LEARNING OBJECTIVES:
After reading articles in this issue of OnsiteInsight®, participants should be able to:
- Discuss the latest data on the efficacy and safety of oral and injectable antihyperglycemic treatments used as monotherapy or combination therapy for diabetes
- Describe the effects of antihyperglycemic agents on such parameters as A1C, FPG, hypoglycemia, beta-cell function, and disease progression
- Review the implications of new clinical evidence from latebreaking trials
- Discuss recent data on the proposed association between insulin use and cancer
- Review data for various agents in development for the treatment of diabetes

TARGET AUDIENCE:
This newsletter is designed for primary care physicians, internal medicine specialists, endocrinologists, diabetologists, cardiologists, and other healthcare professionals involved in the care and management of patients with diabetes and its complications and comorbidities.

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OnsiteInsight® provides important reviews of the latest clinically relevant research in diabetes. Some reports may discuss uses for products or devices that are not approved by the US Food and Drug Administration or appropriate regulatory body, or are investigational in nature. Such uses will be noted within the body of the article.

The data reported in this issue of OnsiteInsight® were presented during the American Diabetes Association 72nd Scientific Sessions from June 8-12 in Philadelphia, Pennsylvania. NDEI.org is reporting on data from the Scientific Sessions. This content has not been peer reviewed. Instances of unpublished data and off-label or investigational uses will be disclosed.

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ORIGIN: No Reduction in CV Events With Insulin Glargine and Omega-3 Fatty Acids

No Increased Cancer Risk Seen With Glargine

In the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, treatment with insulin glargine and omega-3 (n-3) fatty acids failed to meet the primary endpoint: reduction of cardiovascular events among patients with type 2 diabetes or those with IFG or IGT. Moreover, treatment with basal insulin glargine did not reduce the composite cardiovascular endpoint of nonfatal MI, nonfatal stroke, and death from cardiovascular causes.

Treatment with insulin glargine did, however, reduce the progression to diabetes in a subset of patients with baseline IFG or IGT. No increased cancer risk was seen with insulin glargine treatment.

ORIGIN is a randomized, double-blind trial with a 2X2 factorial design that enrolled 12,537 patients who were at high risk for CV events and who had IFG, IGT, or newly diagnosed diabetes. Via two arms, the study investigated whether insulin replacement therapy with insulin glargine targeting fasting normoglycemia (FPG ≤95 mg/dL) reduces CV outcomes more than standard approaches, and whether the addition of n-3 fatty acids reduces CV death.

Participants were randomized to receive insulin glargine or standard care. Those randomized to glargine added a once-daily injection of glargine and titrated the dose to a target FPG ≤95 mg/dL. Subjects in the standard care group who had diabetes managed glucose levels based on best-approached guidelines and their healthcare professional’s clinical judgment; those in the standard care group without diabetes were followed for diabetes development. Participants were also randomized to n-3 fatty acids or matching placebo. Follow-up was 6.2 years (median).

Novel Agents for Treating Type 2 Diabetes: Spotlight on SGLT2 Inhibitors

Several inhibitors of sodium-glucose co-transporter 2 (SGLT2) are in development for the treatment of type 2 diabetes. These agents work by inhibiting glucose reabsorption in the kidneys, which prompts glucose urinary excretion, leading to lowered levels of plasma glucose. Data were presented relative to the following SGLT2 inhibitors in development for treatment of type 2 diabetes (unpublished data):

Canafliglozin*

Robert R. Henry, MD, reviewed data from a 2-year crossover study (N=20 healthy subjects) demonstrating that a single, 300-mg oral canagliflozin dose before a meal lowers postprandial plasma glucose in healthy subjects via two mechanisms: increased urine glucose excretion and delayed oral glucose absorption.

Kaj Stenlöf, MD, PhD, shared data from a multicenter, randomized, double-blind, placebo-controlled Phase III trial conducted at 90 centers in 17 countries that compared canagliflozin (100 mg or 300 mg) vs placebo over 26 weeks among 584 subjects with type 2 diabetes inadequately controlled with diet and exercise. Canagliflozin in both doses demonstrated significant improvements in A1C, proportion of patients reaching A1C <7%, FPG, and 2-hr PPG at Week 26 vs placebo. Reductions in body weight and lipid parameters were also observed with canagliflozin; in particular, there was a significant increase in HDL-C.
ORIGIN  Continued from Page 1

Omega-3 Arm
Patients were given a 1-g capsule containing at least 900 mg (90% or more) of ethyl esters of n-3 fatty acids/day in a double-blind fashion. Primary endpoint: CV death; secondary endpoints: CV death, MI, or stroke; all-cause mortality; arrhythmic death.

Results:
No difference seen for n-3 versus placebo for for primary and secondary endpoint (Fig. 1). Neutral results were also seen for other outcomes, including MI, stroke, and revascularization.

TG levels were reduced by 14.5 mg/dL more among patients receiving n-3 versus placebo (P<0.001), without a significant effect on other lipid parameters. N-3 supplementation was well tolerated, with high adherence (88%) and follow-up (99%) at study end.

Glargine Arm
In the glargine group, the same treatment approach was used for people with and without type 2 diabetes. Evening glargine was added to 0 or 1 OAD and self-titrated to 1-2 units twice weekly to target capillary FPG ≤ 95 mg/dL. Metformin could be added to mitigate hypoglycemia. Primary outcomes: CV death, MI, or stroke; CV death, MI, stroke, revascularization, or hospitalized heart failure. Secondary outcomes included a microvascular composite (including doubling of serum creatinine, albuminuria progression), new type 2 diabetes, and all-cause death.

