DIABETES UPDATES: Glucose Lowering Therapy and Insulin

Iskandar Idris

Associate Professor in Diabetes & Honorary Consultant Physician
University of Nottingham & Royal Derby Hospital
Agenda

• Setting the scene
  – Rise in young onset type 2 diabetes
  – Case presentation

• Target for glucose control

• NICE guidelines

• Pharmacological therapies for type 2 diabetes

• Non pharmacological therapies

• Conclusions
Prevalence of diabetes is rising
Type 2 diabetes rise in under-40s, says Cardiff research
Long-Term Complications and Mortality in Young-Onset Diabetes: Type 2 diabetes is more hazardous and lethal than type 1 diabetes

A: Kaplan-Meier survival curve for T2DM15–30 (n = 357) and T1DM15–30 (n = 470) patients.

A: Kaplan-Meier survival curve for T2DM15–30 (n = 357) and T1DM15–30 (n = 470) patients.
SW 29 years old

- Diagnosed type 2 diabetes January 2011
- BMI 37; minimal alcohol intake
- HbA1c 6.8% fasting glucose :10.1
- Total cholesterol 5.3mmol/L HDL cholesterol 0.8mmol/l Triglyceride 5.8mmol/L
- Blood pressure 151/88
- GP prescribed metformin therapy
SW 29 years old

• Lost 4 stones in weight by May 2011 – training for marathon
• HbA1c 7.6%; fasting glucose 11.1mmol/L
• Total cholesterol 4.8 mmol/L, HDL 1.0mmol/L, Triglyceride 3.9mmol/L
• Blood pressure 139/82 mmHg
• GP added a sulphonylurea therapy
SW 29 years old

- December 2012 – attended clinic here at RDH
- BMI 36.8 HbA1c 8.1% fasting glucose 11.7
- Total cholesterol: 5.0mmol/L; Triglyceride 4.0
- Blood pressure 142/82
- ‘Healthy lifestyle’ – physically active, still runs, healthy balanced diet
- No retinopathy; ACR 5.0
- Epworth: 6; Berlin score: low risk for Sleep Apnoea
Questions?

• What HbA1c target should we strive for?
• What options do we have to manage this patients ‘glucose’?
• What are the potential problems associated with that?
• Can we ‘cure’ his diabetes?
Glucose Control Legacy Effect (metabolic memory)

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D.,
David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.
Combination therapy: A conservative target-based approach

Adapted from Campbell IW. Br J Cardiol 2000; 7: 625–631.
Combination therapy: An early, intensive, target-based approach

<table>
<thead>
<tr>
<th>Time since diagnosis</th>
<th>Monotherapy</th>
<th>Combination therapy</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HbA$_1^c$ (%)

Target HbA$_1^c$?

? Insulin ? GLP-1, ?alternatives
How low should we go with HbA$_{1c}$ for prevention of cardiovascular disease in type 2 diabetes?

- $<6.0\%$
- $<6.5\%$
- $<7.0\%$
- or $<7.5\%$

**ACCORD**$^1$  
Action to Control Cardiovascular Risk in Diabetes

**ADVANCE**$^2$  
Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation

ACCORD: Treatment effect on all-cause mortality

Patients with events (%)

Time (years)

Intensive therapy

Standard therapy

HR 1.22 (1.01-1.46)
P = 0.04

ADVANCE: Treatment effect on all-cause mortality

Cumulative incidence (%) vs. Follow-up (months)

- Standard control
- Intensive control

HR 0.93 (0.83-1.06)
P = 0.28

ADVANCE: Treatment effect on primary microvascular outcome

New/worsening nephropathy, retinopathy

Cumulative incidence (%)

Follow-up (months)

