Recent Advances in Management of Diabetes Mellitus
Diabetes: Also A Global Disease...

Estimated global prevalence of diabetes

151 million
2000

382 million
2013

592 million
2035

The Top 10s
(Number of People with Diabetes)

<table>
<thead>
<tr>
<th>COUNTRY/TERRITORY</th>
<th>2013 MILLIONS</th>
<th>COUNTRY/TERRITORY</th>
<th>2035 MILLIONS</th>
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<tbody>
<tr>
<td>China</td>
<td>98.4</td>
<td>China</td>
<td>142.7</td>
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<tr>
<td>India</td>
<td>65.1</td>
<td>India</td>
<td>109.0</td>
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<tr>
<td>United States of America</td>
<td>24.4</td>
<td>United States of America</td>
<td>29.7</td>
</tr>
<tr>
<td>Brazil</td>
<td>11.9</td>
<td>Brazil</td>
<td>19.2</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>10.9</td>
<td>Mexico</td>
<td>15.7</td>
</tr>
<tr>
<td>Mexico</td>
<td>8.7</td>
<td>Indonesia</td>
<td>14.1</td>
</tr>
<tr>
<td>Indonesia</td>
<td>8.5</td>
<td>Egypt</td>
<td>13.1</td>
</tr>
<tr>
<td>Germany</td>
<td>7.6</td>
<td>Pakistan</td>
<td>12.8</td>
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<tr>
<td>Egypt</td>
<td>7.5</td>
<td>Turkey</td>
<td>11.8</td>
</tr>
<tr>
<td>Japan</td>
<td>7.2</td>
<td>Russian Federation</td>
<td>11.2</td>
</tr>
</tbody>
</table>

The “Ominous Octet” Of Type 2 Diabetes

- Hyperglycemia
- Increased Glucose Absorption
- Islet-α cell
- Increased Glucagon Secretion
- Increased HPG
- Decreased Incretin Effect
- Decreased Insulin Secretion
- Decreased Glucose Uptake
- Increased Lipolysis
- Increased Glucose Re-absorption
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

Glycaemic Control is Only Part of the Story…

Control of cardiovascular risk factors

HbA$_{1c}$ at target

Lower risk of hypoglycaemia

Fewer complications and a longer life span

Avoid weight increase

Gæde et al. NEJM 2003;348:383–93
The Challenge of Blood Glucose Control

Hypoglycaemia / weight gain

HbA\textsubscript{1c}
Goals of Therapy

- Improve patient outcomes
- Minimize the risk of complications and their cost
- Ideally and simultaneously address
  - deteriorating β-cell function
  - A1C, fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels
- Lower risk of hypoglycemia, weight gain, or cardiovascular disease contributors
- 1% reduction in A1C
  - 37% decrease in risk for microvascular complications
  - 21% decrease in risk of death related to diabetes

An ideal treatment would reduce cardiovascular risk factors as well as control blood glucose levels
Available Anti-Diabetic Drugs

Oral Anti-diabetic Agents (OADs)

- **SU**: Glibenclamide, Glipizide, Gliclazide, Glimepiride
- **Biguanides**: Metformin
- **Alpha Glucosidase Inhibitors**: Acarbose, Voglibose, Miglitol
- **Glitazones**: Pioglitazone, Rosiglitazone
- **Meglitinides**: Repaglinide, Nateglinide
- **DPP4 inhibitors**: Sitagliptin, Saxagliptin
- **SGLT2 Inhibitors**: Canagliflozin, Dapagliflozin

Injectable

1. GLP-1 Analogs
2. Insulins
Limitations of Current Treatments

- American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)
  - advocate a stepwise escalation of intervention
  - starting with lifestyle modification and metformin
- Oral antidiabetic drug (OAD) therapies
  - improve β-cell function during the first year of treatment
  - β-cell function declines progressively thereafter
  - A1C level parallels these changes in β-cell function
- Need therapies to sustain improvements in β-cell function

Unmet Needs in Diabetes

Current antidiabetic treatments

Unmet need: Increasing level of importance

Future potential: targeting cardiometabolic symptoms

Routine Screening | Patient Compliance | Side-effect profile | Safety | Prolonged Efficacy | Disease Modification

Obesity | Hypertension | Diabetes | Dyelipidemia

Incretin mimetics | PPAR agonists | SGLT inhibitors | Cb1 receptor antagonists | GK activators | Other novel agents

Advances in Therapy: Falling Short of Goals

SU=Sulfonylurea; TZDs=thiazolidinediones; T2DM=type 2 diabetes.

