CLINICAL INSIGHTS® IN Diabetes

ASSOCIATION BETWEEN STATIN USE AND DIABETES INCIDENCE AMONG PATIENTS AT HIGH RISK FOR TYPE 2 DIABETES: INSIGHTS FROM FIN-D2D

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MATREATMENT with statins has been linked to an increased risk for type 2 diabetes in several post-hoc evaluations of previous completed trials, leading to controversy regarding the risk/benefit profile of statin therapy for primary prevention in patients who are at low risk for developing cardiovascular (CV) events. A 2012 analysis of the JUPITER trial (Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) showed that the CV and mortality benefits of statin therapy exceeded the risk for developing diabetes among the JUPITER population as a whole (healthy individuals with no prior CV event or diabetes), as well as JUPITER participants at increased diabetes risk.  

Rautio and colleagues further the dialogue on this topic by examining whether statin treatment was associated with type 2 diabetes incidence and changes in glucose metabolism among patients in the Programme for the Prevention of T2D in Finland 2003-2008 (FIN-D2D). Subjects in this observational, prospective follow-up study were at high risk for developing type 2 diabetes and received lifestyle interventions (group or individual counseling sessions) over 1-year of follow-up.

Self-reported data from 2,798 subjects were analyzed; 484 (17.3%) subjects were using statins at baseline. The primary outcomes were type 2 diabetes incidence, and fasting and 2-h glucose measured at baseline and follow-up.

Findings at 1 year:

Type 2 diabetes developed among 7.5% (n=31) of subjects using statins at baseline vs 6.5% (n=126) of subjects not taking statins at baseline. The incidence of type 2 diabetes did not differ between groups (odds ratio, 1.17; 95% confidence interval [CI], 0.78-1.76; P=0.442). (See Figure at top of next column.)
Association Between Statin Use and Diabetes Incidence Among Patients at High Risk for Type 2 Diabetes: Insights from FIN-D2D

Continued

At baseline statin users were more likely to be older, male; had lower body mass index, diastolic blood pressure, total cholesterol, HDL-C, LDL-C; and had higher triglycerides, fasting glucose, and 2-h glucose vs nonusers.

*Deemed high risk based on their score on a modified version of the Finnish Diabetes Risk Score test


More on Statins and Diabetes Risk: Data from JUPITER

The JUPITER trial, published in 2008, was the first placebo-controlled statin trial to report an increased risk of developing diabetes among users of statin therapy.1 About JUPITER:

- Examined whether rosuvastatin treatment compared with placebo would decrease the rate of first cardiovascular (CV) events
- N=17,802 men aged ≥50 years and women aged ≥60 years with LDL-C <130 mg/dL, high-sensitivity C-reactive protein levels ≥2.0 mg/L, and no history of CV disease or diabetes
- JUPITER was stopped after median follow-up of 1.9 years due to “unequivocal benefit” of statin therapy vs placebo
  - Rates of the primary endpoint (composite of myocardial infarction [MI], stroke, arterial revascularization, hospitalization for unstable angina, or death from CV causes) were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively
  - 47% risk reduction in the combined endpoint of MI, stroke, or death from CV causes
  - 20% risk reduction in all-cause mortality
  - Small increases in physician-reported diabetes were noted in the rosuvastatin group (270 reports vs 216 reports in the placebo group)

A 2012 analysis provided additional information on the CV benefits and diabetes risks of statin therapy in the JUPITER population, showing that:2

- Risk of diabetes development among statin-treated patients appears limited to those with baseline evidence of impaired fasting glucose, metabolic syndrome, severe obesity, and elevated A1C
- The CV and mortality benefits of statin therapy exceeded the risk for developing diabetes, in the trial as a whole and also among patients at increased diabetes risk
- Statin use accelerated average time to diabetes diagnosis by 5.4 weeks

Rosuvastatin is not FDA approved for risk reduction of unstable angina hospital admission, CV death, venous thromboembolism, all-cause mortality, or diabetes.

Do the Benefits of Roux-en-Y Gastric Bypass Surgery Show Long-Term Durability?

Recent trials have examined the benefits of bariatric surgery with regard to remission and prevention of type 2 diabetes in obese individuals. Are these benefits durable? Findings from the SOS study (Swedish Obese Subjects) showed a type 2 diabetes incidence rate of 6.8 cases/1,000 person-years among obese subjects who received bariatric surgery (banding, vertical banded gastroplasty, or gastric bypass) compared with 28.4 cases/1,000 person-years in the usual care group over 15 years of follow-up. See Figure 3 on page 4 for more on SOS.