HR 0.86 (0.77-0.97)
P = 0.01

Standard control

Intensive control

## Differences between the ACCORD and ADVANCE studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACCORD</th>
<th>ADVANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome (intensive vs standard)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median HbA&lt;sub&gt;1c&lt;/sub&gt; at study end (%)</td>
<td>6.4 vs 7.5*</td>
<td>6.4 vs 7.0*</td>
</tr>
<tr>
<td>Death from any cause (%)</td>
<td>5.0 vs 4.0*</td>
<td>8.9 vs 9.6</td>
</tr>
<tr>
<td>Death from cardiovascular cause (%)</td>
<td>2.6 vs 1.8*</td>
<td>4.5 vs 5.2</td>
</tr>
<tr>
<td>Nonfatal MI (%)</td>
<td>3.6 vs 4.6*</td>
<td>2.7 vs 2.8</td>
</tr>
<tr>
<td>Nonfatal stroke (%)</td>
<td>1.3 vs 1.2</td>
<td>3.8 vs 3.8</td>
</tr>
<tr>
<td>Major/severe hypoglycemia (%/y)</td>
<td>3.1 vs 1.0*</td>
<td>0.7 vs 0.4</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>3.5 vs 0.4</td>
<td>0.0 vs -1.0*</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>10 vs 10</td>
<td>8 vs 8</td>
</tr>
</tbody>
</table>

*The comparison between the intensive and the standard arms was significant.
## Further analysis of tight glucose control studies on CVD risk outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Earlier diabetes</th>
<th>More advanced diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UKPDS</td>
<td>ADVANCE</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0</td>
<td>7 years</td>
</tr>
<tr>
<td>Hba1c at baseline</td>
<td>7.1%</td>
<td>7.5%</td>
</tr>
<tr>
<td>% on insulin</td>
<td>0</td>
<td>1.5%</td>
</tr>
<tr>
<td>CV mortality</td>
<td>1.02</td>
<td>0.88</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.96</td>
<td>0.93</td>
</tr>
</tbody>
</table>
Rapid Update NICE Glycaemic Algorithm

<table>
<thead>
<tr>
<th>Consider first</th>
<th>MET</th>
<th>SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considered as recommended in CG66*</td>
<td>Considered as recommended in CG66</td>
<td></td>
</tr>
</tbody>
</table>

*NICE Clinical guideline 66 Type 2 diabetes: the management of type 2 diabetes (update)*

www.nice.org.uk/Guidance/CG66

<table>
<thead>
<tr>
<th>Consider second</th>
<th>SU</th>
<th>TZD</th>
<th>DPP-4 inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considered as recommended in CG66*</td>
<td>Significant risk of hypoglycaemia</td>
<td>SU/MET not tolerated (or contraindicated)</td>
<td>Significant risk of hypoglycaemia</td>
</tr>
</tbody>
</table>

- Agree level of %HbA1c for intervention – generally HbA1c=6.5%, but may differ by individual
- Monitor for expected deterioration

<table>
<thead>
<tr>
<th>Consider third</th>
<th>NPH Insulin</th>
<th>Other insulin</th>
<th>TZD</th>
<th>DPP-4 inhibitor</th>
<th>Exenatide</th>
<th>Acarbose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considered as recommended in CG66*</td>
<td>1. Long-acting insulin analogues - if require assistance from a carer/HCP to administer insulin, and where this would reduce injections from twice to once a day - if lifestyle restricted by recurrent, symptomatic hypoglycaemia - if would otherwise need twice-daily basal insulin and oral glucose-lowering medications - if cannot manage device for injection of NPH insulin 2. Premix insulin as recommended in CG66*</td>
<td></td>
<td>Significant risk of hypoglycaemia</td>
<td>SU/MET not tolerated (or contraindicated)</td>
<td>Insulin not acceptable or inappropriate</td>
<td>Considered as recommended in CG66*</td>
</tr>
</tbody>
</table>

- BMI=35 kg/m² and other specific psychological/medical problems associated with high body weight
- BMI<35 kg/m² and for whom initiation of insulin would have significant implications, or where weight loss would benefit other comorbidities