A New Paradigm

Earlier Insulin Introduction

Glycemic Burden for > 15 yrs...
Five fold more risk of complications...

Current Paradigm

Progression of disease

Diet & exercise
Oral monotherapy
Oral combination
Insulin ± oral agents

Brown et al Diab care 2004, 27; 1535-1540
Problems with Oral Therapy

• Only moderately effective  
  (~1% lowering of HBA1c)

• Type 2 diabetes is a progressive disease  
  (~1% rise in HBA1c in 4 years)

• Progressive addition of therapies necessary to achieve target blood sugars

• Specific problems:
  • Long acting sulphonylureas: prolonged hypoglycaemia
  • Metformin: lactic acidosis (renal failure / low output cardiac failure)
Rationale for Early Insulin Therapy in Type 2 Diabetes

- Majority of patients remain poorly controlled with OADs alone
- Adding insulin therapy can help correct insulin resistance and impaired insulin secretion
- Proven safe & effective; no “insulin failure”
- Insulin therapy earlier in the course of disease may preserve β-cell function and improve long-term glycemic control
Early Insulin Treatment Prolongs B-cell Function; Promotes Metabolic Control

Early Insulin Therapy Improves B-cell Function And Glycaemic Control

Weng et al. Lancet 2008; 371: 1753-60
Early, Intensive Glycaemic Control Reduces Incidence Complications

Better Subsequent Glycaemic Control After Intensive Treatment

- 20-year interventional trial from 1977 to 1997
- 10-year post-trial monitoring from 1997 to 2007
- Median overall follow-up 17.0 years, range 16 to 30 years

**Conventional therapy, median HbA$_1c$ 7.9%**

**Intensive therapy, median HbA$_1c$ 7.0%**

Recommended treatment target <7.0%

Steno2: Follow-up Period Demonstrated Previous Intensive Therapy Confers Long-term Benefits

- Reduced risk of mortality at end of follow-up period, despite HbA$_{1c}$ returning to similar levels in both conventional and intensive groups

<table>
<thead>
<tr>
<th>years of follow up</th>
<th>Conventional therapy</th>
<th>Intensive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 yr</td>
<td>Microvascular</td>
<td>Microvascular</td>
</tr>
<tr>
<td>8 yr</td>
<td>Macrovascular</td>
<td>Macrovascular</td>
</tr>
<tr>
<td>13 yr</td>
<td>Mortality</td>
<td>Mortality</td>
</tr>
</tbody>
</table>

Adapted from [http://www.steno.dk](http://www.steno.dk)
Steno2: Benefits From Earlier Intensive Treatment Continue To Be Seen Many Years Later

- Kaplan–Meier estimates of the composite endpoint of death from cardiovascular causes, nonfatal MI, coronary-artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, amputation, or surgery for peripheral atherosclerotic artery disease in the conventional therapy and the intensive therapy groups.

Adapted from [http://www.steno.dk](http://www.steno.dk)
Legacy Effect Points To Benefits Of Early Glycaemic Control

- Risk of long-term complications acquired by initially failing to achieve glycaemic control is not eliminated by obtaining control in later years
- Early hyperglycaemia may therefore be an important factor in developing long-term risk
- This ‘metabolic memory’ or ‘legacy effect’ suggests that intensifying insulin treatment early to achieve control has long-term benefits

Mechanisms of Metabolic Memory

- Hyperglycaemia
- Mitochondria
- AGE
- Proinflammatory cytokines
- Diabetic complications
- DNA damage
- PKC
- PARP
- Peroxynitrite
- Nitrotyrosine
- Endothelial dysfunction

AGE, advanced glycation end products; PARP, poly(ADP-ribose) polymerase; PKC, Protein kinase C; ROS, reactive oxygen species;

The Importance of Achieving Early Glycaemic Control

- Early hyperglycaemia may be an important factor in developing long-term risk
- ‘Metabolic memory’ or ‘legacy effect’
  - Damaging effects of early hyperglycaemia persists despite later correction of hyperglycaemia
- Early insulin treatment benefits:
  - Blood glucose control
  - Anti-inflammatory
  - Anti-oxidant
  - Anti-apoptotic
  - Cardioprotective
  - Neuroprotective

