The Alphabet Soup of Diabetes

Egils Bogdanovics M.D.
Hungerford Diabetes Center
Insulin: January 11, 1922

• 12 year old Leonard Thompson, on a starvation diet for 2 years received his first insulin injection

• A “thick brown muck” prepared by Banting and Best – 7.5cc in each buttock lowered glucose from 440 to 320 and resulted in an abscess at each injection site
“Diabetes is a chronic, debilitating and costly disease associated with severe complications, which poses severe risks for families, Member States and the entire world.”

UN Resolution 61/225. World Diabetes Day
Pathogenesis of Type 2 Diabetes

- Impaired Insulin Secretion
  - Increased HGP
  - Decreased Glucose Uptake

HGP = hepatic glucose production.
The Ominous Octet

- Impaired Insulin Secretion
- Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Reabsorption
- Increased Glucagon Secretion
- Increased HGP
- Neurotransmitter Dysfunction
- Decreased Glucose Uptake

DeFronzo RA, *Diabetes* 2009
Incretin Effect Is Reduced in Type 2 Diabetes

![Graphs showing plasma glucose and insulin levels in controls and Type 2 Diabetes patients after oral glucose load and IV glucose infusion.](image)

- *P≤0.05 compared with respective value after oral load.
Post-Meal Glucose Control Is Impaired in Type 2 Diabetes Due to Insufficient Insulin and Elevated Glucagon

The Kidney and Glucose Homeostasis

~180 g of glucose filtered per day

SGLT-2

S1 segment of proximal tubule

~90%

Reabsorption

~180 g/d

Distal S2/S3 segment of proximal tubule

~10%

Collecting duct

Virtually no glucose excreted in the urine

Renal Threshold for Glucose Excretion in Healthy Subjects

There is a Threshold Relationship Between Plasma Glucose and UGE

*Renal threshold for glucose
Renal Threshold for Glucose Excretion in T2DM: Increased

Renal Glucose Reabsorption and $RT_G$ are Elevated in T2DM

<table>
<thead>
<tr>
<th>Plasma Glucose (mg/dL)</th>
<th>Urinary Glucose Excretion (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>150</td>
<td>75</td>
</tr>
<tr>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>250</td>
<td>125</td>
</tr>
</tbody>
</table>

*Renal threshold for glucose

Healthy Subjects

$RT_G \sim 180$ mg/dL

T2DM

mean $RT_G \sim 240$ mg/dL

FDA Advisory Committee Sponsor Slide Presentation 10Jan2013
# 2016: 12 Classes of Drugs for Diabetes

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route of Administration</th>
<th>Year of approval</th>
<th>HbA1c reduction with monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Parenteral</td>
<td>1921</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Oral</td>
<td>1946</td>
<td>1.5</td>
</tr>
<tr>
<td>Metformin</td>
<td>Oral</td>
<td>1995</td>
<td>1.5</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Oral</td>
<td>1995</td>
<td>0.5-0.8</td>
</tr>
<tr>
<td>Thiazoladenediones</td>
<td>Oral</td>
<td>1997</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Metiglinides</td>
<td>Oral</td>
<td>1997</td>
<td>1.0-1.5</td>
</tr>
<tr>
<td>GLP-1 analogs</td>
<td>Parenteral</td>
<td>2005</td>
<td>0.6-1.5</td>
</tr>
<tr>
<td>Amylin Analogs</td>
<td>Parenteral</td>
<td>2005</td>
<td>0.6</td>
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<tr>
<td>DPP-IV inhibitors</td>
<td>Oral</td>
<td>2006</td>
<td>0.5-0.9</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Oral</td>
<td>2008</td>
<td>0.5</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Oral</td>
<td>2009</td>
<td>0.7</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Oral</td>
<td>2013</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Approach to the Management of Hyperglycemia

