What’s New in Type 2?

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Therapy considerations in T2DM

- Thiazolidinediones
- DPP IV inhibitors
- GLP 1 agonists
- Insulin
  - Type
  - Delivery
- Horizon scanning
Therapeutic targets


Harrogate and District NHS Foundation Trust
Panel 2: Desired characteristics of glycaemic control therapies in type 2 diabetes

The therapy, in addition to achieving target HbA₁c, should:

- Be disease modifying (i.e., reverse one or more of the underlying pathophysiological processes)
  - (i) Reduce chronic fuel surfeit
  - (ii) Protect islet β-cells from progressive failure
  - (iii) Prevent adipose tissue dysfunction, including abnormal fat distribution and inflammation
  - (iv) Restore normal islet α-cell function and incretin physiology
  - (v) Restore normal regulation of hepatic glucose production
  - (vi) Enhance skeletal muscle mitochondrial function/oxidative metabolism
  - (vii) Enhance energy expenditure and thermogenesis
- Sustain good metabolic control with low therapy-associated unwanted effects
- Enhance quality of life of patients
- Reduce diabetes microvascular and macrovascular complications
- Reduce diabetes-related mortality (includes cardiovascular disease-related), and all-cause mortality

HbA₁c = glycated haemoglobin A₁c
ADA and EASD algorithm

- Reinforce lifestyle interventions at every visit and check HbA$_{1C}$ every 3 months until HbA$_{1C}$ is <7% and then at least every 6 months. The interventions should be changed if HbA$_{1C}$ is ≥7%.

**Tier 1: Well validated core therapies**

- **At diagnosis:**
  - Lifestyle + metformin

  **Step 1**
  - Lifestyle and metformin + basal insulin
  - Lifestyle and metformin + sulphonylurea\(^a\)

  **Step 2**
  - Lifestyle and metformin + pioglitazone
    - No hypoglycaemia
    - Oedema/CHF
    - Bone loss
  - Lifestyle and metformin + GLP-1 agonist\(^b\)
    - No hypoglycaemia
    - Weight loss
    - Nausea/vomiting

  **Step 3**
  - Lifestyle and metformin + intensive insulin
  - Lifestyle and metformin + pioglitazone + sulphonylurea\(^a\)
  - Lifestyle and metformin + basal insulin

**Tier 2: Less well validated studies**

- Lifestyle and metformin + pioglitazone
  - No hypoglycaemia
  - Oedema/CHF
  - Bone loss

\(^a\)Sulphonylureas other than glybenclamide (glyburide) or chlorpropamide.

\(^b\)Insufficient clinical use to be confident regarding safety.

Nathan et al. Diabetes Care 2008;31:1–11
Natural History of Type 2 Diabetes

Adapted from Kendall DM, Cuddihy RM, Bergenstal RM. 2009 International Diabetes Center. All rights reserved.
## Legacy Effect of Earlier Glucose Control

*After median 8.5 years post-trial follow-up*

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
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</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR: 12%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>(P): 0.029</td>
<td>0.040</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 25%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>(P): 0.0099</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 16%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>(P): 0.052</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 6%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>(P): 0.44</td>
<td>0.007</td>
</tr>
</tbody>
</table>

\(RRR = \text{Relative Risk Reduction}, \ P = \text{Log Rank}\)
There is no place for pioglitazone in the management of type 2 diabetes
Pioglitazone – pros and cons

• Bladder cancer: RR 1.12-1.33
  – Avoid if active or PH of bladder ca, or if have uninvestigated haematuria
  – Consider risk factors: smoking, age

• Osteoporosis

• PROACTIVE study: 16% RR in all-cause mortality, non-fatal MI and stroke
Pioglitazone – case study

- PH, 78 M
- Jan’11: wt 90.1 kg, HbA1c 72 mmol/mol (8.7%)
  - Glargine 20 u am, 50 u pm
  - Metformin 850 mg tds
  - Sitagliptin 100 mg od
- Added pioglitazone 30 mg od
  - Glargine dose reduced to 16 u am, 44 u pm
- July ’11: wt 98.1 kg, HbA1c 57.5 mmol/mol (7.4%)
  - Lows during the night
Physiological effects of GLP1

**Pancreas**
- Insulin secretion (glucose-dependent) and beta-cell sensitivity
- Insulin synthesis
- Glucagon secretion (glucose-dependent)
- Beta-cell mass*

**Brain**
- Energy intake*

**Liver**
- Hepatic glucose output

**GI tract**
- Decreased motility

*in animal studies
The family of incretin-based therapies

- Human GLP-1 analogues, e.g. liraglutide
- Exendin-based therapies, e.g. exenatide
- GLP-1 receptor agonists
- DPP-4 inhibitors, e.g. sitagliptin, vildagliptin