Timely Insulin Rather than Aggressive Therapy is Necessary to Maintain Control

“The evidence obtained from ACCORD, ADVANCE and VADT does not suggest the need for major changes in glycaemic control targets”

**Macrovascular disease**
- In high-risk patients, there was no significant reduction in CVD outcomes with intensive therapy
- Lowering HbA₁c to <7% soon after diagnosis is associated with reduced long-term risk of macrovascular disease
- Thus, a general HbA₁c goal of <7% appears reasonable

**Microvascular disease**
- Lowering HbA₁c to <7% has been shown to reduce microvascular and neuropathic complications
- Thus, HbA₁c goal in general is <7%

Insulins are Changing….

- Recombinant DNA technology allowed large-scale production of synthetic human insulin
Types of Insulin

- Regular insulins
- Insulin analogs
- Pre-mixed insulin
Limitations of Soluble Human Insulin

- Slowly absorbed → Sub-optimal postprandial glycemic control
- Longer duration of action → increased hypoglycaemic risk
- Lower quality of life → Injections and meals must be planned
Modern Insulins: Definition

- Modified or 'Modern insulins’or Newer Insulins
- Molecules
  - differ by one or a few amino acids from primary structure of insulin
- Developed
  - to provide more physiologic replacement after s.c injection than human insulin
- Made possible by the advent of Biotechnology- rDNA technology
- Provide more optimal time-action profiles
Modern Insulin provides

- Meal-time flexibility (Rapid acting)
- Superior PPG Reduction
- Better Glycemic control
- Less variability
- Less Hypoglycemia
- Less undesired weight gain (Insulin detemir only)
- Available in Easy-to-use Pens with painless needles
# Currently Available Insulin Analogues

<table>
<thead>
<tr>
<th></th>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting analogues</strong></td>
<td>Insulin aspart</td>
<td>NovoRapid®</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td></td>
<td>Insulin lispro</td>
<td>Humalog®</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td></td>
<td>Insulin glulisine</td>
<td>Apidra®</td>
<td>sanofi aventis</td>
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<tr>
<td><strong>Basal analogues</strong></td>
<td>Insulin detemir</td>
<td>Levemir®</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td></td>
<td>Insulin glargine</td>
<td>Lantus®</td>
<td>sanofi aventis</td>
</tr>
<tr>
<td></td>
<td>Insulin Degludec</td>
<td>Tresiba®</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td><strong>Biphasic premixed analogues</strong></td>
<td>Biphasic insulin aspart</td>
<td>NovoMix®</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td></td>
<td>Biphasic insulin lispro</td>
<td>Humalog® Mix</td>
<td>Eli Lilly</td>
</tr>
</tbody>
</table>
Unmet Needs of Existing Insulins

- Current basal insulins need to be administered at the same time every day\textsuperscript{1}
- Variability of glucose lowering effect of current insulins – A limiting factor
- Currently available long-acting insulin analogues may not always last 24 hours\textsuperscript{2}
- Reducing variability & extending duration of action can reduce incidence of hypoglycaemia\textsuperscript{2} without compromising glycaemic control

Ideal Basal Insulin: Key Characteristics

- Duration of action: control fasting blood glucose with one injection in all individuals
- Flat time–action profile: lower risk of hypoglycaemia
- Day-to-day variability: less hypo- and hyperglycaemia
Insulin Degludec

- A novel ultralong-acting basal insulin analogue with unique mechanism of protraction
- Flat peakless pharmacokinetic profile
- Half life of 25.4 hours and duration of action: up to 42 hours
- Significantly lower episodes of nocturnal hypoglycaemia
Stable 24-hour Coverage in T1DM
Mean & Individual Blood Glucose Profiles

Figure shows mean and individual blood glucose profiles following once-daily s.c. dosing of IDeg (0.6 U/kg) for 8 days.

Kurtzhals et al. Diabetologia 2011;54(Suppl. 1):S426; Diabetes 2011;60(Suppl. 1A):LB12.
Within-subject Variability over Time- 4 Times Lower for Insulin Degludec

Day-to-day variability (CV %)

Area under the GIR curve (time interval, hours)

T1D, 54 patients, single-centre, randomised, double-blind, parallel-group, 12-day trial. Variability was assessed at steady state by clamps on days 6, 9 and 12.