<table>
<thead>
<tr>
<th>Consider fourth</th>
<th>NPH Insulin</th>
<th>Other insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considered as recommended in CG66*</td>
<td>1. Long-acting insulin analogues - initiate as above - switch if • target HbA1c not reached because of significant hypoglycaemia • significant hypoglycaemia on NPH insulin regardless of the HbA1c level. • cannot manage device for insulin • require assistance from carer /HCP to administer insulin injections where this would reduce injections from twice to once a day 2. Premix insulin as recommended in CG66*</td>
<td></td>
</tr>
</tbody>
</table>

- Agree level of %HbA1c for intervention – generally HbA1c=7.5%, but may differ by individual
- Monitor for expected deterioration
- Increase insulin dose and intensify regime with time

NICE Clinical Guideline 87 May 2009
Mortality in patients with metformin vs SU vs non diabetes (matched controls)

Bannister CA et al. Diabe Obes Metab2014
What options do we have to manage this patient’s ‘glucose’?

- SU
- Insulin
- GLP-1 analogue
- DPP-4 inhibitors
- SGLT2 inhibitors
- Diet
Pathogenesis of type 2 diabetes – from the Triumvurate to.......
.......the Ominous Octet
Relationship between change in HbA1c and change in weight at one year post insulin initiation in type 2 diabetes

Owen et al. Diabetes, Obesity and Metabolism, 2010

N=6032
Responders* to insulin therapy in patients with type 2 diabetes: Relationship with weight

To determine the best cut-off for BMI that would predict response/non response we tested all possible cut-points and select the most significant (having made an adjustment for the repeated testing). This gives a cut-point of 35.3, so fitting this back into the models above gives the following:

<table>
<thead>
<tr>
<th>BMI at baseline</th>
<th>Odds ratio for response</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt;35.3</td>
<td>0.797</td>
<td>(0.612, 0.919)</td>
<td>0.040</td>
</tr>
</tbody>
</table>

*Responders: *HbA1c reduction by >1% or
*HbA1c achieving target value of <7% at one year after insulin initiation

Owen et al. Diabetes, Obesity and Metabolism, 2010
U-shaped association between glycaemic control and mortality in type 2 diabetes

Adapted from Lancet 2010; doi:10.1016/S0140-6736(09)61969-3
ACCORD: Mortality HR for Individual Agents

Mortality Hazard Ratios for Post-Randomization Prescription of Glycemia Medications After Also Adjusting for the Glycemia Intervention Effect

Avandia SPC March 2008
## Comparison between DPP-IV inhibitors and GLP-1 analogues

<table>
<thead>
<tr>
<th>DPP-IV inhibitors</th>
<th>GLP-1 analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>Exenatide</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Liraglutide</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Lixisenatide</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Exenatide LAR (Bydureon)</td>
</tr>
</tbody>
</table>

- **Orally available**
- **Injectable only**
- **Small increase in endogenous GLP-1**
- **Large increase in GLP-1 level**
- **Little effect on gastric emptying**
- **Induces delay in gastric emptying**
- **Do not cause nausea/ vomiting**
- **Likely to induce nausea/ vomiting**
- **No effect on weight**
- **Induces weight loss**
- **Effects are mediated by multiple receptors**
- **Effects are mediated by GLP-1 Receptor**
Choice of GLP-1 receptor agonist: short acting versus long acting

The pharmacological profile and half-life of a GLP-1 receptor agonist influences its effects on postprandial and basal (fasting) glycaemia

SHORT ACTING
GLP-1 receptor agonists
eg. Lixisenatide OD, Exenatide BD

Effect on
FPG

Effect on
PPG

LONG ACTING
GLP-1 receptor agonists
eg. Liraglutide OD, Exenatide QW

Effect on
FPG

Effect on
PPG

FPG = fasting plasma glucose  PPG = postprandial glucose

Fineman MS et al. Diabetes Obes Metab 2012;14:675-88
Indication for GLP-1 analogue

• BMI >35
• BMI <35, where alternative therapy may induce further weight gain which may adversely effects comorbidities

