Diabetes: What is on the Horizon

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Program Director, Endocrinology Fellowship
UB|MD Internal Medicine – Endocrinology, Diabetes & Metabolism
Director, Kaleida’s Diabetes & Endocrinology Center of WNY, President WNY ADA, Buffalo
HOPE AND OPTIMISM
• **Prediabetes- We can Prevent Diabetes !!**

• **Diabetes**
  – Get more patients with type 1 and type 2 diabetes to goal without increasing the risk of hypoglycemia
  – Prevent complications
  – Reverse Complications
Prediabetes
Screening For Diabetes

Testing at least every 3 yrs starting at age 45

<table>
<thead>
<tr>
<th>Test</th>
<th>Prediabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>100-125 mg/dL</td>
<td>≥126 mg/dL</td>
</tr>
<tr>
<td>OGTT</td>
<td>140-199 mg/dL</td>
<td>≥200 mg/dL</td>
</tr>
<tr>
<td>A1C</td>
<td>5.7-6.4%</td>
<td>≥6.5%</td>
</tr>
</tbody>
</table>
Intervention and Follow-Up

Screen for Diabetes:
- A1C - or -
- FPG – or -
- 2-hour, 75-g OGTT

1. A1C ≥ 5.7%
   - IFG or IGT
   - Lifestyle intervention, follow-up @1 year

2. A1C ≥ 6.0%
   - IFG and IGT + Other Features
   - Lifestyle intervention and/or metformin, follow-up @6 mo

3. Re-evaluate in 3 years if risk factors remain
   - Lifestyle intervention plus metformin, follow-up @3 mo

Normal

Re-evaluate in 3 years if risk factors remain

METFORMIN IS NOT FDA APPROVED FOR PREVENTION

Diabetes Prevention Program

Cumulative Incidence of Diabetes (%)

Placebo 10.8
Metformin 9.6
Lifestyle 3.1

Knowler WC, et al. NEJM. 2002;346:393-403
IRIS: Pioglitazone Lowers Rate of Progression to Diabetes Vs Placebo

Rate of progression to diabetes

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>% Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>0.48</td>
<td>(0.33, 0.69)</td>
<td>&lt;0.001</td>
<td>3.8% (n=73)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td>12% (n=149)</td>
</tr>
</tbody>
</table>

**About the trial**
Multicenter, double-blind trial assessed whether pioglitazone may benefit patients with cerebrovascular disease. N=3,876 patients with recent ischemic stroke or TIA and insulin resistance randomized to pioglitazone (target 45 mg/d; n=1,939) or placebo (n=1,937). Primary outcome: fatal or nonfatal stroke, or MI over 4.8 years.
Management of diabetes

Preventing Complications
Landmark Clinical Trials Have Influenced Clinical Practice

1993-1997

- **Microvascular Focus**
  - DCCT
  - UKPDS
  - Kumamoto

2005-2010

- **Macrovascular Focus**
  - DCCT/EDIC
  - ACCORD
  - VADT
  - UKPDS Long Term
  - ADVANCE
DCCT/EDIC: Risk of CVD Outcome

Any CV Outcome

42% risk reduction
\( P=0.02 \)

Cumulative Incidence

Years Since Entry*

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
<td>714</td>
<td>705</td>
</tr>
<tr>
<td>0.5</td>
<td>688</td>
<td>683</td>
</tr>
<tr>
<td>1.0</td>
<td>618</td>
<td>629</td>
</tr>
<tr>
<td>1.5</td>
<td>92</td>
<td>113</td>
</tr>
</tbody>
</table>

UKPDS 10-Year Follow-Up: Benefits of Intensive Glucose Control Sustained for up to 10 Years Despite Early Loss of A1C Level Advantage

Macrovascular benefits emerged only during observational follow-up

- Sulfonylurea insulin group (n=2,729; median follow-up=16.8 years)
  - Any diabetes-related end point disease: -9, P=0.04
  - Microvascular disease: -15, P=0.01
  - Myocardial infarction: -13, P=0.007
  - Death from any cause: -21, P=0.01