Results:
Similar rates of incident CV outcomes were seen for glargine and standard care (Fig. 2).

Analysis of additional outcomes found:
✦ No significant difference in cancer incidence between the two groups: HR, 1.00 (95% CI, 0.88-1.13; P=0.97) (For more on insulin and cancer risk, see The Latest on Insulin and Cancer Risk, pg 5.)
✦ The odds ratio for new diabetes (up to and including first OGTT) and diabetes diagnosed after second OGTT favored insulin: OR, 0.72 (95% CI, 0.58-0.91; P=0.006) and OR, 0.80 (0.64-1.00; P=0.050), respectively

Rates of severe hypoglycemia were 1.00 per 100 person-years in the glargine group versus 0.31 per 100 person-years in the standard group (P<0.001)—the investigators noted that the rate of severe hypoglycemia was consistent with that reported in other trials, including ACCORD, ADVANCE, UKPDS, and VADT. Median weight increased by 1.6 kg for glargine, while a 0.5-kg decrease was seen for standard care.

TODAY Trial: Treatment and Clinical Course of Recent-Onset Type 2 Diabetes in Youth
Philip S. Zeitler, MD, PhD, discussed design, interpretation, and implications of the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial, noting that the synergy between pubertal status and insulin resistance in this age group demonstrates why data from diabetes trials with adult populations are not always applicable to children/adolescents. Key data:1
✦ Among the total study population (N=699), 319 subjects (45.6%) reached the primary outcome of loss of glycemic control (A1C ≥8% for 6 months). Rates of failure among each treatment group were as follows:
  • Continued metformin monotherapy: 51.7% (95% CI, 45.3–58.2)
  • Rosiglitazone + metformin: 38.6% (95% CI, 32.4–44.9)
  • Metformin + intensive lifestyle-intervention program: 46.6% (95% CI, 40.2–53.0)
✦ No difference in mean A1C over time prior to treatment failure—subjects who did and did not reach failure had similar A1C levels
✦ Reduction in the percentage of overweight subjects in the lifestyle arm

<table>
<thead>
<tr>
<th>Number</th>
<th>Rate</th>
<th>HR (95% CI)</th>
<th>P for log rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3 (N=6,281)</td>
<td>Placebo (N=6,255)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death (primary outcome)</td>
<td>574</td>
<td>1.55</td>
<td>581</td>
</tr>
<tr>
<td>MI, stroke, CV death</td>
<td>1,034</td>
<td>2.92</td>
<td>1,017</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>951</td>
<td>2.57</td>
<td>964</td>
</tr>
<tr>
<td>Death from arrhythmia</td>
<td>288</td>
<td>0.78</td>
<td>289</td>
</tr>
</tbody>
</table>

Fig. 1

<table>
<thead>
<tr>
<th>Number</th>
<th>Rate</th>
<th>HR (95% CI)</th>
<th>P for log rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, or stroke (primary endpoint)</td>
<td>1.02 (0.94–1.11)</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>CV death, MI, stroke, revascularization, hosp’d heart failure</td>
<td>1.04 (0.97–1.11)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Microvascular composite</td>
<td>0.97 (0.90–1.05)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.98 (0.90–1.08)</td>
<td>0.70</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2
Novel Agents for Treating Type 2 Diabetes:
Spotlight on SGLT2 Inhibitors  Continued from Page 1

Peter P. Stein, MD, discussed results from a study that evaluated renal and nonrenal effects of canagliflozin on post-meal glucose excursion in a 4-period crossover study among subjects inadequately controlled on metformin (N=37). Canagliflozin 300 mg reduced both FPG and PPG in those with type 2 diabetes who were inadequately controlled on metformin. For subjects treated with canagliflozin on Day 2, an additional dose of canagliflozin 300 mg premeal on Day 3 provided a greater reduction in PPG vs placebo and canagliflozin 150 mg. No meaningful differences were observed in urinary glucose excretion when canagliflozin 300 mg was compared with placebo and canagliflozin 150 mg.

Tofogliflozin
Takashi Kadowaki, MD, PhD, shared results from a double-blind, randomized, placebo-controlled Phase II 12-week dose range finding study in patients with type 2 diabetes; 398 subjects were treated with diet and exercise, and a stable dose of metformin, or treated with diet and exercise alone, and randomized to tofogliflozin (in 2.5-, 5-, 10-, 20-, or 40-mg doses) or placebo. A statistically significant dose-dependent A1C-lowering effect was observed after 12 weeks of treatment for tofogliflozin 5 mg to 40 mg vs placebo. Tofogliflozin was well tolerated and associated with weight reduction.

Dapagliflozin
Elise Hardy, MD, reviewed data from a pooled analysis of Phase III clinical trials of subjects with type 2 diabetes (N=1,379) receiving dapagliflozin (2.5 mg, 5 mg, or 10 mg qd) or matched placebo for 24 weeks:
✦ Greater urinary glucose excretion was observed with higher baseline A1C
✦ Greater A1C reductions were observed with higher baseline A1C categories
✦ Change in body weight was not associated with baseline A1C
✦ Trend observed toward association between blood pressure change and A1C

Several posters also discussed SGLT2 inhibitors in development.