Degludec Plus

Degludec Plus is a new generation ultra-long acting basal insulin with a bolus boost

- offers a unique powerful once-daily start option for people with type 2 diabetes
- offers to bring a majority of patients to HbA1c target without hypoglycaemia
Insulin Glargine (U300)

- **EDITION 1 study**
  - 21% reduction in severe or confirmed nocturnal hypoglycemia from month 3 to 6
  - Similar HbA1c control versus U100
- Flatter profile than U100
- Only ~3 hours prolonged duration of action may limit opportunity for flexible dosing

Sources: EASD 2013 abstract 220 & ADA 2013 abstracts 43-LB, 113-OR and 920-P
Pegylated Insulin Lispro

- A flatter profile than glargine in T1DM
- Improved glycemic control in T1DM compared to glargine despite reductions in mealtime insulin
  - Total hypoglycaemia rate was higher
  - Rate of nocturnal hypoglycaemia lower than glargine

Source: EASD 2013 abstract 1030
Other Insulins

• Biodel’s U400 human insulin formulation shows similar onset of action as insulin lispro in preclinical diabetes model
• Hyaluronidase administered as pre-treatment in insulin pump therapy improves postprandial glucose in T1DM, increased time in euglycemia & lowered PP hypoglycaemic risk by 42%
• Pulmonary human insulin (Afrezza) showed dose proportionality when given by inhaler but with high rate of hypoglycemia (85% vs 12% of sc route)
• Limited & varying effect seen with ORAMED’s oral insulin
Smart Insulins

• The new, injectable nano-network is composed of a mixture containing nanoparticles with a solid core of insulin, modified dextran and glucose oxidase enzymes.

• Nanoparticle cores is given either a positively charged or negatively charged biocompatible coating.

• This technology effectively creates a ‘closed-loop’ system that mimics the activity of the pancreas in a healthy person, releasing insulin in response to glucose level changes,”

Zhen Gu et al. ACS Nano 2013, vol 7; No 5: 4194-4201
Injectable Nano Network For Glucose Mediated Insulin Delivery

Zhen Gu et al. ACS Nano 2013, vol 7; No 5: 4194-4201
Non-invasive forms of Insulin via New Drug Delivery Technologies

**Inhaled insulins:**
- Exubera, withdrawn from market in October 2007.
- Novo Nordisk’s AERx iDMS inhaled insulin system suspended in January 2008
- March 2008 Lilly/Alkermes decided to cease the development of AIR inhaled insulin program

**Future potential of inhaled insulins:**
- Technosphere Insulin - phase III clinical trials.
- Nasulin - Phase II clinical trials

**Oral insulins:**
- Oral-lyn, phase III studies (GEN084-OL) in US

**Future potential of oral insulins**
- Emisphere developed an oral insulin tablet
- Biocon’s IN-105 - phase IIa
- Oramed’s oral insulin capsule - phase IIa clinical trials

**Future potential of insulin patches**
- Alteza Therapeutics’ PassPort System consists of a basal insulin transdermal patch
- Encapsulation System’s U-Strip Insulin System
These new classes of drugs that have entered the market or are expected to enter the market include:

- Glucagon-like peptide-1 (GLP-1) agonists;
- DPP-IV inhibitors;
- PPAR agonists;
- Sodium glucose cotransporter (SGLT) inhibitors;
- Cannabinoid CB1 receptor antagonists;
- Glucokinase activators (GKA);
- Other novel agents

Incretin-based Therapies

- Human GLP-1 analogs, e.g. Liraglutide
- Exendin-based therapies, e.g. Exenatide
- GLP-1 receptor agonists
- DPP-4 inhibitors, e.g. Sitagliptin, Saxagliptin, Vildagliptin

History of Developments in Incretin Based Therapies

- Exenatide: 2005
- Sitagliptin: 2006
- Vildagliptin: 2007
- Saxagliptin: 2009
- Liraglutide: 2010
- Linagliptin: 2011
- Alogliptin: 2013
- Exenatide once weekly: 2012
# GLP-1 Receptor Agonists & DPP-4 Inhibitors: Launched Products