- Metformin group (n=342; median follow-up=17.7 years)
  - Any diabetes-related end point disease: -33, P=0.005
  - Myocardial infarction: -27, P=0.002
  - Death from any cause: -24, P=0.001

Summary of the Landmark Clinical Trials

- Intensive glycemic control reduces microvascular complications

- Intensive glycemic control reduces macrovascular complications
  - without established CVD
  - In long term follow up studies
STENO-2

A Multifactorial Approach to the Patient With Type 2 Diabetes
STENO-2

• Intensive Treatment Goals:

Hemoglobin A$_{1c}$, <6.5%
cholesterol, <175 mg/dL
triglycerides, <150 mg/dL
systolic blood pressure, <130 mm Hg
diastolic blood pressure, <80 mm Hg
COMPOSITE ENDPOINT OF DEATH FROM CV CAUSES, NONFATAL MI, CABG, PCI, NONFATAL STROKE, AMPUTATION, OR SURGERY FOR PAD: STENO-2

Primary Composite Endpoint (%)

- Conventional Therapy
- Intensive Therapy

Hazard ratio = 0.47 (95% CI, 0.24–0.73; P=0.008)

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ABC of Diabetes Care

A     A1C
B     Blood pressure
C     Cholesterol
Trends in Rates of Diabetes-Related Complications from 1990 to 2010 among U.S. Adults with Diagnosed Diabetes
Prevention of Complications with ABC of diabetes
DIABETES ENDOCRINOLOGY CENTER OF WESTERN NEW YORK OUTCOMES
OUTCOMES OF PATIENTS FROM DIABETES ENDOCRINOLOGY CENTER OF WNY

- Mean Hba1c: 6.8%
- Mean LDL-C: 75mg/dl
- Mean HDL-C: males: 38mg/dl; females: 45mg/dl
- Mean Systolic BP: 125mm Hg
- Mean Diastolic BP: 78mm Hg
- 85% on statins
- 90% on ACE inhibitors/ ARBs
- 85% on aspirin
- 65% on insulin
Clinical Outcomes of Patients from Diabetes Endocrinology Center of WNY

- No foot ulcers, gangrene or amputations for 11 years
- No endstage renal failure, dialysis or transplantation for 7 years
- Mean microalbuminuria diminished
- Cessation of laser therapy within two years of attending
Management of diabetes

Achieve Glycemic goals without hypoglycemia
Risk of Progression of Complications: DCCT Study

DCCT = Diabetes Control and Complications Trial.

Pathophysiology Of Type 2 Diabetes
Ominous Octet

Decreased Insulin Secretion

Increased Hepatic Glucose Production

Increased Glucagon Secretion

Decreased Glucose Uptake

Islet–A cell

Decreased Incretin Effect

Increased Lipolysis

Increased Glucose Reabsorption

Decreased Glucose Uptake

Neurotransmitter Dysfunction

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Targeting the Core Defects of Type 2 Diabetes
Ominous Octet

**ETIOLOGY OF T2DM**
- **Decreased Glucose Uptake**
- **Impaired Insulin Secretion**
- **Increased Lipolysis**
- **Increased Hepatic Glucose Production**
- **Decreased Insulin Secretion**
- **Increased Glucagon Secretion**
- **Decreased Incretin Effect**
- **Increased Glucose Reabsorption**
- **Neurotransmitter Dysfunction**

**Incretins**

**SGLT2 inhibitor**

**HYPERGLYCEMIA**

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### Antidiabetes Therapy: Treatment Effects\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Class</th>
<th>Expected Decrease in A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Glinides</td>
<td>0.5 – 1.5</td>
</tr>
<tr>
<td>Alpha glucosidase inhibitors</td>
<td>0.5 – 0.8</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5 – 1.4</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>0.5 – 0.8</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>0.5 – 1.5</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.5 – 3.5</td>
</tr>
</tbody>
</table>