**Patient/Disease Features**

- Risks associated with hypoglycemia & other drug adverse effects
- Disease Duration
- Life expectancy
- Important comorbidities
- Established vascular complications
- Patient attitude & expected treatment efforts
- Resources & support system

**Glycemic targets.** Diabetes Care 2016; 39 (Suppl. 1): S39-S46
Metformin 1995

- First line therapy
- Weight neutral or negative
- No hypoglycemia risk
- Reduces liver glucose production
- DC if eGFR <30
- Not rec to start if <45
Sulfonylureas

The right dose differentiates a poison from a useful medicine

Paracelsus 1493-1541
ADA/EASD General Recommendations for Hyperglycemia Management

Healthy eating, weight control, increased physical activity

- Initial drug monotherapy
  - Efficacy (HbA1c)
  - Hypoglycemia
  - Weight
  - Side effects
  - Costs

- Two drug combinations
  - Efficacy (HbA1c)
  - Hypoglycemia
  - Weight
  - Major side effects
  - Costs

- Three drug combinations

- More complex insulin strategies

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

Metformin
- Metformin + Sulfonylurea (high efficacy, moderate risk of hypoglycemia)
- Metformin + Thiazolidinedione (low risk of hypoglycemia)
- Metformin + DPP-4 Inhibitor (intermediate efficacy, low risk of hypoglycemia)
- Metformin + GLP-1 receptor agonist (low efficacy, low risk of hypoglycemia)

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

Metformin + Sulfonylurea + TZD
- Metformin + Sulfonylurea + DPP-4-i
- Metformin + Sulfonylurea + GLP-1-RA

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 2-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

Insulin (multiple daily doses)
GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%
- MONOTHERAPY*
  - Metformin
  - GLP-1 RA
  - SGLT-2i
  - DPP-4i
  - TZD
  - AGI
  - SU/GLN

Entry A1C ≥ 7.5%
- MET or other 1st-line agent + 2nd-line agent
  - MET or other 1st-line agent + 2nd-line agent

Entry A1C > 9.0%
- SYMPTOMS
  - NO
    - DUAL Therapy
  - YES
    - INSULIN ± Other Agents

MONOTHERAPY*
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGI
- SU/GLN

DUAL THERAPY*
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGI
- SU/GLN

TRIPLE THERAPY*
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGI
- SU/GLN

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND
- Few adverse events and/or possible benefits
- Use with caution

PROGRESSION OF DISEASE

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Type 2 Diabetes and Glucagon

“One wonders if the development of a pharmacological means of suppressing glucagon to appropriate levels would not increase the effectiveness of available insulin, markedly reduce insulin requirements, and perhaps improve control of the diabetic state.”

Unger RH, NEJM 1971
Exendin-4: Exocrine gland **Endocrine** function

*Heloderma suspectum*
GLP1 Receptor Agonists

- Byetta; Bydureon  exenatide
- Victoza  liraglutide
- Tanzeum  albiglutide
- Trulicity  dulaglutide
- semaglutide
Large CV Outcomes Trials in T2D

SAVOR N
EXAMINE N
SUSTAIN 6 B
EXSCEL
NCT01986881


TECOS N
LEADER B
ELIXA N
EMPA REG B

CARMELINA
CAROLINA
CANVAS

REWIND
DECLARE

DPP-4 inhibitor
SGLT2 inhibitor
GLP-1 RA

LEADER trial: Primary Outcome

First occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis in patients with type 2 diabetes and high CV risk.

Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial

Adapted from: Marso SP et al., NEJM 2016
LEADER trial: Death from Cardiovascular Causes

Hazard ratio, 0.78 (95% CI, 0.66–0.93)
P=0.007

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial

Adapted from: Marso SP et al., NEJM 2016
Semaglutide Cardiovascular Outcomes.