<table>
<thead>
<tr>
<th>GLP-1 receptor agonists</th>
<th>DPP-4 inhibitors</th>
</tr>
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<tbody>
<tr>
<td>Exenatide BID</td>
<td>Sitagliptin</td>
</tr>
<tr>
<td>Liraglutide OD</td>
<td>Vildagliptin</td>
</tr>
<tr>
<td>Exenatide OW</td>
<td>Saxagliptin</td>
</tr>
<tr>
<td>Lixisenatide OD (EU, Mexico, Japan &amp; Australia)</td>
<td>Linagliptin</td>
</tr>
<tr>
<td></td>
<td>Alogliptin (Japan)</td>
</tr>
<tr>
<td></td>
<td>Analaglptin (Japan)</td>
</tr>
<tr>
<td></td>
<td>Teneligliptin (Japan)</td>
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</table>
## GLP-1 Receptor Agonists & DPP-4 Inhibitors: Pipeline

<table>
<thead>
<tr>
<th>GLP-1 receptor agonists</th>
<th>DPP-4 inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Dulaglutide OW</td>
<td>Dutogliptin</td>
</tr>
<tr>
<td>Albiglutide OW / Bi-weekly</td>
<td>Gemigliptin</td>
</tr>
<tr>
<td></td>
<td>SK-0403</td>
</tr>
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</table>
The Incretin Effect

• Incretin effects on the beta cell
Incretin Effect on Insulin Secretion

Control subjects (n=8)

People with Type 2 diabetes (n=14)

Incretin effect

Oral glucose load
Intravenous glucose infusion

Nauck et al. *Diabetologia*. 1986
How Do Incretins Work?

Food triggers the release of incretin hormones (GLP-1 and GIP) by the intestines into the blood.

The body makes DPP-4, an enzyme that rapidly breaks down GLP-1 and GIP.

GIP = glucose-dependent insulinotropic polypeptide.
GLP-1 has Effects on GI, CVS & CNS

- Learning & memory function (animal studies)
- Neuroprotection (animal studies)
- Satiety
- Food intake
- Gastric emptying & acid secretion
- Protection & improved function

Postulated Effects of GLP-1 in the Cardiovascular System

**Kidney**
- Increases diuresis and sodium excretion in response to sodium overload and volume expansion

**Heart** (myocardium)
- Increases glucose uptake (non-insulin mechanisms)
  - nitric oxide synthesis
  - p38 MAP kinase activity
  - GLUT-1 translocation
- Activates anti-apoptotic kinases

**Vascular system**
- Nitric oxide-dependent vasorelaxation
- Reduces TNFα-mediated secretion of PAI-1 by cultured endothelial cells

Limitation of Human GLP-1

- Therapeutic use of human GLP-1 is not practical
- Rapid degradation by DPP-4 enzyme
  - elimination half-life of about 2 minutes
- Two alternative approaches to harnessing the therapeutic potential of the incretin system have been pursued
  - GLP-1 receptor agonists
  - DPP-4 inhibitors

# Incretin Mimetics and Incretin Enhancers

<table>
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<tr>
<th>Properties/effect</th>
<th>Incretin mimetics</th>
<th>DPP-4 inhibitors</th>
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<tbody>
<tr>
<td>Mechanism of stimulation of insulin secretion exclusively through GLP-1 effect</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Restitution of insulin secretion (2 phases)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Maintained counter-regulation by glucagon in hypoglycaemia</td>
<td>Yes</td>
<td>Not tested</td>
</tr>
<tr>
<td>Inhibition of gastric emptying</td>
<td>Yes</td>
<td>Marginal</td>
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<tr>
<td>Effect on body weight</td>
<td>Weight loss</td>
<td>Weight neutral</td>
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<tr>
<td>Side effects</td>
<td>Nausea</td>
<td>None observed</td>
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<tr>
<td>Administration</td>
<td>Subcutaneous</td>
<td>Oral</td>
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<tr>
<td>GLP1 concentrations</td>
<td>Pharmacological</td>
<td>Physiological</td>
</tr>
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</table>