Data from the ILLUMINATE study* showed that when added to metformin in Japanese patients with type 2 diabetes, ipragliflozin* significantly reduced A1C levels vs placebo over 24 weeks; reductions in body weight with ipragliflozin therapy were also seen. (Goto K, et al. Ipragliflozin reduces A1C and body weight in type 2 diabetes patients who have inadequate glycemic control on metformin alone: ILLUMINATE study. Poster 1046-P.)

A study that examined the safety and efficacy of empagliflozin* as monotherapy or add-on to metformin showed sustained glycemic control and weight loss over 78 weeks. Treatment with empagliflozin did not result in an increase of hypoglycemia events or adverse events related to urinary tract infection. However, more adverse events related to genital infection were seen with empagliflozin. (Woerle HJ, et al. Safety and efficacy of empagliflozin as monotherapy or add-on to metformin in a 78-week open-label extension study in patients with type 2 diabetes. Poster 49-LB.)

A study examining luseogliflozin* in Japanese patients with type 2 diabetes showed decreases in A1C, FPG, PPG, and body weight across 1-, 2.5-, 5-, and 10-mg doses vs placebo, with similar decreases seen at 2.5 mg doses or higher. No hypoglycemia was observed; there were mild pollakiuria or urine output increases seen that were mild in severity. (Seino Y, et al. Luseogliflozin (TS-071), a selective SGLT2 inhibitor, improves glycemic control and lowers body weight in Japanese patients with type 2 diabetes mellitus.)

*Agent not FDA approved for the treatment of diabetes.
TODAY  Continued from Page 2

✦ Half of those on metformin had loss of glycemic control (median time: 11 months)
✦ Addition of rosiglitazone reduced loss of glycemic control by 23%
✦ Overall failure rates were greater among boys (48.2%) vs girls (44.3%)

Implications: metformin monotherapy is inadequate for nearly half of youth with type 2 diabetes; the role of intensive lifestyle in youth with type 2 diabetes is uncertain; nearly half of youth with type 2 diabetes maintained long-term control, irrespective of treatment; and gender and racial differences suggest the need for therapy individualization.

Sonia Caprio, MD, discussed new, unpublished data from TODAY pertaining to insulin sensitivity and secretion over time among 674 subjects who had baseline and follow-up OGTT; all data were for subjects prior to treatment failure. Insulin sensitivity, beta-cell function, and oral disposition index at baseline were comparable between groups. At 6 months, there was a 20% increase in insulin sensitivity in the rosiglitazone + metformin group vs the other treatment groups; at 48 months, the groups were similar. Beta-cell dysfunction had a slower rate of decline in the rosiglitazone + metformin group vs metformin alone or metformin + intensive lifestyle intervention.

Distribution of treatment assignments across control groups:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Maintained treatment (%)</th>
<th>Failed Treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin monotherapy</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>Rosiglitazone + metformin</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>Metformin + intensive lifestyle intervention</td>
<td>35</td>
<td>34</td>
</tr>
</tbody>
</table>

Significant differences were observed for race:

<table>
<thead>
<tr>
<th>Race</th>
<th>Maintained treatment (%)</th>
<th>Failed Treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>27</td>
<td>38</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Neil H. White, MD, CDE, provided an overview of the burden of comorbidities that occurred among the TODAY cohort, noting that comorbidities start early in the course of type 2 diabetes, and long-term follow-up is needed. Findings included:
✦ LDL-C: no difference between groups in rate of dyslipidemia
✦ Triglycerides: no difference between groups
✦ Echocardiography results: above population median levels; data showed that subjects have large hearts
✦ No subjects had macular edema or proliferative retinopathy
✦ Occurrence of comorbidities within 2-6 years of diagnosis included
  ● CV risk factors: dyslipidemia, 10-30%; hypertension, 34%
  ● Nephropathy-HTN; microalbuminuria: 17%
  ● Nonproliferative diabetic retinopathy: ~14%

Note: only metformin and insulin are currently FDA approved to treat youth with type 2 diabetes. Rosiglitazone was used in TODAY as an investigational agent with an IND from the FDA


A poster featuring data from the SEARCH study further underscores the clinical impact of diabetes in youth. Based on 2009 estimates from five SEARCH centers, prevalence of type 1 or type 2 diabetes was 2.2/1,000 overall. Prevalence of types 1 and 2 diabetes increased with increasing age; type 1 was more prevalent among minorities. There has been an increase of at least 21.7% in the total number of youth with diabetes from 2001 to 2009, highlighting the impact of this public health problem. (Hamman RF, et al; for The Search for Diabetes in Youth Study Group. Estimates of the burden of diabetes in United States youth in 2009. Poster 1369-P.)
Latebreaking Data from EASIE, EUREXA, DPPOS

As part of a joint symposium from the American Diabetes Association and The Lancet, data from three latebreaking clinical trials—EASIE, EUREXA, and DPPOS—were presented.

EASIE

The Evaluation of insulin glargine versus Sitagliptin in Insulin-naïve patients (EASIE) study is a multicenter, randomized, parallel, open-label trial that examined efficacy, safety, and tolerability of insulin glargine vs sitagliptin among insulin-naïve patients with type 2 diabetes uncontrolled on metformin.

