Tight Glycemic Control with Intensive Treatment Reduces Macrovascular Events

Presenter: Joseph E. Thomas, MD, Yale University School of Medicine, New Haven, Connecticut

Data from clinical trials have shown significantly better cardiovascular outcomes in both type-1 and type-2 diabetes with tight glycemic control. An analysis of data from nearly 70,000 patients treated in “real-world” clinical practices confirms the benefit and suggests that early intervention with intensive treatment may reduce macrovascular risks.

Dr. Thomas and his colleagues conducted a retrospective chart analysis of 69,418 patients with diabetes from the Integrated Health Care Information System. Patients were stratified into four groups according to their index glycosylated hemoglobin (HbA1c) values:

- below 6%
- 6% to 7%
- 7% to 9%
- 9% or higher

Patients were monitored for an average of 27 months.

In the group of patients with HbA1c levels of 9% or higher at baseline, their levels of total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and triglycerides were higher and their high-density lipoprotein-cholesterol (HDL-C) levels were lower than those in the other groups. As expected, the use of oral antidiabetic agents and insulin was higher in those patients with poorer glycemic control.

Reporting the unadjusted incidence rate for acute myocardial infarction (MI), coronary artery bypass grafts, stroke, and a combination of these, Dr. Thomas said that all parameters were generally higher with increasing HbA1c levels except for stroke (Table 1). He explained that the team was unable to account for the lower stroke incidence, although he later added that transient ischemic attacks (TIAs) had been excluded.

After the researchers adjusted for baseline characteristics, the hazard ratios (HRs) for survival and acute MI, compared with a level of HbA1c below 6% at baseline, increased with worsening glycemic control (HR = 1.57 for HbA1c levels of 9% or above; P < 0.001). The same general pattern persisted for survival and CABG as follows:

- HR = 1.19 for an index HbA1c of 6% to 7%
- HR = 1.56 for an index HbA1c of 7% to 9%
- HR = 1.38 for an index HbA1c of 9% or more

With adjustments made for survival and stroke, however, the differences were not significant. The authors concluded that an elevated index HbA1c concentration was a significant risk factor for acute MI, CABG, and poorer survival. The data suggested that early intervention with intensive diabetes treatment might be able to reduce macrovascular risks.

**Table 1** Unadjusted Incidence Rates of Myocardial Infarction, Bypass Grafting, and Stroke per 1,000 Person-Years

<table>
<thead>
<tr>
<th>Index HbA1c (%)</th>
<th>AMI</th>
<th>CABG</th>
<th>Stroke</th>
<th>AMI/CABG/Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>16.5</td>
<td>4.4</td>
<td>63.3</td>
<td>76.5</td>
</tr>
<tr>
<td>6–7</td>
<td>18.2</td>
<td>6.0</td>
<td>65.0</td>
<td>80.5</td>
</tr>
<tr>
<td>7–9</td>
<td>21.6</td>
<td>6.9</td>
<td>63.8</td>
<td>81.7</td>
</tr>
<tr>
<td>≥9</td>
<td>20.6</td>
<td>6.9</td>
<td>48.1</td>
<td>65.2</td>
</tr>
<tr>
<td>Overall</td>
<td>19.4</td>
<td>6.1</td>
<td>60.0</td>
<td>76.0</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; HbA1c = glycosylated hemoglobin.

Mr. Alexander is a freelance medical writer living in New York City.
of their patients’ cholesterol levels were above targets, stated Dr. Farnier. The survey was funded by the Merck Schering-Plough Cholesterol Partnership.

The Fourth European Joint Taskforce guidelines, published by the European Society of Cardiology, recommend LDL-C levels below 2.5 mmol/L (97 mg/dL) as a target for patients with cardiovascular disease or diabetes, and they urge the more stringent target of less than 2 mmol/L (77 mg/dL) if feasible. This year the guidelines, released by the European Society of Cardiology and the EASD, recommend an even lower level—below 1.8 mmol/L (70 mg/dL)—for patients with both cardiovascular disease and diabetes.

More than 97% of cardiologists and 95% of diabetologists agreed that an aggressive approach to cholesterol level management is warranted when patients have diabetes and elevated LDL-C levels.

To what do diabetes specialists attribute the low rate of achieving LDL-C targets? Fifty-eight percent of respondents cited one or more of the following reasons:

- Statin monotherapy is not effective for getting at-risk patients to achieve their goal.
- Titrating statins requires time and multiple physician visits.
- High-dose statins entail risks.