\textsuperscript{2} American Association of Clinical Endocrinologists. *Endocrine Practice.* 2007;13:3-68.
# Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGI</th>
<th>TZD</th>
<th>SU</th>
<th>GLN</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
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<tbody>
<tr>
<td>HYPO</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
<td></td>
</tr>
<tr>
<td>RENAL/GU</td>
<td>Contraindicated CKD Stage 3B,4,5</td>
<td>Exenatide Contraindicated CrCl &lt; 30</td>
<td>Genital Mycotic Infections</td>
<td>Dose Adjustment May be Necessary (Except Linagliptin)</td>
<td>Neutral</td>
<td>May Worsen Fluid Retention</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk &amp; Fluid Retention</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>GI Sx</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
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<tr>
<td>CHF</td>
<td>Neutral</td>
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<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>Benefit</td>
<td>Increased LDL</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>?</td>
<td>Neutral</td>
<td>Safe</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Bone Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
</tbody>
</table>

- **Few adverse events or possible benefits**
- **Use with caution**
- **Likelihood of adverse effects**

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Common Principles in AACE/ACE and ADA/EASD T2DM Treatment Algorithms

- Individualize glycemic goals based on patient characteristics and avoid hypoglycemia
- Promptly intensify antihyperglycemic therapy to maintain blood glucose at individual targets
  - Combination therapy necessary for most patients
  - Base choice of agent(s) on individual patient medical history, behaviors and risk factors, ethno-cultural background, and environment
- Insulin eventually necessary for many patients
- SMBG vital for day-to-day management of blood sugar
  - All patients using insulin
  - Many patients not using insulin
Type 1 Diabetes - Closed Loop systems
Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

A Glycated Hemoglobin
- At randomization
- At 3 months

B Mean AUC for Nocturnal Hypoglycemic Events
- Run-in phase
- Study phase

C Sensor Glucose <70 mg/dl
- 60 to <70 mg/dl
- 50 to <60 mg/dl
- <50 mg/dl

DOI: 10.1056/NEJMoal303576
Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes

Figure 3. Distributions of Mean Glucose Levels and Hypoglycemia among Adults and Adolescents.
# Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Run-in Period</th>
<th>Study Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensor glucose, mean (SD) [median], mg/dL</td>
<td>150.2 (22.7) [150.1]</td>
<td>150.8 (13.7) [149.9]</td>
</tr>
<tr>
<td>Percentage of time with glucose level in range, mean (SD); median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensor glucose values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;300 mg/dL</td>
<td>2.3 (4.2); 1.3 (0.2-2.6)</td>
<td>1.7 (1.9); 0.9 (0.5-2.1)</td>
</tr>
<tr>
<td>&gt;180 mg/dL</td>
<td>27.4 (13.7); 26.7 (16.0-37.2)</td>
<td>24.5 (9.2); 24.1 (17.3-29.8)</td>
</tr>
<tr>
<td>71-180 mg/dL</td>
<td>66.7 (12.2); 67.8 (59.0-75.1)</td>
<td>72.2 (8.8); 73.4 (67.7-78.4)</td>
</tr>
<tr>
<td>≤70 mg/dL</td>
<td>5.9 (4.1); 5.2 (3.0-7.6)</td>
<td>3.3 (2.0); 2.9 (1.7-4.3)</td>
</tr>
<tr>
<td>≤50 mg/dL</td>
<td>1.0 (1.1); 0.6 (0.2-1.3)</td>
<td>0.6 (0.6); 0.4 (0.2-0.8)</td>
</tr>
<tr>
<td>Glycated hemoglobin, mean (SD) [median], %</td>
<td>7.4 (0.9) [7.3]</td>
<td>6.9 (0.6) [6.8]</td>
</tr>
<tr>
<td>Total daily dose of insulin, mean (SD) [median], U</td>
<td>47.5 (22.7) [43.9]</td>
<td>50.9 (26.7) [44.1]</td>
</tr>
<tr>
<td>Weight, mean (SD) [median], kg</td>
<td>76.9 (17.9) [73.5]</td>
<td>77.6 (16.1) [74.7]</td>
</tr>
</tbody>
</table>
Use of Liraglutide with insulin in Type1 diabetes
Addition of Liraglutide to Insulin in Patients With Type 1 Diabetes: A Randomized Placebo-Controlled Clinical Trial of 12 Weeks