A Primary Outcome

Hazard ratio, 0.74 (95% CI, 0.58–0.95)
P<0.001 for noninferiority
P=0.02 for superiority

No. at Risk
Placebo 1649 1616 1586 1566 1534 1508 1479
Semaglutide 1648 1619 1601 1584 1568 1543 1524

B Nonfatal Myocardial Infarction

Hazard ratio, 0.74 (95% CI, 0.51–1.08)
P=0.12

No. at Risk
Placebo 1649 1621 1598 1587 1562 1542 1516
Semaglutide 1648 1623 1609 1595 1582 1560 1543

C Nonfatal Stroke

Hazard ratio, 0.61 (95% CI, 0.38–0.99)
P=0.04

No. at Risk
Placebo 1649 1629 1611 1597 1571 1548 1528
Semaglutide 1648 1630 1619 1606 1593 1572 1558

D Death from Cardiovascular Causes

Hazard ratio, 0.98 (95% CI, 0.65–1.48)
P=0.92

No. at Risk
Placebo 1649 1637 1623 1617 1600 1584 1566
Semaglutide 1648 1634 1627 1617 1607 1589 1579

Newest Class: Sodium Glucose Transporter 2 Inhibitors
Phlorizin 1835
Familial Renal Glucosuria

- SLCA2 gene mutations
- Persistent UGE <0.1 to >100 g/day
- No hyperglycemia or diabetes
The Kidney and Glucose Homeostasis

~180 g of glucose filtered per day

S1 segment of proximal tubule
~90%

Reabsorption
~180 g/d

Distal S2/S3 segment of proximal tubule
~10%

SGLT-2

SGLT-1

Collecting duct

Virtually no glucose excreted in the urine

The Newest Antihyperglycemic Class

SGLT2 Inhibitors

SGLT2 inhibitors suppress the action of SGLT2

Increase urinary glucose excretion

Lost in urine

Reduce glucose reabsorption

Renal Threshold for Glucose Excretion in T2DM: Increased

Renal Glucose Reabsorption and RT_G are Elevated in T2DM

- Healthy Subjects: RT_G ~ 180 mg/dL
- T2DM: Mean RT_G ~ 240 mg/dL

*Renal threshold for glucose
SGLT2 Inhibition Lowers Renal Threshold for Glucose Excretion
SGLT2 Inhibitors

• INVOKANA canagliflozin
• FARXIGA dapagliflozin
• JARDIANCE empagliflozin
  sotagliflozin
Mean change from baseline in body weight (kg)

Control

Data presented are not from head-to-head studies


SGLT2 Inhibitors and Blood Pressure

Pressure change from baseline (mmHg)

Dapagliflozin 10 mg
Canagliflozin 300 mg

* P<0.001 vs PBO
** P<0.001 vs sitagliptin
a Comparison not specified


SGLT2 Inhibitor-Induced Euglycemic DKA

- Misdiagnosis? Type 2 diabetes vs latent autoimmune diabetes (LADA)

- Patients with type 2 diabetes can be susceptible to DKA under stressful conditions

- SGLT2-induced glycosuria lowers plasma glucose levels, predisposing to increased ketogenesis

Demonstration of the cascade of clinical events and metabolic changes that contribute sequentially to progressive clinical deterioration and development of full-blown episodes of euDKA.

Sliding Toward Euglycemic DKA

**Rapid development of euglycemic DKA**

- BG mildly high so further
- Insulin

**SGLT2 inhibitors**

- ↑ lipid oxidation lipolysis and glucagon

**↑ ketones**

- Induces nausea, ↓ caloric intake, volume depletion

**Worsened by**

- ↓ insulin and ↓ CHO intake

**↑ ketogenesis**

- ↑ β-hydroxybutyrate

**↑ mobilization of FFA and TGs**

Julio Rosenstock, and Ele Ferrannini Dia Care
2015;38:1638-1642

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DKA Prevention

• Euglycemic DKA is detectable, and therefore, preventable

• Patients can test their blood ketone at home

• Ketouria and ketonemia can be monitored

• Clinicians and patients need to be educated on the unique presentation of euglycemic DKA