Among cardiologists, 79% expressed reluctance to prescribe high doses of statins for these patients because of concerns over safety and side effects. In addition, 54% of diabetologists and 57% of cardiologists recognized the small cholesterol-lowering increment (6%) achieved by doubling statin doses. Most of the diabetologists (93%) agreed that a more successful strategy would be one that targets cholesterol absorption in the intestine and cholesterol production in the liver.

Attaining lower HbA1c levels with biphasic or prandial insulin in type-2 diabetes entails a trade-off in weight gain and hyperglycemia risk, according to the Treating to Target in Type 2 Diabetes (4-T) study. The 4-T trial also indicated that most patients usually need more than one type of insulin to achieve target glucose levels over the long term.

The rationale for the 4-T trial, said EASD discussant Dr. Roden, was that it is unclear which strategy of insulin treatment is most favorable for patients with type-2 diabetes who still produce insulin and exhibit hyperinsulinemia in the fasting state.

Increasingly, initiating insulin therapy will be in the hands of primary care physicians, stated Dr. Levy, who presented the protocol for the 4-T trial. In 4-T, 708 patients with type-2 diabetes from 58 centers in the United Kingdom and Ireland were randomly assigned, in an open-label fashion, to one of three Novo Nordisk regimens:

- twice-daily biphasic insulin (NovoMix 30)
- three-times daily prandial insulin (NovoRapid)
- once-daily basal insulin (Levemir) before bed, with an additional morning injection if necessary

The primary outcome was a change in HbA1c levels. Patients enrolled in the study had type-2 diabetes for at least one year, HbA1c levels of 7% to 10%, and a body mass index (BMI) not exceeding 40 kg/m². Only patients taking sulfonylureas (99% of patients) or metformin (96% of patients) or both were included.

Insulin titration was performed according to an online, single-algorithm trial management system. Patients were instructed about their doses and how to modify them between scheduled visits.

Presenting the 4-T findings, Dr. Holman said that 8.9% receiving the biphasic regimen, 4.2% receiving the prandial plan, and 17.9% receiving basal insulin needed a second insulin formulation. The requirement with basal insulin was significantly higher (P < 0.001) than with the other two regimens. Primary results are presented in Table 2.

A higher proportion of patients had HbA1c levels below 6.5% with prandial insulin (23.9% vs. 17.0% for biphasic insulin and 8.1% for basal insulin).

Weight gain was highest for prandial insulin, at 5.7 kg, compared with a gain of 4.7 kg with the biphasic regimen and a gain of 1.9 kg with the basal regimen.

Median doses were 0.53 units/kg per day for biphasic insulin, 0.61 units/kg for prandial insulin, and 0.49 units/kg for basal insulin.

The mean number of hypoglycemic events (for grade 2 or above) was significantly greater with prandial insulin (12.0) than with biphasic (5.7) or basal (2.3) insulin.

Dr. Roden recommended that patients with elevated HbA1c add basal insulin, even though they were taking maximal doses of metformin plus sulfonylureas, because “[basal] is as effective as biphasic and prandial insulin to decrease HbA1c, at least when HbA1c is 8.5% or below.” The rationale, he said, is that basal insulin allows more patients to achieve optimal HbA1c targets (6.5% or below) without grade 2 or grade 3 hypoglycemia. This was achieved by 79% of patients using basal insulin, by 53% using biphasic insulin, and by 44% using prandial insulin.

Dr. Roden added that long-term randomized controlled trials comparing different insulins and oral antidiabetes drugs, in terms of macrovascular endpoints, were still lacking to support a specific therapeutic regimen in patients with type-2 diabetes.

**Better Glycemic Control with Sitagliptin plus Metformin**

**Presenter:** Michael Nauck, MD, Head, Diabeteszentrum Bad Lauterberg, Harz, Germany
Meeting Highlights: European Diabetes and “Shaping a Healthy Future”

Used as an initial investigational therapy in combination with metformin (Glucophage, Bristol-Myers Squibb), sitagliptin (Januvia, Merck) provided significant and sustained improvement in blood glucose control and was generally well tolerated compared with metformin alone over one year.

Sitagliptin is a selective, once-daily dipeptidyl peptidase-4 (DPP-4) inhibitor that enhances the incretin system, thereby helping to regulate glucose by affecting beta cells in the pancreas. Sitagliptin is indicated as an adjunct to diet and exercise for improving glycemic control. When the single agent alone, in addition to diet and exercise, does not provide adequate glycemic control, sitagliptin is indicated in combination with metformin or a thiazolidinedione (TZD).

The combination is sold in the U.S. as Janumet in doses of sitagliptin 50 mg/metformin 500 mg and as 50 mg/1,000 mg.