Nitesh D. Kuhadiya,1 Sandeep Dhindsa,1,2 Husam Ghanim,1 Aditya Mehta,1 Antoine Makdissi,1 Manav Batra,1 Sartaj Sandhu,1 Jeanne Hejna,1 Kelly Green,1 Natalie Bellini,1 Min Yang,3 Ajay Chaudhuri,1 and Paresh Dandona1

Diabetes Care Publish Ahead of Print, published online April 5, 2016
Background

- Addition of Liraglutide to Insulin in patients with well controlled type 1 diabetes results in the reduction of mean fasting & weekly glucose concentrations, a reduction in glycemic excursions and HbA1c

- Decrease in insulin requirements with no increase in hypoglycemia
Dapagliflozin as Additional Treatment to Liraglutide and Insulin in Patients With Type 1 Diabetes

Nitesh D. Kuhadiya, Husam Ghanim, Aditya Mehta, Manisha Garg, Salman Khan, Jeanne Hejna, Barrett Torre, Antoine Makdissi, Ajay Chaudhuri, Manav Batra, and Paresh Dandona

Division of Endocrinology, Diabetes, and Metabolism, State University of New York at Buffalo, Buffalo, New York 14215

J Clin Endocrinol Metab, September 2016, 101(9):3506–3515
Dapagliflozin as Additional Treatment to Liraglutide and Insulin in Patients With Type 1 Diabetes

Results: In the dapagliflozin group, glycated hemoglobin fell by 0.66% ± 0.08% from 7.8% ± 0.21% (P < .01 vs placebo), whereas it did not change significantly in the placebo group from 7.40% ± 0.20% to 7.30% ± 0.20%. The body weight fell by 1.9 ± 0.54kg (P < .05 vs placebo). There was no additional hypoglycemia (blood glucose < 3.88 mmol/L; P = .52 vs placebo). In the dapagliflozin group, there were significant increases in the plasma concentrations of glucagon by 35% ± 13% (P < .05), hormone-sensitive lipase by 29% ± 11% (P < .05), free fatty acids by 74% ± 32% (P < .05), acetoacetate by 67% ± 34% (P < .05), and β-hydroxybutyrate by 254% ± 81% (P < .05). Urinary ketone levels also increased significantly (P < .05). None of these changes was observed in the placebo group. Two patients in the dapagliflozin group developed diabetic ketoacidosis.

Conclusions: Addition of dapagliflozin to insulin and liraglutide in patients with T1D results in a significant improvement in glycemia and weight loss while increasing ketosis. If it is decided to use this approach, then it must be used only by a knowledgeable patient along with an endocrinologist who is well versed with it. (J Clin Endocrinol Metab 101: 3506–3515, 2016)
Management of diabetes

Reversing complications
Reversal of Complications with ABC
GLP-1 Receptor Agonists Reverse Albuminuria

Akshata Desai, MD
Mentor: Paresh Dandona, MD, PhD

Department of Endocrinology, SUNY at Buffalo
**EVOLUTION OF ALBUMINURIA**

- **Baseline Normoalbuminuria**
- **Baseline Microalbuminuria**
- **Baseline Macroalbuminuria**

The percentages indicate the distribution of albuminuria types:
- **Normoalbuminuria**: 89%
- **Microalbuminuria**: 48%
- **Macroalbuminuria**: 46%
Per annum comparison of evolution of albuminuria between GLP users and non users