**Comparison of Liraglutide & Exenatide**

<table>
<thead>
<tr>
<th><strong>Liraglutide</strong></th>
<th><strong>Exenatide</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Human GLP-1 analogue</td>
<td>Exendin-4 analogue</td>
</tr>
<tr>
<td>97% homology to native GLP-1</td>
<td>53% homology to native GLP-1</td>
</tr>
<tr>
<td>Once daily</td>
<td>twice daily</td>
</tr>
<tr>
<td>Can be taken without relation to meal timing</td>
<td>To be taken before meals</td>
</tr>
<tr>
<td>Safe in mild to moderate renal failure</td>
<td>Safety in renal failure not established</td>
</tr>
<tr>
<td>Approved for use in combination with metformin, sulfonylureas &amp; TZD’s</td>
<td>Approved for use in combination with metformin and sulfonylureas</td>
</tr>
</tbody>
</table>

Taspoglutide

Converting Native GLP-1 into Taspoglutide

- The active form of native GLP-1 is rapidly degraded by peptidase
- Aminoisobutylic acid (Aid) substitutions block enzymatic degradations
- Agonist activity comparable with native form
- Once weekly dosing supported by zinc-based formulation

Amylin

- Discovered in 1987
- Co-secreted with insulin
  - Absent in type 1 DM, deficient in type 2 DM
- Slows gastric emptying and digestion
- Decreases post-prandial glucagon
- Satiety effect CNS
Pramlintide

• Analog of a beta-cell protein named amylin (islet-associated polypeptide)

• Physiologic actions
  • Delayed gastric emptying
  • Reduced post-prandial glucose excursion
  • Neuroendocrine effects on appetite and satiety

• FDA approved for use in type 1 and type 2 diabetes who are not controlled on insulin therapy

• Injected with each meal

• Trend to weight loss (or no gain with improved A1c)
Bromocriptine

- Annual / seasonal metabolic rhythm
- Hibernation in vertebrates – seasonal insulin resistance
- During winter more calorie consumption & conservation, vice-versa in summers
- In modern lifestyle annual metabolic clock got stuck in winter mode
- Dopaminergic brain pathways involved
### Lipids in Diabetics Before & After Bromocriptine

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol</th>
<th>LDL cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bromocriptine</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Before</td>
<td>190 ± 7</td>
<td>117 ± 7</td>
<td>42 ± 2</td>
<td>157 ± 15</td>
</tr>
<tr>
<td>After</td>
<td>176 ± 7</td>
<td>110 ± 7</td>
<td>38 ± 2</td>
<td>140 ± 17</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>202 ± 10</td>
<td>123 ± 10</td>
<td>43 ± 3</td>
<td>180 ± 14</td>
</tr>
<tr>
<td>After</td>
<td>192 ± 13</td>
<td>117 ± 13</td>
<td>38 ± 3</td>
<td>186 ± 26</td>
</tr>
</tbody>
</table>

Data are means ± SD

Approved by FDA in May 2009 for T2DM

**Cycloset 0.8mg tab, up titrated weekly up to 6 tabs**

**To be taken within 2 hr after awakening in morning**

Diabetes Care 23:1154–1161, 2000
Rationale for Sodium Dependent Glucose Transporters – 2 (SGLT 2) Inhibitors

- Inhibit glucose reabsorption in renal proximal tubule
- Resultant glucosuria leads to a decline in plasma glucose & reversal of glucotoxicity
- This therapy is simple & nonspecific
- Even patients with refractory type 2 diabetes are likely to respond
SGLT2 Mediates Glucose Reabsorption in The Kidney

Major transporter of glucose in the kidney

- Low affinity, high capacity for glucose
- Nearly exclusively expressed in the kidney
- Responsible for ~90% of renal glucose reabsorption in the proximal tubule

Mechanism of Action of SGLT2 Inhibitors

**Inhibition of SGLT2**  ➔  **Reversal of glucotoxicity**

**Insulin sensitivity in muscle**
- ↑ GLUT4 translocation
- ↑ Insulin signaling
- Other

**Insulin sensitivity in liver**
- ↓ Glucose-6-phosphatase

**Gluconeogenesis**
- Decreased Cori cycle
- ↓ PEP carboxykinase

**β-Cell function**

# Investigational SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Phase</th>
<th>Agent</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>Empagliflozin</td>
<td>AstraZeneca/Bristol-Myers Squibb</td>
</tr>
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**Canagliflozin:** FDA Approved in 2013  
**Dapagliflozin:** EMEA approved in 2012, recommended by USFDA advisory committee, Dec 2013
Glucagon Receptor Antagonists

