulatory immune cells part of the disease process?
- What are the epitopes of beta-cell antigens recognized by different T lymphocyte subsets?
- Can manipulation of T lymphocytes be a basis for immunotherapy?

Etiology. Mechanisms that initiate the failure of immune tolerance to beta-cells remain elusive, Prof. Boitard wrote, but type 1 diabetes is considered a multifactorial disease in which environmental factors concur with a highly multigenic susceptibility background. Impressive progress has been made in defining gene variants involved and their biological consequences. Epidemiological evidence suggests that environmental exposures that are likely to intervene early in development have a role in susceptibility. A metabolic signature of early changes is seen.

Pathogenesis. While proinflammatory T cells are key effector players, other T-cell subsets play a regulatory role in inhibiting the pathogenic immune response against pancreatic beta-cells. The long delay between the first indication of autoreactivity against beta cells, evidenced by the presence of autoantibodies, and the actual onset of diabetes suggests that regulatory mechanisms are controlling the destructive immune process. The predominant role of T lymphocytes in type 1 diabetes underscores the need for characterizing the beta-cell antigens and developing T-cell assays for human type 1 diabetes. Defining type 1-related epitopes is likely to be a prerequisite to further studies of the natural history of type 1 diabetes and to peptide-based strategies in immunotherapy of type 1 diabetes. Significant advances have been made in this field, he wrote.

Early diagnosis. There are obvious limitations in the use of autoantibody detection in the immunological diagnosis of type 1 diabetes. Following characterization of major epitopes recognized by T lymphocytes along the disease process, T-cell assays are currently developed but will need careful evaluation of their diagnostic accuracy.

Immunotherapy. Immunosuppressive approaches in diabetes treatment have not reached the milestone of clinical application. Progress is to be expected from vaccination-type approaches based on characterization of beta-cell autoantigens and epitopes recognized. Prof. Boitard concluded that expansion of regulatory lymphocytes is also being developed as an intermediate approach to restore the physiological tolerance of lymphocytes to beta-cell autoantigens. ■