- **Normal**
  - GLP users: 97.3%
  - Non GLP users: 95.24%

- **Microalbuminuria**
  - GLP users: 2.3%
  - Non GLP users: 4.4%

- **Macroalbuminuria**
  - GLP users: 0.4%
  - Non GLP users: 0.36%

**p** values:
- Normal: **p** < 0.0005
- Microalbuminuria: **p** < 0.0001
- Macroalbuminuria: **p** < 0.0005
ALBUMINURIA IN THE TWO GROUPS

GLP-1RA users

Non-GLP users
Reduction in Macrovascular and Microvascular complications:

IRIS/ LEADER/ EMPA-REG
IRIS: Does Pioglitazone Benefit Patients With Cerebrovascular Disease?

- Multicenter, double-blind trial
- Assessed whether pioglitazone may be beneficial to patients with cerebrovascular disease
  - Insulin resistance has been identified as a risk factor for stroke and MI
  - Pioglitazone improves insulin sensitivity
- N=3,876 patients* with insulin resistance who experienced a recent ischemic stroke or TIA randomized to:
  - Pioglitazone (target dose, 45 mg/d) (n=1,939)
  - Placebo (n=1,937)
- Primary outcome: Fatal or nonfatal stroke, or MI over 4.8 years

<table>
<thead>
<tr>
<th>Select baseline characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>63.5 yrs</td>
</tr>
<tr>
<td>Index event:</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>88% pioglitazone</td>
</tr>
<tr>
<td>Mean A1C</td>
<td>5.8%</td>
</tr>
<tr>
<td>Mean FPG</td>
<td>98.2 mg/dL</td>
</tr>
<tr>
<td>Mean HOMA-IR</td>
<td>5.4</td>
</tr>
</tbody>
</table>

*Cohort was nondiabetic according to baseline FPG
IRIS=Insulin Resistance Intervention after Stroke
HOMA-IR=homeostatic model assessment of insulin resistance;
MI=myocardial infarction; TIA=transient ischemic attack

IRIS: Pioglitazone Lowers Risk for Stroke and TIA Vs Placebo

Rate of fatal or nonfatal stroke, or MI

HR=0.76 (0.32, 0.93)  
P=0.007

- Pioglitazone (n=1,939)
- Placebo (n=1,937)

% Subjects

9.0% (n=175)  
11.8% (n=228)

Stoke*

% Subjects

6.3% (n=150)  
7.7% (n=123)

MI

% Subjects

2.7% (n=52)  
4.0% (n=78)

About the trial:
Multicenter, double-blind trial assessed whether pioglitazone may benefit patients with cerebrovascular disease. N=3,876 patients with recent ischemic stroke or TIA and insulin resistance randomized to pioglitazone (target 45 mg/d; n=1,939) or placebo (n=1,937). Primary outcome: fatal or nonfatal stroke, or MI over 4.8 years.

*First event only
IRIS=Insulin Resistance Intervention after Stroke
MI=myocardial infarction
Kernan WN, et al; for the IRIS Trial Investigators.  
LEADER: Cardiovascular Safety Study of Liraglutide

- Assessed the long-term effects of the GLP-1 receptor agonist, liraglutide, on cardiovascular outcomes in high-risk patients with type 2 diabetes
- N=9,340 receiving standard care for type 2 diabetes assigned 1:1 to:
  - Liraglutide 1.8 mg/d* (n=4,668)
  - Placebo (n=4,672)
- Primary composite endpoint in time-to-event analysis over median 3.8 years:
  - First occurrence of death from CV causes, nonfatal (including silent) MI, or nonfatal stroke

<table>
<thead>
<tr>
<th>Select baseline characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Established CVD</td>
<td>72.4%</td>
</tr>
<tr>
<td>CKD stage 3 or higher</td>
<td>24.7%</td>
</tr>
<tr>
<td>CVD and CKD stage ≥3</td>
<td>15.8%</td>
</tr>
<tr>
<td>Mean diabetes duration</td>
<td>12.8 yrs</td>
</tr>
<tr>
<td>Mean A1C</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