• Discovery:
  ➢ Potent, selective, competitive and reversible glucagon receptors antagonists with acceptable pharmacokinetics have been identified
  ➢ The glucagon receptor antagonists improve glucose handling in animal models of type 2 diabetes

• Development:
  ➢ The glucagon receptor antagonist NN2501 is currently in phase 1 with the aim of evaluating the concept in humans
Dual-Acting Peptide for Diabetes (DAPD): a GLP1/glucagon hybrid peptide, exhibits both GLP-1 receptor agonist & glucagon receptor antagonist activities

A PEGylated version of DAPD prolongs plasma half-life

*In vitro* PEG-DAPD stimulated glucose-dependent insulin secretion from rat islets & inhibited glucagon activity in rat hepatocytes

No effect on gastric emptying – GI side effects less likely

Peroxisome Proliferator – Activated Receptor (PPAR) Agonists & Their Potential Therapeutic Indications

- PPAR alpha agonists – dyslipidemia
- PPAR gamma agonists – type 2 diabetes
- PPAR alpha/gamma (dual, co-agonists) – Muraglitazar, Tesaglitazar, Ragaglitazar, Naveglitazar
- PPAR alpha/gamma/delta (pan agonists) - being developed for type 2 diabetes and dyslipidemia
- PPAR delta – obesity, prevention of fluid retention?

The 1st Approved Agent in Glitazar's Class: Saroglitazar
Only approved in India
Development of Tesaglitazar & Muraglitazar has been discontinued
Glucokinase (GK) is a member of the hexokinase family of enzymes. It is responsible for the phosphorylation of glucose to glucose-6-phosphate for further utilization in cells. It plays a key role in glucose homeostasis. Phosphorylation of glucose promotes glycogen synthesis, while in the β-cell it results in insulin release. Activators of glucokinase increase the sensitivity of the enzyme to glucose, leading to increased insulin secretion and liver glycogen synthesis and a decrease in liver glucose output.
# Status Summary of Selected Glucokinase Activators (GKAs)

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<th>Status</th>
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<tr>
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<td>Hoffmann-La-Roche</td>
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<td>R1511 or GK3</td>
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<td>Phase 1</td>
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<tr>
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Continuous Glucose Monitoring System (CGMS) & Insulin Pump
ADA Recommendations: Glucose Monitoring

- Self-monitoring of blood glucose should be carried out 3+ times daily for patients using multiple insulin injections or insulin pump therapy (A)

- For patients using less frequent insulin injections, noninsulin therapy, or medical nutrition therapy alone
  - SMBG may be useful as a guide to success of therapy (E)
  - However, several recent trials have called into question clinical utility, cost-effectiveness, of routine SMBG in non–insulin-treated patients

What Does NICE Say about SMBG in Type 2 Diabetes?

**Self-monitoring**
- Offer self-monitoring of plasma glucose to a person newly diagnosed with type 2 diabetes only as an integral part of his or her self-management education. Discuss its purpose and agree how it should be interpreted and acted upon.

**Make available to:**
- Those on insulin
- Those on oral medication to provide information on hypoglycaemia
- Assess changes during medication or lifestyle changes, or illness
- Ensure safety during activities, including driving.

**Assess at least annually in a structured way:**
- Self-monitoring skills
- Quality and appropriate frequency of testing
- The use made of results obtained
- The impact on quality of life
- The continued benefit
- The equipment used.

NICE Clinical Guideline 87; May 2009
What is a CGM? (Continuous Glucose Monitor)

- A device that provides “real-time” glucose readings and data about trends in glucose levels

- Reads the glucose levels under the skin every 1-5 minutes (10-15 minute delay)

- Provides alarms for high and low glucose levels and trend information
Continuous Glucose Monitoring

WHY?

• Prevention of low blood sugars (alarms)
• Prevention of high blood sugars (ketones)
• Minimize wide glucose fluctuations
• Behavior Modification
• Prevention of Complications (?)
Continuous Glucose Monitoring: The Technology

Three Parts

A. Sensor
B. Transmitter
C. Receiver/Monitor

*(Understanding Pumps and CGMs, p.103)*
**Interstitial Fluid (ISF) Measurement**

- ISF (G2) is highly comparable to blood glucose (G1) because ISF is fed by the capillaries.
- Steady-state difference between blood and ISF is compensated for by sensor calibration.
- During rapid changes in blood glucose, the 10 minute ISF response lag time is accounted for in the CGMS software algorithm.