• HbA1c >7.5%
• Occupational reasons where Insulin initiation is not appropriate
Incretin-Based Therapy of Type 2 Diabetes: Incretin Mimetics vs. Incretin Enhancers

GLP-1 level during treatment with GLP-1 agonist

GLP-1 level during treatment with DPP-IV inhibitor

Incretin-Based Therapy of Type 2 Diabetes: Incretin Mimetics vs. Incretin Enhancers

GLP-1 effects

Increasing plasma GLP-1 concentrations

GLP-1 effects

Insulin secretion

Gastric emptying

Glucagon secretion

Appetite

Food intake

Weight loss

Vomiting

Diarrhoea

Nausea

Abdominal pain

Plasma glucose
GLP-1: Typical Results?

Not magic wand for everyone-
  15% no effect
evidence for loss of treatment response

Fullness sensation- Gastric or CNS?

A1c reduction and weight loss do not correlate

Relearning to eat- satiety sense

Data support 20% fewer calories ingested

Expense and insurance coverage
HbA1c at baseline independently predict response to DPP4 inhibitor

Table 2 Effect of DPP-4 inhibitors on HbA1c reduction from baseline (Δ)

<table>
<thead>
<tr>
<th>DPP-4 inhibitor</th>
<th>Arms</th>
<th>Number</th>
<th>Mean agea</th>
<th>Mean basal HbA1ca</th>
<th>ΔHbA1c</th>
<th>95 % CI</th>
<th>I² (%)</th>
<th>P value</th>
<th>Model</th>
<th>Q test P value</th>
<th>ΔHbA1c (%)b</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vildagliptin</td>
<td>24</td>
<td>8,283</td>
<td>56.1</td>
<td>8.05</td>
<td>−0.85</td>
<td>−1.0, −0.70</td>
<td>99</td>
<td>&lt;0.0001</td>
<td>RE</td>
<td>&lt;0.0001</td>
<td>−0.79</td>
<td>−0.88, −0.71</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>24</td>
<td>5,129</td>
<td>55.1</td>
<td>7.96</td>
<td>−0.71</td>
<td>−0.80, −0.61</td>
<td>94</td>
<td>&lt;0.0001</td>
<td>RE</td>
<td>&lt;0.0001</td>
<td>−0.70</td>
<td>−0.78, −0.61</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>12</td>
<td>2,312</td>
<td>55.3</td>
<td>7.98</td>
<td>−0.70</td>
<td>−0.79, −0.61</td>
<td>87</td>
<td>&lt;0.0001</td>
<td>RE</td>
<td>&lt;0.0001</td>
<td>−0.70</td>
<td>−0.82, −0.58</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>8</td>
<td>2,986</td>
<td>58.0</td>
<td>8.05</td>
<td>−0.51</td>
<td>−0.69, −0.33</td>
<td>96</td>
<td>&lt;0.0001</td>
<td>RE</td>
<td>&lt;0.0001</td>
<td>−0.46</td>
<td>−0.60, −0.31</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>11</td>
<td>1,793</td>
<td>55.2</td>
<td>8.14</td>
<td>−0.76</td>
<td>−0.86, −0.66</td>
<td>90</td>
<td>&lt;0.0001</td>
<td>RE</td>
<td>&lt;0.0001</td>
<td>−0.73</td>
<td>−0.86, −0.61</td>
</tr>
<tr>
<td>All</td>
<td>79</td>
<td>20,503</td>
<td>56.0</td>
<td>8.03</td>
<td>−0.74</td>
<td>−0.80, −0.67</td>
<td>97</td>
<td>&lt;0.0001</td>
<td>RE</td>
<td>&lt;0.0001</td>
<td>−0.71</td>
<td>−0.76, −0.66</td>
</tr>
</tbody>
</table>

RE random effect

a Mean value weighted by sample size

b Adjusted by basal HbA1c value (8 %)

Esposito et al. Endocrine 2013
HbA1c at baseline independently predict response to DPP4 inhibitor
HbA1c at baseline independently predict response but obesity predict non responders to DPP4 inhibitors