*Or max tolerated dose
MI=myocardial infarction

LEADER: Fewer CV Events With Liraglutide Vs Placebo in High-Risk Patients

Primary composite endpoint: first occurrence of CV death, nonfatal (including silent) MI, or nonfatal stroke

13% lower relative risk with liraglutide

HR=0.87 (0.78, 0.97)

P<0.001 for noninferiority

P=0.01 for superiority

% Subjects who experienced a primary endpoint event

Liraglutide 1.8 mg/d* (n=4,668)

13.0% (n=608)

Placebo (n=4,672)

14.9%

*Or max tolerated dose
MI=myocardial infarction

LEADER: Rates of CV and All-Cause Death Lower With Liraglutide Vs Placebo in High-Risk Patients

Liraglutide 1.8 mg/d\(^*\) (n=4,668) vs Placebo (n=4,672)

**CV death:**
- 22% lower relative risk with liraglutide

- HR=0.78 (0.66, 0.93)
- \(P=0.007\)

**All-cause death:**
- 15% lower relative risk with liraglutide

- HR=0.85 (0.74, 0.97)
- \(P=0.02\)

*Or max tolerated dose

LEADER: Numerically Lower Rates of Nonfatal MI and Stroke, Heart Failure Hospitalization With Liraglutide Vs Placebo in High-Risk Patients

Nonfatal MI: 12% lower relative risk with liraglutide

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide 1.8 mg/d* (n=4,668)</th>
<th>Placebo (n=4,672)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Subjects</td>
<td>6.0% (n=281)</td>
<td>6.8% (n=317)</td>
</tr>
<tr>
<td>HR</td>
<td>0.88 (0.75, 1.03)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

Nonfatal stroke: 11% lower relative risk with liraglutide

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide 1.8 mg/d* (n=4,668)</th>
<th>Placebo (n=4,672)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Subjects</td>
<td>3.4% (n=159)</td>
<td>3.8% (n=177)</td>
</tr>
<tr>
<td>HR</td>
<td>0.89 (0.72, 1.11)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.30</td>
<td></td>
</tr>
</tbody>
</table>

Heart failure hospitalization: 12% lower relative risk with liraglutide

<table>
<thead>
<tr>
<th></th>
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<th>Placebo (n=4,672)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Subjects</td>
<td>4.7% (n=218)</td>
<td>5.3% (n=248)</td>
</tr>
<tr>
<td>HR</td>
<td>0.88 (0.75, 1.03)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

*Or max tolerated dose

LEADER: Lower Rate of Microvascular Events With Liraglutide Vs Placebo in High-Risk Patients

- Liraglutide 1.8 mg/d* (n=4,668)
- Placebo (n=4,672)

**Microvascular events:**
- 16% lower relative risk with liraglutide
  - HR=0.84 (0.73, 1.05)
  - P=0.14
  - 7.6% (n=355)
  - 8.9% (n=416)

**Retinopathy:**
- no between-group difference
  - HR=1.15 (0.87, 1.52)
  - P=0.33
  - 2.3% (n=106)
  - 2.0% (n=92)

**Nephropathy:**
- 22% lower relative risk with liraglutide
  - HR=0.78 (0.67, 0.2)
  - P=0.003
  - 5.7% (n=268)
  - 7.2% (n=337)