Illustration adapted from Rebrin K, et al., Amer Phys Soc 1999; E562
What Type of Data Will We Get?

“Real-time” (Immediate)

- Trend graphs
- Alarms
- Trend arrows
Trend graphs – Knowing a glucose level is 240 mg/dl may not be as important as knowing the “trend.”

- **Projected alarms**: 10, 20, or 30 minute warning of impending hypo- or hyperglycemia (Navigator and Guardian devices)
- **Threshold alarms**: warning when glucose is below or above a set value (all devices)

Gives the up-to-the-minute glucose value and a rate of change arrow

*(Understanding Pumps and CGMs, Chapter 17, p.109)*
History of Insulin Pumps

• First introduced in the 1960’s by a Los Angeles Physician by the name of Dr. Arnold Kadish.
Insulin Pumps today

- ACCU-CHEK SPIRIT – ROCHE
- AMIGO – NIPRO CORPORATION
- DANA DIABECARE 11S – SOAIL DEVELOPMENT
- MINIMED PARADIGM REVEL – MEDTRONIC
- OMNIPOD – INSULET CORPORATION
- ONE TOUCH PING – ANIMAS CORPORATION
Indications for Insulin Pump Therapy

Intermittent insulin injections are not meeting treatment goals & leads to suboptimal outcome measures including:

1. Frequent & unpredictable fluctuations in blood glucose levels
2. Patient perception that diabetes management impedes the pursuit of personal or professional goals.
3. A1C >7.0-7.5%, accompanied by frequent severe hypoglycemia (<55mg/dl).
4. Hypoglycemic events requiring third-party assistance or interfering with work, school, or family obligations.

2009 The American Association of Diabetes Educators.
Indications for Insulin Pump Therapy

- Recurrent hypoglycemia, Nocturnal hypoglycemia, Activity induced Hypoglycemia & Hypoglycemic Unawareness.
- Pregnancy
- Recurrent DKA
- Dawn Phenomenon
- Gastroparesis
- Patient preference, Meal time flexibility & normalization of lifestyle
Insulin Used In Pumps

Rapid-Acting Analogs are Preferred

- Insulin Aspart (Novorapid)
- Insulin Lispro (Humalog)
- Insulin Glulisine (Apidra)

Modes of Delivery

- Basal
- Bolus
Basal Insulin

- Steady “Drip” of Insulin
- Matches glucose released by liver
- Meets body’s basic energy needs
- May need different settings at different times of day
Bolus Insulin

- Given to “cover” carbs in meals and snacks.
- Used to “correct” high blood glucose levels
Insulin Infusion

- Durable, clog-resistant tubing carries insulin from the pump to the infusion set.
- Infusion set delivers insulin into the fatty layer below skin.
- Set uses either a flexible plastic catheter (cannula) or a steel needle.
- Almost always disconnectable near the infusion site.
Pharmacokinetic Advantages: Insulin Pumps vs. MDI

- Uses rapid acting insulin
- More predictable absorption than with human insulin (Pump 2.8% variation and S/C 10-52%)
- Uses one injection site for 2 to 3 days.
- Reduces variations in absorption due to site rotation
- Eliminates most of the subcutaneous insulin depot
- Programmable insulin delivery allows closest match with physiological needs

Lauritzen: Diabetologia 1983; 24:326-9
Pharmacokinetic Advantages

**Basal Rate** (Precise 0.05 or 0.1u pulses)
- Preprogrammed
- Continuous flow of fast-acting insulin
- Matching variable metabolic needs

**Meal Boluses**
- Matching insulin to carbohydrates in meal

**Correction bolus**
- For high BG

![Graph showing basal rate and meal boluses](image)
Clinical Advantages of Pump Therapy

- Reduction in HbA1c
- Less BG Variability
- Reduction in duration, frequency and severity of hypoglycemia
- Better psychosocial outcomes & quality of life
To Summarize…

- Diabetes has reached epidemic proportions in India
- Many drugs available but unmet need persists
- Numerous drugs in the pipeline but long term safety & efficacy needs to be evaluated
- However, each patient unique… thus individualize treatment
Thank You...!!!