Subjects (aged 35-70 yrs, type 2 diabetes ≥6 months, A1C >7 and <11%, BMI 25-45 kg/m², insulin naïve) were randomized over 24 weeks to:

✦ Insulin glargine (titrated from initial subcutaneous dose of 0.2 units/kg body weight to attain FPG 4.0-5.5 mmol/L) + metformin; n=250
✦ Sitagliptin (100 mg qd oral dose) + metformin; n=265

Results for the primary outcome, change in A1C from baseline to Week 24:

✦ Greater reduction in A1C was observed for glargine vs sitagliptin (-1.72% vs -1.13%)

<table>
<thead>
<tr>
<th></th>
<th>Insulin glargine (n=227)</th>
<th>Sitagliptin (n=253)</th>
<th>Mean difference (95% CI); P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean reduction in A1C</td>
<td>-1.72% (0.06)</td>
<td>-1.13 (0.06)</td>
<td>-0.59 (-0.77 to -0.42); &lt;0.0001</td>
</tr>
</tbody>
</table>

✦ 41% of glargine-treated subjects had A1C <6.5% vs 18% of sitagliptin-treated subjects. Glargine was 1.6 times more likely than sitagliptin to achieve A1C <7% and 2.5 times more likely to achieve A1C <6.5%
✦ A slight increase in weight was seen with glargine, and a slight decrease was observed with sitagliptin (1.51-kg between-group difference; P<0.0001)
✦ Among subjects in the safety analysis, symptomatic hypoglycemia occurred among more subjects receiving glargine vs sitagliptin (mean difference, 8.45 [95% CI, 5.55-12.87]; P<0.0001). Both severe symptomatic and severe nocturnal hypoglycemia were rare in either group.
✦ There were no differences in adverse events between the treatment groups; serious treatment-emergent adverse events occurred in 6%
Latebreaking Data from EASIE, EUREXA, DPPOS Continued from Page 5


EUREXA
European Exenatide (EUREXA) is an open-label, randomized, controlled trial comparing add-on exenatide with glimepiride for durability of glycemic control among subjects with type 2 diabetes not adequately controlled with metformin monotherapy. EUREXA is currently the longest randomized, controlled GLP-1 study.

Subjects (aged 18-85 yrs, A1C ≥6.5% and <9%, BMI ≥25 to <40 kg/m²) were randomized to exenatide bid (n=490) or glimepiride qd (n=487), both as add-on therapy to metformin, and were stratified by A1C into the following groups: ≤7.3%; 7.3% to ≤8.2%; and >8.2%.

Primary outcome: time to inadequate glycemic control (A1C >9% after the first 3 months of study treatment, or >7% at two consecutive study visits 3 months apart after the first 6 months). Results over average treatment time of ~2 years:

- Mean exenatide dose: 17.35 μg/day; mean glimepiride dose: 2.01 mg/day
- 41% (n=203) of exenatide-treated subjects had treatment failure vs 54% (n=262) of those in the glimepiride group (risk difference, 12.4%, 95% CI, 6.2-16.6)
- Time to treatment failure was longer among exenatide-treated subjects vs those treated with glimepiride (180 weeks vs 142 weeks, respectively; P=0.032)
- Exenatide was associated with lower A1C levels over time vs glimepiride, and a greater number of subjects treated with exenatide achieved A1C <6.5% and <7.0% vs those in the glimepiride group
- Exenatide patients experienced significantly greater weight loss over time vs those who received glimepiride (P<0.001)
- A significantly higher number of exenatide-treated subjects discontinuous treatment due to adverse events over the first 6 months of treatment, but not thereafter. There was no pancreatic cancer over the 4.5 year study period.
- Hypoglycemia incidence was lower with exenatide vs glimepiride (<0.001)
- At least 1 hypoglycemic episode reported: 36% of those in the exenatide group vs 67% in the glimepiride group (P<0.0001)


DPPOS
Several studies, including the Diabetes Prevention Program (DPP), have demonstrated the efficacy of lifestyle modifications or antihyperglycemic therapies—or both—for reduction of diabetes incidence. What many of these studies may not discuss, however, are the young age, weight loss, and intensive lifestyle changes were associated with regression to NGR. The long-term follow-up to DPP, DPPOS also related to diabetes risk during DPPOS follow-up (HR, 1.14; 95% CI, 1.05-1.25; P=0.0021). Higher beta-cell function (HR, 0.80; 95% CI, 0.71-0.89; P<0.001) and insulin sensitivity (HR, 0.84; 95% CI, 0.74-0.94; P=0.0001) were protective.

This report sought to quantify and predict diabetes risk reduction during the DPPOS in participants who regressed to NGR at least once during the DPP, and compare this group against those participants who maintained a prediabetes state.

Achievement of NGR status at least once during DPP equated with a 56% reduced risk of diabetes development during DPPOS (HR, 0.44; 95% CI, 0.37-0.55; P<0.0001). Risk reduction was associated with the frequency of achieving NGR:

<table>
<thead>
<tr>
<th>Number of times NGR achieved</th>
<th>Diabetes risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47% (HR, 0.53; 95% CI, 0.42–0.66; P&lt;0.0001)</td>
</tr>
<tr>
<td>2</td>
<td>61% (HR, 0.39; 95% CI, 0.28–0.56; P&lt;0.0001)</td>
</tr>
<tr>
<td>3</td>
<td>67% (HR, 0.33; 95% CI, 0.19–0.58; P=0.0001)</td>
</tr>
</tbody>
</table>

Increased weight loss during DPP adversely affected diabetes risk (HR, 1.26; 95% CI, 1.15-1.39; P<0.0001); increased BMI at the beginning of DPPOS also related to diabetes risk during DPPOS follow-up (HR, 1.14; 95% CI, 1.05-1.25; P=0.0021). Higher beta-cell function (HR, 0.80; 95% CI, 0.71-0.89; P<0.001) and insulin sensitivity (HR, 0.84; 95% CI, 0.74-0.94; P=0.0001) were protective.

