



A publication for cardiovascular specialists, specifically practicing clinicians and primary care providers
Providing an update on interesting and informative recent publications highlighting cardiometabolic diseases

New Data on Intensive Glucose Control in Type 2 Diabetes Reported: Benefit or Harm?

Cardiovascular disease is the primary cause of death in persons with diabetes. There is increasing questioning whether intensive glucose control is beneficial or harmful to the risk of cardiovascular events, or may even increase mortality.

The VA Diabetes Trial of Glycemic Control and Complications in Diabetes Mellitus Type 2, also known as the VA Diabetes Trial, enrolled 1,791 U.S. veterans at 20 Veterans' Affairs Medical Centers. Among the participants: 97% were men; 16% were African-Americans; 16% were Hispanic whites; 62% were non-Hispanic whites with an average age at study entry was 60 years.

The patients were high risk with about 80% with hypertension; 50% with dyslipidemia; and 40% or more with prior cardiovascular disease. They were randomized to intensive or less intensive control. Data from the VA Diabetes Trial, at the American Diabetes Association's 69th Scientific Sessions, in New Orleans, June 2009.

It was noted that initiation of intensive control in the first 15 years after type 2 diabetes diagnosis reduced the risk of cardiovascular events, including mortality, but not initiation of tight control 16 to 20 years post diagnosis. Even more troubling was the actual increased risk of events with intensive control 20 or more years after diagnosis in this trial. The adverse events were increased by, but not all due to increased age.

On the other hand, these recent findings contrast those in VADT, reported in 2008, where intensive control did not have a statistically significant effect on reducing cardiovascular (CV) events. These more recent data suggest that although intensive control is appropriate in the first 15 years after diagnosis, it should not be initiated if the patient has longstanding diabetes for 20 years or more.

The research pointed to two factors – HDL levels and hypoglycemia levels – potentially affecting the risk of CV events. There was an 80% decrease in risk of CV events, including mortality, for every 10 mg increase in HDL above each individual's baseline, a 50% decrease in risk of a first primary CV event for every 10 mg. Also, interestingly, an increase in HDL for every 10 mg was associated with a 55% decrease in risk of all-cause mortality. Therefore, in patients with diabetes levels of HDL may have profound effects.

In the VADT, episodes of severe hypoglycemia may have some effect, related or causal, to CVD and mortality. Inpatients with severe hypoglycemia with a change in consciousness, there was an 88% increase in primary CV events and a three-fold increase in CV death.

The overall implications of these findings is that clinicians need to adjust A1C goals based on the individual patient, avoiding hypoglycemia, especially in older patients and those with longstanding diabetes over decades.

The DASH Diet May Prevent Heart Failure

DASH (Dietary Approaches to stop Hypertension) diet may be beneficial to prevent heart failure. A recent observational study published in the archives of internal medicine demonstrated the potential benefit of the DASH diet in preventing heart failure. (1). This diet, high in fresh fruits, vegetables, low fat dairy products, and whole grains has shown to be beneficial in lowering blood pressure, especially in African Americans. The latest data for a cohort of Swedish women with food intake patterns similar to those seen with the DASH recommendations noted a 51 percent lowering of heart failure when compared with those who had food patterns less like the DASH diet.

The study consisted of data for 36,019 women, age 48-83 based on a self-administered food frequency questionnaire in Sweden. A score was rendered based on how similar the dietary patterns were to the diet. After a seven-year follow-up, 443 women developed heart failure. A comparison of those with the lowest quartile-scores versus the highest quartile, revealed a 37 percent reduced rate of heart failure in those with DASH-like diets (rate ratio 0.63, 95% CI 0.482, 0.81). The apparent benefit of the DASH diet remained significant after multiple adjustments including age, physical activity, caloric intake, education, and family history of cardiovascular disease, smoking, hormonal use, hypertension, hyperlipidemia, obesity, and incident myocardial infarction. The apparent ability of the DASH diet to reduce heart failure may be linked to previously described benefit in lowering systolic blood pressure and/or possible novel mechanisms, including benefits on reducing LDL cholesterol, oxidative stress, and the estrogenic effects of phytochemicals.