The current prospective study by Adams and colleagues focused on Roux-en-Y gastric bypass (RYGB) surgery in particular, and explored the weight loss and cardiometabolic benefits of RYGB among severely obese patients over 6 years of follow-up. Patients who sought and received RYGB (n=418) were compared with two nonsurgical, noninterventional control groups: control group 1 sought but did not have RYGB (n=417), and control group 2 was comprised of a random population-based sample without prior history of bariatric surgery (n=321).

The main outcome measures included weight loss, type 2 diabetes, hypertension, and dyslipidemia, which were compared between subjects who underwent RYGB and the control groups.

Results at Year 6 post-surgery:

Weight loss
Patients who underwent RYGB surgery had a 27.7% reduction in weight from baseline (95% confidence interval [CI], 26.6 to 28.9), with 96% maintaining >10% weight loss, and 76% maintaining >20% weight loss. Percent weight gain in control groups 1 and 2 was 0.2% (95% CI, -1.1% to 1.4%) and 0% (95% CI, -1.2% to 1.2%), respectively.

Diabetes remission
The rate of diabetes remission among surgical patients was 62% (95% CI, 49%-75%). In control groups 1 and 2, the rates of remission were 8% (95% CI, 0%-16%) and 8% (95% CI, 0%-13%), respectively. Remission odds ratios (ORs) were 16.5 (95% CI, 4.7-57.6; P<0.001) compared with control group 1 and 21.5 (95% CI, 5.4-85.6; P<0.001) compared with control group 2. See Figure.

Diabetes incidence
Diabetes incidence was 2% in the surgery group (95% CI, 0%-4%), compared to 17% in control group 1 (95% CI, 10%-24%; OR, 0.11; 95% CI, 0.04-0.34 for surgery group compared with control group 1; P<0.001) and 15% in control group 2 (95% CI, 9%-21%; OR, 0.21; 95% CI, 0.06-0.67 for surgery group compared with control group 2; P<0.001).

Additional cardiometabolic outcomes
Incidence and remission of hypertension and dyslipidemia values showed greater improvement for surgical patients compared with either control group.

<table>
<thead>
<tr>
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<th>Surgical group</th>
<th>Control group 1</th>
<th>Control group 2</th>
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<tr>
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<td>31%</td>
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<tr>
<td>High TG</td>
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Participants were primarily female (82%) and non-Hispanic white (96%); body mass index (BMI) was ≥35 kg/m² (mean BMI: 45.9 kg/m²).

*Defined as fasting blood glucose ≥126 mg/dL, A1C ≥6%, or use of antihyperglycemic medication
†Defined as resting blood pressure ≥140/90 mm Hg or use of antihypertensive medication
‡Considered present if fasting LDL-C ≥160 mg/dL, fasting HDL-C <40 mg/dL, fasting triglycerides (TG) ≥200 mg/dL, or use of lipid-lowering medication
§Remission defined as return to normal levels without reported medication use for the specified outcomes

Two classes of incretin therapies are currently available for treatment of type 2 diabetes: dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. The mechanisms of action for both classes is through increasing insulin secretion and decreasing glucagon secretion in a glucose-dependent manner; the GLP-1 receptor agonists also slow gastric emptying and increase satiety. How do these two incretins compare regarding treatment of type 2 diabetes?

In 2011, Pratley and colleagues reported 52-week data from a trial that explored treatment with the DPP-4 inhibitor, sitagliptin, and the GLP-1 receptor agonist, liraglutide, among subjects with type 2 diabetes and A1C 7.5%–10%. Participants had been receiving metformin ≥1,500 mg/day for ≥3 months; they continued metformin treatment and were randomized to sitagliptin 100 mg/day, or liraglutide 1.2 mg/day or 1.8 mg/day. The primary composite endpoint was A1C <7.0% with no weight gain or hypoglycemia. Other outcomes assessed included change in A1C, fasting plasma glucose (FPG), and weight,* and proportion of patients achieving A1C <7.0% (American Diabetes Association [ADA] target) or ≤6.5% (American Society of Clinical Endocrinologists [AACE] target).