Participants who consistently stayed in a prediabetes state during DPP had increased diabetes risk despite intensive lifestyle intervention
Latebreaking Data from EASIE, EUREXA, DPPOS Continued from Page 6

(HR, 1.31; 95% CI, 1.03-1.68; P=0.0304) and a lower chance of achieving NGR (OR, 0.59; 95% CI, 0.42-0.82; P=0.0014) versus the placebo group in DPPOS.

Predictors of achieving NGR during DPPOS included:

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased weight during DPP</td>
<td>0.78 (0.72–0.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NGR status vs prediabetes</td>
<td>3.01 (2.25–4.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>1.16 (1.08–1.25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beta-cell function</td>
<td>1.28 (1.18–1.39)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


Hypoglycemia in Diabetes—Consequences and Prevention

As part of a symposium discussing the consequences of hypoglycemia in diabetes, Gabriella Gruden, MD, shared results from the EURODIAB Complications Study of 3,250 patients with type 1 diabetes (aged 15-60 yrs, diabetes duration ≥ 1 yr). A total of 32% of subjects experienced a severe hypoglycemic event (significance noted for age, duration, and A1C; P<0.0001).

The EURODIAB Prospective Complications study, the follow-up to the EURODIAB IDDM Complications Study, sought to determine whether the frequency of severe hypoglycemia at baseline is a risk factor for incident CVD. The study followed 2,181 patients with no evidence of CVD at baseline for 6-8 years for incidence of fatal CVD, nonfatal CVD, and severe or nonsevere hypoglycemia.

CVD Incidence According to Hypoglycemia Categories (7.3-Yr Follow-Up)

<table>
<thead>
<tr>
<th>SH episodes</th>
<th>Nonfatal CVD</th>
<th>Fatal CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>102 (6.8%)</td>
<td>29 (10.8%)</td>
</tr>
<tr>
<td>1-2</td>
<td>38 (7.2%)</td>
<td>33 (7.9%)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>29 (10.8%)</td>
<td>29 (10.8%)</td>
</tr>
</tbody>
</table>

SH=severe hypoglycemia

Dr Gruden also presented data showing that hypoglycemia induces endothelial dysfunction, inflammation (levels of CRP, IL-6, TNF-α), and blood abnormalities.

David Brillon, MD, presented data from a post-hoc epidemiological analysis of ACCORD, which investigated potential determinants of severe hypoglycemia, including baseline characteristics, and the association of severe hypoglycemia with levels of A1C achieved during therapy. A higher incidence of hypoglycemia was seen in the intensive versus standard group (3.14% vs 1.03%). For standard, every 1% unit higher A1C level was associated with a 30% higher risk of hypoglycemia requiring medical assistance (HR=1.30; 95% CI, 1.15-1.47). The risk was 76% higher for every 1 unit higher A1C increase (HR=1.76; 95% CI, 1.50-2.06). Baseline characteristics that placed participants at increased risk for mortality in the intensive and standard arms included female gender (P=0.03), African-American race (P<0.0001), history of peripheral neuropathy (P=0.0300), lower BMI (P<0.0001), and older age (P<0.0001).

More from ACCORD: Participants in the intensive group reported a mean of 1.06 hypoglycemic episodes in the 7 days preceding their regular 4-month visit, whereas those in the standard group reported an average of 0.39 episodes. Hazard ratios for mortality in models, including frequency of hypoglycemic episodes, were 0.93 (95% CI 0.9-0.97; P=0.001) for intensive and 0.98 (0.91-1.06; P=0.615) for standard. Hazard ratios for mortality in models, including unrecognized hypoglycemia, were not statistically significant for either group. In this analysis, there was a small but statistically significant inverse relationship between the number of hypoglycemic episodes and mortality risk.

Simon Heller, MB, DM, presented data from a meta-analysis that evaluated the effect of intensive glucose control on major adverse cardiovascular events in patients with type 2 diabetes. Six reports from four randomized trials, including ADVANCE, ACCORD, and VADT; (n=27,544); mean follow-up was 5.4 years. A1C at study end was 6.6% vs 7.4% for intensive versus standard. Intensive control did not affect the incident rate ratio for all-cause mortality (1.01, 95% CI 0.86–1.18; P=0.54). Severe hypoglycemia with intensive therapy was a strong independent predictor of mortality, especially in VADT, and predicts mortality after the event has occurred.
Incretin-Based Therapies: Are They All the Same?

A Closer Look at DPP-4 Inhibitors and GLP-1 Receptor Agonists

In a symposium discussing incretin-based therapies, Adrian Vella, MD, provided an overview of DPP-4 inhibitors with the goal of differentiating these relatively new antihyperglycemic agents from one another. Three DPP-4 agents are currently approved for use in type 2 diabetes: sitagliptin (Januvia®), saxagliptin (Onglyza®), and linagliptin (Tradjenta™). Each produces rapid, significant inhibition of DPP-4—but are they all the same?