Latest Data Describes Diabetes Prevalence and Therapeutic Target Achievement in the US

A recent report from the National Health and Nutritional Examination Service (NHANES) revealed new data on diabetes prevalence in their assessment of therapeutic targets in the United States (2). NHANES is conducted by the National Study of Health Statistics, Centers for Disease Control and Prevention, and uses multi-stage probability sampling design to obtain national data on the presence of multiple biometrics in Americans, including African Americans, Mexican Americans, and Whites. With increasing evidence of a potential epidemic of obesity in the US, it is expected that the rates of Type II Diabetes will become more widespread. Provisions will need to increasingly attempt to control multiple risk factors to avoid a tsunami of cardiovascular disease as the population ages and the extent of the impact of diabetes manifests itself on the health of the people in the United States. Approximately 80 percent of persons with diabetes will need medications to lower blood pressure, glucose and cholesterol levels with enormous impact on healthcare resources.

Data were analyzed for 17,306 participants in the NHANES from 1999 to 2006 for adults aged 20 years or more for prevalence of diabetes and achievement of glycemic, blood pressure, and cholesterol targets. The targets analyzed were glycosylated hemoglobin less than 7.0 %, blood pressure less than 130/80 mm Hg, and low-density lipoprotein (LDL) cholesterol less than 100 mg/dL. The prevalence of diagnosed diabetes increased from 6.5 % in the period 1999 to 2002 to 7.8 % from 2003 to 2006 ($P < .05$) with significant increases in women, non-Hispanic whites, and obese people.

A review of the data comparing various targets showed an improvement for a glucose control 43.1 % to 57.1 % ($P < .05$) for hemoglobin A1c <7 % and improvement in LDL <100 mg/dL from 36.1% to 40.5%. ($P < .05$). Nevertheless, overall although the percentage of persons achieving all three targets improved, they remained extremely low, increasing from 7.0% to 12.2%

The recent data confirms that with the increased incidence of diabetes, medical therapy appears to have some benefit but the achievements simultaneously of multiple goals of glycemic, blood pressure, and LDL targets remains problematic.

These data confirm that at the present time and beyond diabetes will continue as a prominent health concern with approximately 15 million Americans or 7.2 percent of the adult population diagnosed with diabetes.

An increase from 39.2% to 45.5% of the age-adjusted blood pressure control rate was significant in men and Mexican Americans in the 20 to 39 years age group but did not achieve overall statistical significance. Men, non-Hispanic blacks, and obese people achieved LDL adjusted target with a

significant increase in the adjusted proportion from 36.1 % to 46.5%. Statistical significance was not achieved ($P = .06$) by the age-adjusted percentage that reached the 3 target levels, with an increase from 7.0 % to 12.2%.

Unfortunately many low-income minority individuals lack knowledge regarding diabetes and the associated risks. Common misconceptions include the idea that Type II Diabetes can be cured and most do not recognize the hemoglobin A1C as an appropriate gauge of long term glucose control. A recent study in *Diabetes Care*, April 2009 confirmed these misunderstandings in a population of low-income minority patients. At Mount Sinai School of Medicine in New York, 151 people with diabetes were surveyed. 58 percent were Latino and 34 percent were African American. Most had annual incomes below \$30,000 and had diabetes for an average of 13 years with regular medical care. Fifty-six percent thought normal blood glucose levels were less than 200 milligrams per deciliter (mg/dL) and forty-two percent said glucose levels of 110 mg/dL were too low. Additionally, fifty-four percent noted they could “feel when their blood glucose levels were too high.” (3)

This study confirmed perceptions of lack of knowledge by many minority patients and the need to continue community.

Recent Heart Failure Guidelines Highlight A-HeFT

Recently the American College of Cardiology and American Heart Association updated guidelines on the evaluation and treatment of heart failure. The 2009 document was developed by the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) with input from the International Society for Heart and Lung Transplantation (4). The Heart Failure Guidelines cited latest evidence to help guide physicians. The above highlights included confirmation of the threshold of less than or equal to 35 percent left ventricular ejection fraction for the use of implantable cardio defibrillators (ICDs) for primary prevention. (Class I evidence level A). Also there were specific concrete recommendations for the first time for the use of a fixed-combination of hydralazine and isosorbide dinitrate for self-identified African Americans who are symptomatic on angiotensin-converting enzyme (ACE inhibitors), beta blockers, and diuretics. The strength of evidence is based on the African American heart failure trial (A-HeFT), which demonstrated significant improvement in survival and hospitalization. Another new recommendation is that “it is reasonable” to use RHYTHM or RATE-control strategy in patients with heart failure and atrial fibrillation. Furthermore, there are also new recommendations on when to use cardiac resynchronization therapy and a stronger warning against the routine intermittent infusions of inotropic agents in end-heart failure.