Large CV Outcomes Trials in T2D

Primary Outcome
3-Point MACE

HR 0.86 (95.02% CI: 0.74, 0.99)
P = .04

Death From CV Cause

HR 0.62 (95% CI: 0.49, 0.77)
P < .0001

**EMPA-REG CV death, MI and stroke**

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with event/analysed</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86 (0.74, 0.99)*</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62 (0.49, 0.77)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87 (0.70, 1.09)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24 (0.92, 1.67)</td>
</tr>
</tbody>
</table>

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction

*95.02% CI
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

- **Simvastatin**¹ for 5.4 years: 30
  - High CV risk
  - 5% diabetes, 26% hypertension

- **Ramipril**² for 5 years: 56
  - High CV risk
  - 38% diabetes, 46% hypertension

- **Empagliflozin** for 3 years: 39
  - T2DM with high CV risk
  - 92% hypertension

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¹ 4S investigator. Lancet 1994; 344: 1383-89, [http://www.trialresultscenter.org/study2590-4S.htm](http://www.trialresultscenter.org/study2590-4S.htm);
Insulin
Decline in $\beta$ Cell Function in UKPDS

Rx: Insulin, metformin, sulfonylurea

$\beta$-Cell function (%) vs. Years from diagnosis

Dashed line shows extrapolation forward and backward from years 0 to 6 based on HOMA data from UKPDS.

Insulin concentrations

- 1922 U-5
- 1923 U-10 and U-20
- 1924 U-40
- 1925 U-80
- 1972 U-100 adopted
- 1958 U-500 Reg Beef
- 1998 U-500 Reg Hum
- 2015 U-200 Lispro
- 2015 U-300 Glargine
- 2015 U-200 Degludec
New Basal Insulins
A Basal/Bolus Treatment Program with Rapid-acting and Long-acting Analogs

Breakfast: Novolog, Humalog, or Apidra
Lunch: Aspart, Lispro, or Glulisine
Dinner: Aspart, Lispro, or Glulisine

Plasma insulin levels over time:
- Basal Insulin
- Time markers at 4:00, 8:00, 12:00, 16:00, 20:00, 24:00
Basal Insulin

• NPH
• Glargine: Lantus and Toujeo
• Detemir: Levemir
• Degludec: Tresiba
Insulin Glargine U-300
Glargine U-300

![Graph showing GIR (mg/kg/min) over time after SC injection (hours). The graph compares Toujeo 0.4 units/kg and Insulin glargine (100 units/ml) 0.4 units/kg treatments.]
Glargine U-300

- FDA approved February 25, 2015
- Three times as concentrated as glargine U-100
- Longer duration of action (36 hours or less) than glargine U-100; half-life about 23 hours
- Less variable plasma insulin exposure
- Similar safety and efficacy profile as U-100

Glargine U-300 vs Glargine U-100 in Type 2 Diabetes Meta-Analysis

<table>
<thead>
<tr>
<th></th>
<th>Glargine U-300 (n=1247)</th>
<th>Glargine U-100 (n=1249)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA$_1c$ (%) LS mean</td>
<td>-1.02</td>
<td>-1.02</td>
<td>Not specified</td>
</tr>
<tr>
<td>Weight (kg), LS mean</td>
<td>0.49</td>
<td>0.75</td>
<td>P = .058</td>
</tr>
<tr>
<td>Any hypoglycemia in 24 hr*</td>
<td>67.8</td>
<td>73.8</td>
<td>0.92 (0.87-0.96)</td>
</tr>
<tr>
<td>Any nocturnal hypoglycemia*</td>
<td>31.7</td>
<td>41.3</td>
<td>0.77 (0.69-0.85)</td>
</tr>
</tbody>
</table>