GLP-1 is a gut hormone created by the L-cells that is secreted into the circulation and degraded by DPP-4 to an inactive peptide. DPP-4 inhibitors alter concentrations of GLP-1 by interfering with GLP-1 clearance. In a single daily dose, they produce a 24-hour effect, with >80% DPP inhibition (with the exception of vildagliptin*, which has a 2- to 3-hour half-life). They have a large volume of distribution (not linagliptin), and are not metabolized by cytochrome P450 (metabolites have little activity).

Attributes of DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Reductions, albeit small</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td></td>
</tr>
<tr>
<td>PPG</td>
<td>Significant effect: &lt;50-mg/dL decreases</td>
</tr>
<tr>
<td>Insulin concentrations</td>
<td>No effect, although present at lower glucose concentrations</td>
</tr>
<tr>
<td>Postprandial glucagon concentrations</td>
<td>Lower, especially during the first 2 hours post-meal</td>
</tr>
<tr>
<td>Beta-cell responses</td>
<td>Vildagliptin: Slight but nevertheless significant effects to glucose concentrations; disposition index also improved</td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>Vildagliptin, 14 days’ treatment: no effect; no accommodation effect</td>
</tr>
</tbody>
</table>

Addressing the null effect of DPP-4 inhibitors on the GI tract, Dr Vella surmised that it is possible that other hormones whose actions depend on DPP-4 may also be impaired via DPP-4 inhibition.

Dr Vella also noted the non-glucose effects of DPP-4 inhibitors, among them:
+ DPP-4 also known as adenosine deaminase-binding protein or CD26
+ Widespread extracellular distribution; present in a soluble form
+ Multiple DPP-4–related enzymes
+ 4 of 52 week’s treatment with sitagliptin: increase in endothelial progenitor cells (EPCs) and decrease in MCP-1, which recruits inflammatory cells

Addressing the selectivity of DPP-4 inhibitors, Dr Vella noted that these agents belong to a family of serine peptidases, the function of which is unknown. He further presented data on sitagliptin and vildagliptin. The latter showed an absence of shin lesions and no increase in pancreatitis. He noted, however, that the lack of pancreatitis may be due to the fact that vildagliptin is not very selective. For sitagliptin, he spoke to a study containing 10,000 patients, which showed no evidence of pancreatitis.

Regarding glycemic efficacy:
+ No good data on comparative effectiveness
+ Most data for sitagliptin or vildagliptin
+ Durable A1C reduction (-0.7%) with no associated hypoglycemia or weight gain

Conclusions:
+ DPP-4 inhibitors are mediated by GLP-1 effects on alpha- and beta-cell secretion
+ Differences in pharmacokinetics
+ No differences in glycemic efficacy
+ No differences in adverse events even in context of selectivity

Subsequently, Filip Knop, MD, PhD, posited the same question for GLP-1 receptor agonists: are they all the same? Three GLP-1 analogs are currently approved for use in the United States for type 2 diabetes: exenatide BID (Byetta®), liraglutide (Victoza®), and exenatide QW (Bydureon®). In his talk, Dr Knop also focused on the novel GLP-1 agonists, lixisenatide* and albiglutide*, as these are the only two GLP-1 agonists in development that have been compared in head-to-head studies.

Continued on Page 10
Preserving Beta-Cell Function With Intensive Therapy

Kicking off the ADA Diabetes Care Symposium, Lindsay Harrison, MD, stated that the ideal situation in type 2 diabetes is preservation of beta-cell function with the aim of positively altering disease progression. Glycemic control deteriorates over time, and monotherapy cannot necessarily change the disease landscape and arrest progression. Dr Harrison presented data from an unpublished study assessing beta-cell function among newly diagnosed type 2 diabetes subjects (dx within prior 2 months).

After a 3-month run-in on insulin or metformin, patients were randomized in a 1:1 ratio to their current therapy or switched to triple oral therapy. The insulin + metformin group (INS; n=29) was given NovoLog® 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin]) 0.2 u/kg and metformin 500 mg QD, titrated weekly to 1,000 mg BID. The triple oral therapy (TOT; n=29) regimen included glyburide 125 mg BID, titrated throughout the study; metformin 1 g BID, and pioglitazone 15 mg, titrated to a max dose of 45 mg QD. Visits were logged monthly for the first 4 months, then quarterly thereafter for 3.5 years. Therapy failure was A1C >8% after max daily titration. All patients with treatment failure remained in the study and continued same follow-up.

At 3 months:
- A1C was reduced by 5.9% (note: insulin dose was titrated aggressively)
- Rapid improvement of glycemic control, which was sustained over 3.5 years regardless of treatment type
- Treatment failure was rare

With regard to beta-cell function, the primary endpoint, C-peptide and glucose area under the curve were sustainable in both groups—an unanticipated finding given declines seen in other studies. Weight increased in both groups (nonsignificant). Rates of mild hypoglycemia were 1 event/month for the first 4 months, thereafter declining and staying low through study end.

Dr Harrison concluded by stating that beta-cell function can be preserved for at least 3.5 years after type 2 diabetes diagnosis if intensive therapy is initiated early. Insulin was similar to triple oral therapy with respect to beta-cell function, glycemic control, hypoglycemia, and weight.