The 2009 guidelines update the 2005 ACC/AHA report. It reviews new evidence to incorporate the latest important trends in scientific research and clinical trials that affect patient outcome of quality and care.

Interventional cardiology remains concerned regarding the concept that bare-metal stents are less effective or safe versus drug-eluting stents in patients with myocardial infarction. A recent study gives some reassurance that in patients with ST-segment elevation MI primary percutaneous coronary intervention (PCI) can be done safely and effectively with drug-eluting stent. A report from the HORIZONS-AMI trial investigators randomly assigned 3006 patients with ST segment elevation MI to receive paclitaxel-eluting stents (2257 patients) versus identical bare-metal stents (749 patients). The two primary endpoints were the 12-month rate of target-lesion revascularization for ischemia and a composite safety outcome measure of death; reinfarction, stroke, or stent thrombosis. There was also a major secondary endpoint of angiographic evidence of restenosis at 13 months.

1. Levitane, et al. Consistency With the DASH Diet and Incidence of Heart Failure. *Arch Intern Med.* 2009; 169: 851-857.
2. Cheung, B, et al. Diabetes Prevalence and Therapeutic Target Achievement in the United States. *The American Journal of Medicine.* 2009; 122(5):443-453.
3. Mann, Poniaman, Levanthal, Halm. Misconceptions about Diabetes and its Management among Low-Income Minorities with Diabetes. 2009; 32:591-593.
4. Jessup M, Abraham WT, Casey DE Jr, et al. 2009 focused update incorporated into the ACCF/AHA 2005 guidelines for the diagnosis and management of chronic heart failure in adults with the 2008 focused update incorporated. *J Am Coll Cardiol* 2009; DOI: doi:10.1016/j.jacc.2008.11.009. Available at <http://content.onlinejacc.org/cgi/content/full/jacc.2008.11.009>.
5. Stone, Lansky, Pocock, et al. Paclitaxel-Eluting Stents versus Bare-Metal Stents in Acute Myocardial Infarction. *NEJ.* 2009; 360 (19): 1946-1959, intervention and education.

Use of Aspirin In Primary Prevention of Vascular Disease

It is well established that long-term antiplatelet therapy with aspirin reduces the risk of cardiovascular events in patients with established occlusive vascular disease. A meta-analysis of 195 randomized controlled trials of use of aspirin in 135,640 high-risk patients demonstrated a 22% reduction in the odds of a serious vascular event in patients taking aspirin for secondary prevention. This benefit clearly outweighs the risk of bleeding associated with aspirin use¹.

The role of aspirin in primary prevention of cardiovascular events is less clear.

Current guidelines recommend the use of aspirin for primary prevention of cardiovascular events in patients at higher risk of coronary heart disease especially those with an estimated coronary heart disease risk of greater than 10%.

A recent meta-analysis that was published in *JAMA* challenges the use of aspirin for primary prevention. The authors conducted a meta-analysis of serious vascular events and major bleeding in 6 primary prevention trials involving 660,000 person-years and 16 secondary prevention trials involving 23,000 person-years that compared long-term aspirin use versus control.

Aspirin use for primary prevention was associated with a 12% proportional reduction in cardiovascular events. Aspirin use also significantly increased major gastrointestinal and extracranial bleeding (0.10 versus 0.07% per year, $p < 0.0001$). The main risk factors for coronary heart disease were also risk factors for bleeding. The authors concluded that primary prevention of coronary heart disease with aspirin is of uncertain net value, as the reduction in occlusive event needs to be weighed against an increase in major bleeds².

1 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *Br Med J* 2002;324:71-86

2 Antithrombotic trials collaboration. *Lancet* 2009;373:1849-1860

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