*Or max tolerated dose

**LEADER: Safety of Liraglutide Vs Placebo in High-Risk Patients**

- Incidence of overall adverse events similar for liraglutide and placebo
- Acute pancreatitis significantly lower with liraglutide
- Fewer patients assigned liraglutide experienced confirmed hypoglycemia
- Higher rates of benign and malignant neoplasms with liraglutide – difference not significant
- Gastrointestinal AE was most common leading to liraglutide discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (n=4,668)</th>
<th>Placebo (n=4,672)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>2,909 (62.3%)</td>
<td>2,839 (60.8%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Confirmed hypoglycemia</td>
<td>2,039 (43.7%)</td>
<td>2,130 (45.6%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>18 (0.4%)</td>
<td>23 (0.5%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Benign neoplasm</td>
<td>168 (3.6%)</td>
<td>145 (3.1%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>296 (6.3%)</td>
<td>279 (6.0%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>0</td>
<td>1 (&lt;0.1%)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

AE = adverse event

Lower All-Cause & CV Mortality With Empagliflozin Vs Placebo in High-Risk Patients

**EMP A-REG OUTCOME**

Placebo (n=2,333) vs Empagliflozin (n=4,687)

Death from any cause

- % Subjects: Placebo 8.3%, Empagliflozin 5.7%
- HR = 0.68 (0.57-0.82)
- RRR = 32%
- P < 0.001

Death from CV causes

- % Subjects: Placebo 5.9%, Empagliflozin 3.7%
- HR = 0.62 (0.49-0.77)
- RRR = 38%
- P < 0.001

39 patients would need to be treated over 3 years to prevent 1 death

CV = cardiovascular; MI = myocardial infarction; RRR = relative risk reduction

Lower Heart Failure Hospitalization With Empagliflozin Vs Placebo in High-Risk Patients

Placebo (n=2,333)  Empagliflozin (n=4,687)

Heart failure hospitalization

RRR=35%

% Subjects

4.1%  2.7%

HR=0.65 (0.50-0.85)

P=0.002

RRR=relative risk reduction

Empagliflozin reduces CV events & mortality in high-risk Type 2 diabetes.

Primary composite endpoint:
Death from CV causes, nonfatal MI, or nonfatal stroke

RRR = 14%

HR = 0.86 (0.74-0.99)
P < 0.001 for noninferiority
P = 0.04 for superiority

Key secondary endpoint:
Death from CV causes, nonfatal MI, nonfatal stroke, or UA hospitalization

RRR = 11%

HR = 0.89 (0.78-1.01)
P < 0.001 for noninferiority
P = 0.08 for superiority

EMPA-REG OUTCOME: Empagliflozin Reduces Nephropathy Progression Vs Placebo

Incident or worsening nephropathy: 39% lower relative risk with empagliflozin

- All patients had type 2 diabetes and eGFR $\geq$ 30 ml/min/1.73 kg²
- Consistent benefit seen across prespecified subgroups and empagliflozin 10- and 25-mg/d doses
- Benefit primarily driven by reduction in new-onset albuminuria

Assessment of renal outcomes was a prespecified component of the secondary microvascular outcome in EMPA-REG OUTCOME

EMPA-REG OUTCOME: Serum Creatinine Level & Renal Replacement Therapy After Treatment With Empagliflozin Vs Placebo

**Doubling of serum creatinine level:**
- 44% lower relative risk with empagliflozin
  - HR = 0.56 (0.39, 0.79)
  - P < 0.001

**Initiation of renal replacement therapy:**
- 55% lower relative risk with empagliflozin
  - HR = 0.45 (0.21, 0.97)
  - P = 0.04

<table>
<thead>
<tr>
<th>% Subjects</th>
<th>Empagliflozin (n=4,645)</th>
<th>Placebo (n=2,323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5%</td>
<td>(n=70)</td>
<td></td>
</tr>
<tr>
<td>2.6%</td>
<td>(n=60)</td>
<td></td>
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<table>
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<th>Empagliflozin (n=4,687)</th>
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<tr>
<td>0.3%</td>
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<tr>
<td>0.6%</td>
<td>(n=14)</td>
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All patients had type 2 diabetes and eGFR ≥30 ml/min/1.73 kg²
Assessment of renal outcomes was a prespecified component of the secondary microvascular outcome in EMPA-REG OUTCOME

Safety of Empagliflozin Vs Placebo in High-Risk Patients With Type 2 Diabetes

- Adverse events, serious AEs, and AEs leading to discontinuation were similar for empagliflozin and placebo.
- Rate of genital infections was higher for empagliflozin.