Incretin-based therapies
DPP IV inhibitors

• Comparable improvement in glycaemic control to SUs but with much less hypoglycaemia and weight neutral
• Useful in renal failure
  – Saxagliptin: renal dose 2.5 mg od
  – Linagliptin: biliary excretion, no dose adjustment needed
• CV outcome trials in progress
Exenatide – national audit

6 months after exenatide start in 1959 patients
Exenatide in real clinical use - conclusion

• 60% of patients achieve the ideal of both weight loss and fall in HbA1c

• However many patients experience a predominant response to only one of weight or HbA1c with more minimal response to the other

• Hence only 28% achieve the NICE guideline

• The NICE guideline should change to acknowledge that significant weight loss or significant HbA1c response may represent a beneficial response
Composite end points that matter

\[ HbA_{1c} < 7.0\% \]

+  
No weight gain

+  
No hypoglycaemia
Composite endpoint: $\text{HbA}_1\text{c}<7.0\%$, no weight gain and no hypos

LEAD studies
No head-to-head comparison in the LEAD programme between liraglutide 1.2mg and glargine or exenatide

Liraglutide 1.8 mg is superior (*$p<0.01$; **$p<0.0001$)
Liraglutide 1.2 mg is superior (***$p<0.0001$)
Percentages are from logistic regression model adjusted for trial, previous treatment and with baseline HbA$_1$C and weight as covariates

## Comparative odds ratio for achieving the composite endpoint

HbA$_1c$<7.0%, no weight gain, no minor or major hypoglycaemia

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds ratio favouring liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide 1.8 mg vs TZD</td>
<td>10.3***</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg vs exenatide</td>
<td></td>
</tr>
<tr>
<td>Liraglutide 1.8 mg vs SU</td>
<td>7.3***</td>
</tr>
<tr>
<td>Liraglutide 1.2 mg vs. SU</td>
<td>5.3***</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg vs glargine</td>
<td>3.7***</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg vs sitagliptin</td>
<td>3.4***</td>
</tr>
<tr>
<td>Liraglutide 1.2 mg vs sitagliptin</td>
<td>2.6***</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg vs exenatide</td>
<td>2.0**</td>
</tr>
</tbody>
</table>

*p<0.005; ***p<0.0001 in favour of liraglutide 1.8 mg
Based on meta-analysis of LEAD 1–6. Adjusted for previous treatment, baseline values and randomisation. LOCF, ITT

Exenatide ER

DeYoung MB et al. *Diab Tech Ther* 2011;13:1145-54
Exenatide ER (Bydureon)
Microsphere deposits

DeYoung MB et al. Diab Tech Ther 2011;13:1145-54
Exenatide ER vs Glargine

DURATION 3 Lancet 2010;375:2234-43

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Exenatide ER vs glargine: targets

DURATION 3 *Lancet* 2010;375:2234-43
Exenatide ER vs BD

DURATION 5 J Clin End Met 2011;96:1301-10
Exenatide ER vs BD: targets

DURATION 5 J Clin End Met 2011;96:1301-10
Long vs short-acting GLP 1 agonists

• Advantages:
  – Better glycaemic control
  – Better tolerated
  – Better adherence

• Disadvantages:
  – Less weight loss
  – Slower onset of action
  – More difficult to stop
GLP1 agonists and insulin

Figure 2: Change in HbA1c over 30 weeks.

Figure 3: Changes in body weight and glucose levels over 30 weeks.

GLP1 and insulin – case study

• PC, 52 M
• Jan ’10: wt 135.6 kg HbA1c 86 mmol/mol (10.0%)
  – On 256 units insulin/d
  – Started liraglutide: titrated to 1.8 mg od
  – Treatment costs injectable therapy £5.84/day
• April ’11: wt 129.0 kg HbA1c 62 mmol/mol (7.8%)
  – On 68 units insulin/d
  – Treatment costs injectable therapy £5.69/day
NPH/isophane insulin should be first choice for initiation in type 2 diabetes
Glycaemic control

Waugh N et al. HTA assessment 2010;14:No 6
ACCORD – intensive BG lowering

Figure 2. Kaplan–Meier Curves for the Primary Outcome and Death from Any Cause.

Hypoglycaemia and mortality: The ACCORD experience

Bonds DE et al. *BMJ* 2010; 340: b4909
## Hypoglycaemia and mortality: The ADVANCE experience

### Table: Severe Hypoglycaemia and Mortality

<table>
<thead>
<tr>
<th>Events</th>
<th>Severe Hypoglycaemia (N=231)</th>
<th>No Severe Hypoglycaemia (N=10,909)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major macrovascular events</td>
<td>33 (15.9)</td>
<td>1114 (10.2)</td>
<td>4.05 (2.86–5.74)</td>
</tr>
<tr>
<td>Unadjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major microvascular events</td>
<td>24 (11.5)</td>
<td>1107 (10.1)</td>
<td>2.39 (1.60–3.59)</td>
</tr>
<tr>
<td>Unadjusted model</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>45 (19.5)</td>
<td>986 (9.0)</td>
<td>4.86 (3.60–6.57)</td>
</tr>
<tr>
<td>Unadjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>22 (9.5)</td>
<td>520 (4.8)</td>
<td>4.87 (3.17–7.49)</td>
</tr>
<tr>
<td>Unadjusted model</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular disease</td>
<td>23 (10.0)</td>
<td>466 (4.3)</td>
<td>4.82 (3.16–7.35)</td>
</tr>
<tr>
<td>Unadjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted model</td>
<td></td>
<td></td>
<td>2.80 (1.64–4.79)</td>
</tr>
</tbody>
</table>