Results at 52 weeks showed greater reductions in A1C, FPG, and weight* with the 1.2-mg and 1.8-mg doses of liraglutide vs sitagliptin. Liraglutide therapy was also more effective in allowing patients to reach ADA and AACE treatment targets.

Although liraglutide was superior to sitagliptin over 52 weeks, would this benefit continue over an extended treatment period? And, would outcomes improve for patients who were initially treated with sitagliptin if they were switched to liraglutide therapy?

The authors examined these hypotheses in a 26-week extension of the 2011 trial, in which sitagliptin-treated patients were randomized to liraglutide 1.2 mg/day (n=59) or 1.8 mg/day (n=63); subjects who initially received liraglutide retained their original treatment group assignment (n=124 in the 1.2-mg group; n=135 in the 1.8-mg group). The primary outcomes were safety and efficacy of switching therapies and of continuing liraglutide treatment; these efficacy and safety endpoints were identical to those used in the 52-week study.

Results at Week 78

Subjects switched from sitagliptin to liraglutide during 26-week extension

Reductions from Week 52 to Week 78 seen in

- A1C: Liraglutide 1.2 mg: 0.2% decrease (P=0.006); liraglutide 1.8 mg: 0.5% decrease (P=0.0001) (See Figure.)

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Switching from Sitagliptin to Liraglutide for Treatment of Type 2 Diabetes: Exploring Potential Benefits Continued

- FPG: liraglutide 1.2 mg: 14.4 mg/dL decrease (P=0.004); liraglutide 1.8 mg: 25.2 mg/dL decrease (P=0.0001)
- Weight: liraglutide 1.2 mg: 1.6 kg decrease (P=0.0001); liraglutide 1.8 mg: 2.5 kg decrease (P=0.0001)

After switching to liraglutide, the proportion of patients who achieved A1C <7.0% (ADA target) significantly increased: liraglutide 1.2 mg: P=0.005; liraglutide 1.8 mg: P=0.0026. A significant increase in subjects achieving the AACE target was seen only among those in the liraglutide 1.8-mg group (P=0.0117). There was also a significant increase in the percentage of subjects reaching the primary composite endpoint of A1C <7.0% with no weight gain or hypoglycemia: liraglutide 1.2 mg: P=0.0018; liraglutide 1.8 mg: P=0.0192.

Subjects receiving liraglutide for full 78-week treatment period

Reductions from baseline in
- A1C: liraglutide 1.2 mg: 0.9% decrease; liraglutide 1.8 mg: 1.3% decrease
  (See Figure.)

Subjects achieving ADA, AACE, and composite endpoint targets were met in both treatment groups.
- ADA (% meeting target): liraglutide 1.2 mg: 34.7%; liraglutide 1.8 mg: 12.0%
- AACE (% meeting target): liraglutide 1.2 mg: 51.2%; liraglutide 1.8 mg: 26.6%
- Composite endpoint (% meeting endpoint): liraglutide 1.2 mg: 27.7%; liraglutide 1.8 mg: 43.7%

Safety and tolerability profiles at Week 78 were similar to profiles seen during the first 52 weeks of the study: side effects were mild or moderate and most commonly related to GI issues, and 9-10% of subjects reported minor hypoglycemia. A slight increase in heart rate was seen at both 52 and 78 weeks; this increase was most evident among those who received the 1.8-mg dose of liraglutide.

*Sitagliptin and liraglutide are not FDA approved for weight reduction


Mortality Among Normal and Overweight/Obese Subjects With Diabetes: Data from a Pooled Analysis

Do mortality rates differ for normal vs overweight/obese patients with diabetes? Carnethon and colleagues analyzed data from five clinical trials to compare mortality rates among subjects who were normal weight with subjects who were overweight/obese at the time of incident adult-onset diabetes.

The study included 2,625 subjects (men and women aged >40 years who developed incident diabetes) from the following trials:1-5

- Atherosclerosis Risk in Communities (ARIC)
- Cardiovascular Health Study (CHS)
- Coronary Artery Risk Development in Young Adults (CARDIA)
- Framingham Offspring Study (FOS)
- Multi-Ethnic Study of Atherosclerosis (MESA)

Diabetes was determined as either fasting glucose ≥126 mg/dL or reported new use of oral antihyperglycemic medications or insulin at follow-up examinations. Incident diabetes was determined among subjects who were free from diabetes at baseline and met one of the above criteria.