<table>
<thead>
<tr>
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<th>Placebo (n=2,333)</th>
<th>Empagliflozin* (n=4,687)</th>
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</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>2,139 (91.7%)</td>
<td>4,230 (90.2%)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>988 (42.3%)</td>
<td>1,789 (38.2%)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>453 (19.4%)</td>
<td>813 (17.3%)</td>
</tr>
<tr>
<td>Hypoglycemic AE</td>
<td>650 (27.9%)</td>
<td>1,303 (27.8%)</td>
</tr>
<tr>
<td>Volume depletion event</td>
<td>115 (4.9%)</td>
<td>239 (5.1%)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>155 (6.6%)</td>
<td>346 (5.2%)</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>91 (3.9%)</td>
<td>179 (3.8%)</td>
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</tbody>
</table>

Sharing Best Practices to Improve Care
CDE-Ambassador
A Novel Approach To Comprehensive Diabetes Care At The Primary Care Level

Fida Al-Atrash, MD
Mary Bierbrauer, RN, BSN, CDE
Nitesh D Kuhadiya, MD, MPH
Ajay Chaudhuri, MBBS, MRCP CP

Margaret Mersereau, RN, BSN, CDE
Nasir M. Khan, MD, FACP
Husam Ghanim, PHD
Patients & Methods

- This is a Retrospective review of patients with type 2 diabetes who were managed by their primary care provider and whose treatment was further organized/modified by a CDE-A.
- These patients were not seen by an endocrinologist during that period and for at least 3 years prior to inclusion in this management plan.
- A CDE-A was attached to this primary care group to advise/guide the management of diabetic patients in collaboration with the primary care physicians (PCP’s).
Patients & Methods

- The initial training of the CDE-A’s was for a period of 3 months by the endocrinologists.
- Following the initial training period, the CDE-A continued to be in regular consultation with the endocrinologists in case further advice was needed.
- Any changes to the anti-diabetic regimen that was suggested by the CDE-A had to be authorized by the PCP.
The first consecutive 100 subjects who were referred and seen by CDE-A were included in this analysis.

The start date was the first visit with the CDE-A (i.e. intervention visit).

The follow up visit date was the first scheduled visit with their physician following the intervention.

The last set of HbA1c and labs done prior to intervention was used as baseline data for the purpose of the analysis.
Patients & Methods

- Most patients met with the CDE-A twice during that period
- Follow up data (weight, BP) was documented on the date of follow up with PCP in 6 months then again at one year mark.
- Follow up laboratory values were collected around the dates of follow up
- Another group of 45 patients who had not been referred to the CDE-A and were managed by the PCP’s alone over the same period were used as the controls
In the CDE-A intervention group, HbA1c fell by 1.6±2.1% with a fall in HbA1c was 1.9±2.0% in those in whom anti-diabetic treatment was altered and by 1.1±2.1% in whom drug therapy was not changed six months post intervention.

The reduction in all the parameters were significantly greater in the intervention group when compared to controls.

HIGHLIGHTS OF RESULTS
Our data clearly show that the participation of the CDE-A, under the guidance of an endocrinologist at the primary care level led to a marked reduction in HbA1c, LDLc, triglycerides, blood pressure and body weight within 5 months.

These changes were dependent on changes in dietary habits and drug therapy including the addition or optimization in the doses of anti-diabetic drugs and insulin therapy.
HOPE AND OPTIMISM

- Diabetes can be prevented- Take advantage of the Diabetes Prevention Program

- Control the ABC’s- To prevent and reverse complications

- Understand the pathophysiology and utilize approaches to improve glycemic control without increasing the risk of hypoglycemia