Table 1: Baseline characteristics of type 2 diabetes patients prescribed DPP4 inhibitor as add-on intensification treatment to other OAD therapy and baseline characteristics of subgroup who have stopped all other OAD therapy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Concurrent OAD users</th>
<th>Subgroup of DPP-IV inhibitor-Only users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (17,697)</td>
<td>p value</td>
</tr>
<tr>
<td>Age (Yrs)</td>
<td>62 (12)</td>
<td>0.2</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.7 (1.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>134.6 (15)</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77.6 (9.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>4.3 (1.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.1 (0.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>2.2 (0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>2.2 (2.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>94.3 (22)</td>
<td>0.2</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>32.9 (6.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10593 (60)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7104 (40)</td>
<td></td>
</tr>
<tr>
<td>HbA1c Category (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c &lt; 7 %</td>
<td>5404 (31)</td>
<td></td>
</tr>
<tr>
<td>HbA1c &gt;= 7 to &lt;10 %</td>
<td>5230 (30)</td>
<td></td>
</tr>
<tr>
<td>HbA1c &gt;= 10 %</td>
<td>5864 (33)</td>
<td></td>
</tr>
<tr>
<td>BMI Category (kg/m2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1514 (9)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>5099 (29)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>11084 (63)</td>
<td></td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>6899 (39)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>2642 (15)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>8156 (46)</td>
<td></td>
</tr>
<tr>
<td>Townsend Deprivation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least deprived</td>
<td>3779 (21)</td>
<td></td>
</tr>
</tbody>
</table>

Mamza et al. Due for submission
## Combination therapy: Comparison of MACE outcome between Met +DPP4-I vs Met+ SU

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cohort (in combination with metformin)</th>
<th>n*</th>
<th>Events</th>
<th>Crude rates (per 1000 person-years)</th>
<th>Crude risk ratio (95% CI)</th>
<th>aHR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td>29 865</td>
<td>661</td>
<td>11.3</td>
<td>2.145 (1.629–2.824)</td>
<td>1.710 (1.280–2.285)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>DPP-4i</td>
<td>7091</td>
<td>55</td>
<td>5.3</td>
<td>1.469 (0.965–2.234)</td>
<td>1.323 (0.832–2.105)</td>
<td>0.237</td>
<td></td>
</tr>
<tr>
<td><strong>Directly matched</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td>4423</td>
<td>58</td>
<td>7.7</td>
<td>1.688 (1.191–2.414)</td>
<td>1.547 (1.076–2.225)</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>DPP-4i</td>
<td>4423</td>
<td>35</td>
<td>5.2</td>
<td>1.323 (0.832–2.105)</td>
<td>1.547 (1.076–2.225)</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td><strong>Propensity-matched</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td>6175</td>
<td>88</td>
<td>8.8</td>
<td>1.688 (1.191–2.414)</td>
<td>1.547 (1.076–2.225)</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>DPP-4i</td>
<td>6229</td>
<td>48</td>
<td>5.2</td>
<td>1.323 (0.832–2.105)</td>
<td>1.547 (1.076–2.225)</td>
<td>0.019</td>
<td></td>
</tr>
</tbody>
</table>

**With no prior MACE.**

Morgan CL et al Diabe Obes Metab2014
Normal glucose homeostasis – the role of kidneys

Net balance ~0 g/day

Glucose input ~250 g/day:
- Dietary intake ~180 g/day
- Glucose production ~70 g/day
  - Gluconeogenesis
  - Glycogenolysis

Glucose uptake ~250 g/day:
- Brain ~125 g/day
- Rest of the body ~125 g/day

The kidney filters circulating glucose
Glucose filtered ~180 g/day

The kidney reabsorbs and recirculates glucose
Glucose reabsorbed ~180 g/day

Normal renal glucose handling

Majority of glucose is reabsorbed by SGLT2 (90%)

Remaining glucose is reabsorbed by SGLT1 (10%)