Obesity categories were defined as follows: normal weight, body mass index (BMI) 18.5-24.9 kg/m²; overweight, BMI 25-29.9 kg/m²; and obese, BMI ≥30 kg/m².

Total, cardiovascular (CV; myocardial infarction, stroke), and non-CV mortality were the main outcome measures.

Results:
Among the trials analyzed, there were 449 total deaths during follow-up (18 causes of death were not classified).
- Death from CV cause: 178 deaths (6.8%)
- Death from non-CV cause: 253 deaths (10.4%) (See Figure.)

Across cohorts, 293 subjects (11.2%) had normal-weight diabetes. Normal-weight subjects had significantly higher total and non-CV mortality vs those who were overweight/obese. (See Figure at top of next column.)

- Normal-weight subjects (rate per 10,000 person-years):
  - Total mortality: 284.4
  - CV mortality: 99.8
  - Non-CV mortality: 198.1
- Overweight/obese subjects (rate per 10,000 person-years):
  - Total mortality: 152.1
  - CV mortality: 67.8
  - Non-CV mortality: 87.9

After adjustment for covariates (age, race, sex, education, waist circumference, total cholesterol, HDL-C, systolic blood pressure, and smoking), normal-weight subjects with diabetes had

- Significantly elevated total and non-CV mortality that was consistent across cohorts, although not always statistically significant: total mortality, hazard ratio (HR), 2.08 (95% confidence interval [CI], 1.52-2.85); CV mortality, HR, 1.52 (95% CI, 0.89-2.58); non-CV mortality, HR 2.32 (95% CI, 1.55-3.48).
- Higher mortality from all causes across sex, age, race, smoking subgroups vs obese/overweight subjects.


**Relationship Between DPP-4 Inhibitors and Cardiovascular Event Risk: Meta-analysis**

Dipeptidyl peptidase-4 (DPP-4) inhibitors are one of five drug classes recommended in the 2012 position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as add-on treatment to metformin for management of hyperglycemia. The position statement also stresses individualization of therapy and highlights the need to consider any established vascular complications that may be present in those with type 2 diabetes, as there is increased risk for CV morbidity and mortality in this population. This meta-analysis from Patil and colleagues provides insights into the effects of DPP-4 inhibitors on cardiovascular (CV) events, and is the first adequately powered study that shows a class-wide effect for DPP-4 inhibitors in decreasing CV event risk over long-term treatment (≥24 weeks).

Studies included in the meta-analysis (18 trials; N=8,544) were randomized, controlled trials comparing treatment with DPP-4 inhibitors (n=4,998) to another oral antihyperglycemic agent (n=3,546) for ≥24 weeks (median treatment duration: 46.4 weeks). Studies also included data regarding adverse CV outcomes associated with use of DPP-4 therapy. Development of adverse CV events* was the primary endpoint.

**Results:**
When compared with placebo or other oral antihyperglycemic agents, use of DPP-4 inhibitors conferred:
- Lower risk of adverse CV events: relative risk (RR), 0.48 (95% confidence interval [CI], 0.31-0.75; P=0.001)
- Lower risk of nonfatal myocardial infarction or acute coronary syndrome: RR, 0.40 (95% CI, 0.18-0.88; P=0.02)

DPP-4 inhibitor therapy demonstrated a similar risk of adverse events when compared with placebo, but showed a significantly lower risk when compared with metformin, sulfonylureas, and thiazolidinediones. Longer studies included in the analysis (≥52 weeks’ duration) also showed decreased risk of the primary endpoint vs control treatment.

*Defined as death from CV causes, nonfatal myocardial infarction or acute coronary syndrome, stroke and arrhythmias, and heart failure.


Visit NDEI.org for more on the ADA/EASD Position Statement on Management of Hyperglycemia in Type 2 Diabetes: click the Clinical Guideline link in the left navigation on the NDEI.org homepage.

More on DPP-4 Inhibitors for Type 2 Diabetes

Karagiannis and colleagues conducted a systematic review and meta-analysis of 27 studies to evaluate the efficacy of DPP-4 inhibitors for treatment of type 2 diabetes when compared with other antihyperglycemic therapies.

To learn more about the results of this study, download the May 2012 issue of *Clinical Insights® in Diabetes*!