Pathophysiologival cardiovascular consequences of hypoglycaemia

CRP, C-reactive protein; IL-6, interleukin 6; VEGF, vascular endothelial growth factor

Desouza et al. Diabetes Care 2010;33:1389–94
Hypoglycaemia in clinical practice

- 3% of people with type 2 diabetes experienced severe hypoglycaemia over a 12 month period
- People of all ages who experienced severe hypoglycaemia had a 79% increased risk of suffering an acute cardiovascular event
- Hypoglycaemia directly preceded an acute cardiovascular event in over 25% of people
- People who experienced severe hypoglycaemia incurred a 2 fold greater health related expenditure
Nocturnal hypoglycaemia

- Almost 50% of all episodes of severe hypoglycaemia occur at night during sleep\(^1\)
- Nocturnal hypoglycaemia is a major concern to patients and family, and is a particular barrier to insulin dose titration\(^2,3\)
- Nocturnal hypoglycaemia has a major detrimental effect on mood and well being the following day\(^1\)
- Nocturnal hypoglycaemia is linked to ‘dead in bed’ syndrome\(^4\)
- Recurrent nocturnal hypoglycaemia is linked to development of hypoglycaemia unawareness\(^5\)
- Avoiding nocturnal hypoglycaemia is a key clinical imperative

Consequences of hypoglycaemia for driving in the UK

Patients managed by insulin, **must** inform the DVLA of their treatment and **also if the following apply**:

- You suffer more than one episode of disabling hypoglycaemia (low blood sugar) within 12 months, or if you or your carer feels you are at high risk of developing disabling hypoglycaemia
- You develop impaired awareness of hypoglycaemia (difficulty in recognising the warning symptoms of low blood sugar)
- You suffer disabling hypoglycaemia while driving


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Higher rate of severe hypoglycaemia with intensive glycaemic control*

<table>
<thead>
<tr>
<th>Study</th>
<th>HbA1c (%)</th>
<th>Annualised rate of severe hypoglycaemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS¹</td>
<td>7.9</td>
<td>0.7</td>
</tr>
<tr>
<td>ADVANCE²</td>
<td>7.1</td>
<td>1.4</td>
</tr>
<tr>
<td>ACCORD³</td>
<td>7.2</td>
<td>1.8</td>
</tr>
<tr>
<td>VADT⁴</td>
<td>7.3</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>6.5</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>6.4</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>8.4</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>6.9</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Intensive glycaemic control was defined differently in these trials. †Hypoglycaemia requiring any assistance in glucose-lowering trials. Conv, conventional therapy; Gly, glibenclamide; HbA1c, glycated haemoglobin; HR, hazard ratio; Ins, insulin; Int, intensive therapy; Std, standard therapy

Myth 1: hypoglycaemia does not occur in T2DM

- **T1D**
  - 55% of severe and 43% of all hypoglycaemic episodes occur during sleep in T1D
  - 36% of severe episodes that occurred while awake had no warning signs

SU, sulphonylurea

1UK Hypoglycaemia Study Group *Diabetologia* 2007;50:1140–7;
Myth 2: hypoglycaemia does not have major consequences in T2DM

• Similar clinical (CV and neurological) consequences to T1D

However:

• T2D population is older
  – Symptoms can be different
  – Hypoglycaemia unawareness
  – More comorbidities
    • high frequency of CVD
    • osteoporosis – higher fracture risk
    • longer hospital stay duration

• Event rate increases with disease duration – progressive disease

CV, cardiovascular; CVD, CV disease
Hypoglycaemic event rates are reduced with basal analogue insulins vs. NPH in T2DM

* PM dose

Threshold of <3.1 mmol/L for confirmed hypoglycaemia

Threshold of <3.9 mmol/L for confirmed hypoglycaemia

Hypoglycaemia and basal analogues

Waugh N et al. HTA assessment 2010;14:No 6
Bullet Points for New Clinical Solutions

• There is a legacy effect of good glycaemic control so NICE targets are essential and combination drug therapy is inevitable

• The ideal drug combination therapy for glucose control combines low risk of hypoglycaemia, weight reduction and CV safety

• Newer agents, particularly those targeting the GLP1 receptor show potential but CV safety data is awaited
"Can’t sleep, can’t eat, can’t concentrate, feel worthless, anxious all the time, want to die....."

"I’m sorry to hear that, doctor!"
“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”