The aim was to assess the longer term efficacy and safety of initial combination therapy with sitagliptin and metformin in a patients with glycosylated hemoglobin (HbA1c) values of 7.5% to 11% with diet and exercise. After completing an initial 24-week placebo-controlled phase (n = 1091), 748 patients with type-2 diabetes and mean baseline concentrations of HbA1c of 8.7% continued for an additional 30 weeks on their previously assigned active therapies.

![Sanofi-Aventis R&D: “Shaping a Healthy Future” Products in the Pipeline](image)

**Sanofi-Aventis R&D: “Shaping a Healthy Future”**

**Products in the Pipeline**

On September 17, 2007, Sanofi-Aventis held a research and development press conference in Paris, France, to highlight several pharmaceuticals that show promise in the areas of cardiovascular disease and diabetes. These agents are as follows:

- **AVE 5026.** A new ultra-low-molecular-weight heparin, AVE 5026 has shown efficacy and safety comparable to that of the company’s enoxaparin (Lovenox), an anticoagulant for preventing thrombosis.

- **Idraparinux.** Another antithrombotic agent, biotinylated idraparinux, is designed to target stroke prevention and systemic embolism in patients with atrial fibrillation. It has the potential to replace vitamin K antagonists.

- **AVE 0010.** Also known as ZP10, this glucagon-like peptide-1 agonist has shown encouraging results in preventing diabetes progression with a once-daily injection in a phase 2b study. A phase 3 program is scheduled for early 2008.

- **AVE 2268.** Phase 2b results are anticipated for this agent in the first half of 2008.

- **Dronedarone.** In the first half of 2008, results are expected from the phase 3 ATHENA study for dronedarone (Multaq), an antiarrhythmic agent.

- **Ilepaptin and NV1GF.** Other cardiovascular prospects include Ilepaptin and the first gene therapy for critical limb ischemia, NV1GF, in a phase 3 study. Submission is planned for 2010.

- **AVE 5530.** This cholesterol absorption inhibitor will be entering a phase 3 trial late in 2008.

- **Sitagliptin 50 mg/metformin 1,000 mg twice daily (n = 157)**
- **Sitagliptin 50 mg/metformin 500 mg twice daily (n = 148)**
- **Metformin 1,000 mg twice daily (n = 137)**
- **Metformin 500 mg twice daily (n = 122)**
- **Sitagliptin 100 mg once-daily (n = 106)**

After 54 weeks, 67% of patients who continued therapy longer than 24 weeks achieved the HbA1c goal of less than 7% with sitagliptin 50 mg/metformin 1,000 mg twice daily, compared with 44% of those receiving metformin 1,000 mg twice daily alone.

Target HbA1c goals were reached by 48% of patients with sitagliptin 50 mg/metformin 500 mg twice daily, 25% of patients taking metformin 500 mg twice daily, and 23% of patients receiving sitagliptin 100 mg once daily. In a subgroup of patients with HbA1c levels below 10%, the mean reduction in HbA1c was 3.1% with sitagliptin 50 mg/metformin 1,000 mg twice daily.

Dr. Nauck said: “It is promising that sustained glycemic improvements have been shown up to one year, including in the most severe patients, providing them with an effective and tolerable means of managing their type-2 diabetes.”

**Rimonabant.** Clinical research on the weight-loss agent rimonabant (Acomplia), already approved in Europe for obese patients with type-2 diabetes, is expected to explore combination therapies (metformin, sulfonylureas, and insulin). End-points include weight loss and other cardiovascular risk factors (e.g., serum glycosylated hemoglobin, morbidity, and mortality).

Although the FDA had issued an approvable letter for rimonabant in 2006, in June 2007 the Endocrinologic and Metabolic Drugs Advisory Committee unanimously rejected Sanofi-Aventis’ application for the indication of weight loss in individuals with a BMI of 30 kg/m² or higher or in those with a BMI of 27 kg/m² or higher when accompanied by at least one co-morbid condition.

FDA panel members voiced concern over increased psychiatric side effects, including suicidality, and asked for more longer-term safety data in larger populations. Although Sanofi-Aventis noted that psychiatric side effects were seen predominantly among individuals with histories of depression and stated that only patients without such histories and with very high cardiovascular risks would be given the agent, the panelists worried that other patients in whom added risks were not justified would gain access to it.

Rimonabant is approved in the European Union for obese patients with a BMI of 30 kg/m² or above or for overweight patients with a BMI greater than 27 kg/m² with associated risk factors such as type-2 diabetes and/or dyslipidemia. The product is contraindicated in those patients with ongoing major depression or patients who are using antidepressants.

A risk-management plan has been in place in every country since the drug’s launch, and this plan will be reinforced to increase the effectiveness of education to identify and treat appropriate patients who might benefit from rimonabant therapy.