- Titrate dose every 3 days
- Higher daily dose may be needed

*Percent people with 1 or more events.
Insulin Degludec
Insulin Degludec

desB30 insulin

- Acylated (16 carbon fatty acid chain) at LysB29

FDA approval in 2015

PK

- Onset: 2 to 4 h
- Half life: ~25 h
- Duration of action: ≥ 42 h
- Steady state: ~3 to 4 d
- Detectable: ≥ 5 d
- 36-h stable level

Degludec MOA

- Phenol
  - Zn$^{2+}$
  - Degludec dihexamers ($T_3R_3$-state)

- Degludec multihexamers ($T_6$-state)
  - Zn$^{2+}$

- Degludec dimers
  - Degludec monomers

- Injected formulation
  - Depot formation

- Absorption
Insulin Degludec

- FDA approved September 25, 2015
- Prolonged action profile
- Formation of multihexamers
- Half-life of about 25 hours
- Duration of action longer than 42 hours
- Flat PK/PD profile of both 100 U/mL and 200 U/mL formulations

Degludec Titration

Relative serum trough concentrations of once-daily dosing in adults with type 1 diabetes\textsuperscript{2,3}

STEADY STATE ACHIEVED AFTER 3 TO 4 DAYS\textsuperscript{1}

Serum Tresiba\textsuperscript{®} concentrations (% day 10 concentration)

Days after first dose
Degludec Variable Dosing† vs Glargine U100 or Degludec Dosed Regularly*

Variable dosing with degludec had similar efficacy and similar hypoglycemia compared with either regular dosing regimen

*687 patients with T2D in a 26-wk, randomized, open-label, parallel-group, treat-to-target trial;
†Dosing schedule provided for a maximum dosing interval of 40 h and a minimum dosing interval of 8 h;
‡Morning defined as time period from waking up to first meal of day;
§Evening defined as time period from start of evening meal to bedtime.

## Lower Risk of Nocturnal Hypoglycemia With Insulin Degludec vs Insulin Glargine

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Group</th>
<th>Relative Hypoglycemia Risk Degludec Relative to Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEGIN Once Long (+extension)</td>
<td>Type 2 diabetes</td>
<td>-16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-43</td>
</tr>
<tr>
<td>BEGIN Basal-Bolus</td>
<td>Type 2 diabetes</td>
<td>-18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-25</td>
</tr>
<tr>
<td>BEGIN Basal-Bolus Long</td>
<td>Type 1 diabetes</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-25</td>
</tr>
</tbody>
</table>

**Nocturnal, Confirmed, %**

- BEGIN Once Long (+extension)
  - Type 2 diabetes: -43%
  - Type 1 diabetes: -25%

- BEGIN Basal-Bolus
  - Type 2 diabetes: -25%

- BEGIN Basal-Bolus Long
  - Type 1 diabetes: -25%

---

New Basal Insulins

- Reduced Intrasubject Variability
- True 24 Hour Duration
- Reduced Nocturnal Hypoglycemia
- Reduced Injection Burden in T2DM
Pulmonary Delivery of Insulin

Inhaled insulin device

Airway

Alveoli

PK of Inhaled Insulin vs Insulin Lispro

Maximum serum insulin concentration reached by 12-15 min after inhalation of insulin human 8 U

Afrezza® PI 2014.[8]
Median time to maximum effect of insulin human, inhaled, of approximately 53 min
Continuous Glucose Monitoring (CGM)
The First Step to An Artificial Pancreas: Minimed 530G
Continuous Glucose Monitor Sensor
Where is the ball going?
Hypoglycemia Unawareness

“with Freddie, no reaction occurred after a blood sugar of 60 mg/dl and with Alice S., none occurred when the blood sugar was as low as 40 … Dangerous hypoglycemia may occur without warning symptoms.”

Joslin, E 1924
Case #1: Question

• What do you think this patient’s sensor report will look like with A1C of 7.2%?
“The person with diabetes who knows the most lives the longest”

Elliot Joslin