TINSAL-T2D: Salsalate for Treating Type 2 Diabetes

Targeting Inflammation Using Salsalate in Type 2 Diabetes (TINSAL-T2D) is a parallel, randomized, placebo-controlled multicenter trial that evaluated the safety and efficacy of salsalate* in subjects with type 2 diabetes. Data from a dose-ranging Phase IIb trial of salsalate were published in 2010. Findings presented during this symposium were unpublished TINSAL-T2D data from a 48-week study comparing salsalate 3.5 g/d vs placebo for mean change in A1C among 282 subjects with type 2 diabetes. Results:
- Primary endpoint: 0.24% decrease with salsalate (P<0.001); presenter noted that this is a smaller change than anticipated
- More patients taking salsalate achieved ≥0.5 reductions in A1C (P=0.01)
- Mean change in FPG: 11-mg/dL decrease with salsalate (P<0.001)
- No significant hypoglycemia, though was more common among salsalate-treated subjects
- Hyperglycemia more common in the placebo group
- A greater number of subjects receiving salsalate had a reduction in the number of concomitant medications
- Salsalate increased fasting insulin and decreased C-peptide, likely due to change in insulin clearance and could contribute to change in blood sugars
- Modest weight increase with salsalate; salsalate increased TC and, notably, LDL-C, and lowered TG
- Increase in urinary albumin seen among salsalate-treated subjects, which reversed following discontinuation
- Leading adverse effect was tinnitus in salsalate-treated subjects

*Salsalate is a generic compound that is not used to treat diabetes.

An Update on Insulin Therapies

Geremia B. Bolli, MD, discussed and provided data related to basal insulins.

Key points for insulins on the market
- NPH insulin is not the ideal basal insulin for treatment of type 1 diabetes as its peak occurs 5-6 hours after injection; NPH is a suspension and has high inter- and intra-subject variability. A more physiologic approach is continuous subcutaneous insulin infusion (CSII), which uses soluble insulin only.
- In addition to NPH and CSII, candidates for replacement of basal insulin that are on the market include insulin glargine, which when compared with NPH is relatively peakless, soluble, has duration of action at steady state >24 hours, and is not inferior to CSII. Dr Bolli discussed data demonstrating the superiority of glargine vs NPH in type 1 diabetes, noting that there was less hypoglycemia ( nocturnal) and lower/similar A1C. In type 2 diabetes, basal insulin is deficient relative to hyperglycemia—when you give basal NPH or glargine, patients experience the “dawn phenomenon.” NPH has a peak in the middle of the night, while glargine is more stable. Glargine was also superior to NPH in type 2 diabetes, again demonstrating less hypoglycemia.
- Another candidate for replacement is insulin detemir; it is soluble, lower variable in absorption vs NPH, nearly peakless, shorter in duration,
Incretin-Based Therapies Continued from Page 8

Pharmacokinetic Profiles of GLP-1 Receptor Agonists:

<table>
<thead>
<tr>
<th></th>
<th>Dosing</th>
<th>Tmax</th>
<th>Excretion</th>
<th>Add’l Info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID</td>
<td>10 mg</td>
<td>120 mins</td>
<td>Glomerular filtration</td>
<td>Rapid absorption by cutis</td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>2 mg</td>
<td>2.1-5.1 hrs</td>
<td>Glomerular filtration</td>
<td>10 wks posttreatment washout</td>
</tr>
<tr>
<td>Long-acting</td>
<td>(single dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.6-1.8 mg</td>
<td>~10 hrs</td>
<td>Broken down naturally in body</td>
<td>Protracted</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
<td>Self associated: delays absorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>from injection site</td>
</tr>
<tr>
<td>Lixisenatide*</td>
<td>20 mg BID</td>
<td>2-3 hrs</td>
<td>Kidney (expected)</td>
<td>Rapid absorption</td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albiglutide*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting</td>
<td>6-8 days</td>
<td></td>
<td></td>
<td>5 days to reach peak postinjection</td>
</tr>
</tbody>
</table>

Head-to-Head Data on GLP-1 Analogs

Lixisenatide* versus Liraglutide for PPG in type 2 diabetes
✦ More pronounced PPG responses with lixisenatide* (-70 vs -25 overnight)
✦ Lower postprandial insulin and glucose responses with lixisenatide* (-64 vs +5 and -47 vs -25)

DURATION-1: Exenatide QD vs Exenatide QW
✦ Exenatide QD: Better PPG, higher nausea/vomiting
✦ Exenatide QW: Better FPG, thus more advantageous
✦ Similar findings in DURATION-5

DURATION-6: Exenatide QW vs Liraglutide QD
✦ Exenatide QW: Greater incidence of injection-site nodules
✦ Liraglutide QD: Better A1C, body weight; more vomiting and GI adverse events

LEAD-6: Liraglutide QD vs Exenatide BID
✦ Liraglutide QD: Better A1C, FPG, body weight
✦ Exenatide BID: More nausea/vomiting, injection-site reactions
✦ Dinner/breakfast: PPG better with exenatide BID

GetGoal-X (unpublished data): Liraglutide QD vs Exenatide BID
✦ Exenatide BID: Better A1C, FPG, body weight; more nausea/vomiting, hypoglycemia

HARMONY-7 (unpublished data): Albiglutide* QW vs Liraglutide QD
✦ Liraglutide QD: Better A1C, FPG, body weight; more nausea/vomiting

In his concluding remarks, Dr Knop revisited the initial question of whether all GLP-1 receptor agonists are the same—he answered with an emphatic, “No!”:
✦ Distinct pharmacokinetic properties seen in these agents affect efficacy and adverse events
✦ Different structures/backbones present differences in immunogenicity
✦ Size differences affect CNS signaling

*Agents in development; not FDA approved for the treatment of type 2 diabetes
An Update on Insulin Therapies Continued from Page 10

and weaker with regard to obesity. Data show that detemir is associated with higher insulin dose vs glargine against BMI range; insulin detemir is also protective against hypoglycemia vs NPH. In the context of obesity, the effectiveness of detemir is less vs glargine when there is greater obesity.

**Key points for insulins in development** (not FDA approved for treating diabetes):

- **Insulin degludec** has low relative IGF-IR affinity. Similar to glargine, degludec contains 6 nmol insulin in 1 unit; detemir contains 24 nmol insulin in 1 unit. Pharmacokinetics of degludec show a sustained >24-hour effect, low variation in subcutaneous absorption, and low rate of hypoglycemia. Day-to-day variability in glucose-lowering effect is four times lower with degludec versus glargine. When compared with glargine, one study demonstrated A1C after 1 year was no different for degludec and glargine, with less hypoglycemia.

- **Pegylated insulin lispro** has a large hydrodynamic size, which delays absorption, and a lower binding affinity to IR and IGF-IR vs lispro. Data from Phase II studies show noninferiority/superiority for daily mean blood glucose, A1C, fasting blood glucose; loss in body weight was also seen, and there was more total hypoglycemia, although less nocturnal hypoglycemia. Rates of ALT, AST, TG, LDL-C were higher; HDL-C was lower but still within the normal range compared with glargine. In a type 2 diabetes study, pegylated insulin lispro was noninferior for FPG and A1C, showed a loss in body weight, and less nocturnal hypoglycemia compared with glargine.

Several posters focusing on degludec were also presented, among them:

- Data were compared for insulin-naïve subjects with type 2 diabetes who received once-daily insulin degludec or insulin glargine in combination with OADs. At 52 weeks, degludec significantly lowered FPG vs glargine; A1C between groups was statistically comparable. Confirmed nocturnal hypoglycemia and overall hypoglycemia were less frequent with degludec. (Rodbard H, et al. Insulin degludec reduces hypoglycemia and improves health status vs insulin glargine in insulin-naïve type 2 diabetes.)

- In a study comparing insulin degludec with sitagliptin among insulin-naïve subjects with type 2 diabetes, results at 26 weeks demonstrated greater reductions in A1C and FPG with degludec vs sitagliptin. No statistically significant differences in the rate of confirmed nocturnal hypoglycemia were observed between groups, although there was a higher rate of overall confirmed hypoglycemia among degludec treated subjects. (Philis-Tsimikas A, et al. Insulin degludec is superior to sitagliptin in improving glycemic control in insulin-naïve patients with type 2 diabetes. Poster 1025-P.)

**Evolution of rapid-acting insulin:** Luigi F. Meneghini, MD, discussed pharmacokinetics and pharmacodynamics, limitations of available preparations, and products in development. Key points:

- The available insulin analogs are similar in pharmacokinetics and pharmacodynamics; there is no difference in clinical outcomes among analogs.

- Data comparing rapid-acting vs regular human insulin in type 1 diabetes showed a statistically significant reduction in A1C; hypoglycemia and severe hypoglycemia risk with analogs was lower.

- Another study demonstrated higher insulin concentrations but similar glucose excursions for glulisine vs lispro. Dr Meneghini noted as a key clinical message that glulisine best controls PPG when injected 20 minutes premeal.

- When data were examined for obese subjects with type 2 diabetes, better absorption of insulin was seen in controls vs those who were obese; there is a delayed biologic action of rapid-acting insulin in obese patients with type 2 diabetes.

**Insulin Co-formulations:**

Julio Rosenstock, MD, reviewed data exploring these key points:

- Premix formulations confer an advantage over regular insulin in dealing with excursions. Data from several studies showed that there is little difference in A1C between the various premixed versions. One study comparing triple oral therapy with premixed insulin + metformin showed a similar A1C reduction between groups, but an increase in hypoglycemia with the premixed insulin regimen.

- Premixed insulin should not be used for tight control due to increased risk of hypoglycemia.

- Data comparing premixes vs basal/bolus or basal + 1 prandial insulin demonstrated A1C changes at study end, with basal bolus having a greater change in A1C vs premixed 70/30, which still showed an increase in hypoglycemia.

- Dr Rosenstock noted that most patients cannot realistically be on basal-bolus therapy—it is not ideal treatment for type 2 diabetes, he said.

- When data were examined regarding basal and basal-bolus + premixed 70/30 in type 2 diabetes, premixed showed more weight gain and hypoglycemia, with double the incidence of hypoglycemia.

**Co-formulations in development:**

- Degludec 70/30*: no difference between premixed vs glargine with regard to hypoglycemia in type 2 diabetes.

- Hyaluronidase plus short-acting insulin*: hyaluronidase is an enhancer of subcutaneous administration that is highly reversible and opens subcutaneous tissue.

- Short-acting insulin plus pramlintide*, which shows a very robust PPG effect.

- Basal analogs plus GLP-1 receptor agonists*, which may show a potential complementary and additive effect between the agents.

*Agents and/or combination/co-formulation therapies in development; not FDA approved for the treatment of type 2 diabetes.