Minimal to no glucose excretion

SGLT2, sodium-glucose co-transporter.
Dapagliflozin: A novel insulin-independent approach to remove excess glucose

Dapagliflozin selectively inhibits SGLT2 in the renal proximal tubule

1. FORXIGA Summary of Product Characteristics
Reductions in HbA$_{1c}$ with insulin + dapagliflozin compared with insulin + placebo at 24 weeks

A 24-week, randomised, double-blind, parallel-group, placebo-controlled, multicentre trial followed by a 24-week extension period to evaluate the efficacy and safety of adding dapagliflozin therapy in patients whose type 2 diabetes mellitus is inadequately controlled with insulin with or without oral antidiabetic drugs.

The primary outcome was change in HbA$_{1c}$ from baseline to 24 weeks.

2. FORXIGA Summary of Product Characteristics

Adapted from Wilding J, et al. 2012

Last observation carried forward (LOCF). Data are adjusted mean change from baseline. Mean HbA$_{1c}$ at baseline were 8.47% (69 mmol/mol) for insulin + placebo and 8.57% (70 mmol/mol) for insulin + dapagliflozin 10mg

Consider a reduction in insulin dose on commencement of dapagliflozin to reduce the risk of hypoglycaemia.

A 24-week, randomised, double-blind, parallel-group, placebo-controlled, multicentre trial followed by a 24-week extension period to evaluate the efficacy and safety of adding dapagliflozin therapy in patients whose type 2 diabetes mellitus is inadequately controlled with insulin with or without oral antidiabetic drugs. The primary outcome was change in HbA1c from baseline to 24 weeks.

2. FORXIGA Summary of Product Characteristics
Up8tra8on of insulin is less in patients treated with insulin + dapagliflozin compared with insulin + placebo (± oral antidiabetic drugs)

There was an 8% increase in total daily insulin units from mean baseline total daily insulin dose at 24 weeks and a 14% increase at 48 weeks in the insulin + placebo group compared to a small decrease in the insulin + dapagliflozin arm of 1.5% at 24 weeks and 1% at 48 weeks

42.8% of patients on insulin + placebo needed rescue therapy or were withdrawn from the study vs 15.3% on insulin + dapagliflozin 10mg

Consider a reduction in insulin dose on commencement of dapagliflozin to reduce the risk of hypoglycaemia

Baseline mean daily insulin dose (units): Insulin + placebo = 73.7, Insulin + dapagliflozin 10 mg = 78.0

A 24-week, randomised, double-blind, parallel-group, placebo-controlled, multicentre trial followed by a 24-week extension period to evaluate the efficacy and safety of adding dapagliflozin therapy in patients whose type 2 diabetes mellitus is inadequately controlled with insulin with or without oral antidiabetic drugs.

The primary outcome was change in HbA1c from baseline to 24 weeks.

SGLT2 inhibitions: Genital infections and urinary tract infections*

• Most genital infections† and UTIs were mild to moderate, responded to initial course of standard therapy, and rarely led to discontinuation of dapagliflozin.

• Events of genital infection (vulvovaginitis, balanitis and related genital infections) and UTIs with dapagliflozin 10 mg versus placebo:

<table>
<thead>
<tr>
<th>Frequency at 24 weeks</th>
<th>Genital infections</th>
<th>UTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin 10mg</td>
<td>4.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.9%</td>
<td>3.7%</td>
</tr>
</tbody>
</table>

• Pyelonephritis was uncommon and occurred at a similar frequency to control.

*In a prespecified pooled analysis of 12 placebo-controlled studies;
†Genital infection includes the preferred terms, listed in order of frequency reported: Vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, and vulval abscess.

FORXIGA Summary of product characteristics.
SGLT-2 inhibition: Cardiovascular considerations

A modest decrease in blood pressure was observed with dapagliflozin during clinical trials\textsuperscript{1,2}

Reduction in blood pressure at 24 weeks in a placebo-controlled pooled analysis

- **Systolic blood pressure**
  - Dapagliflozin 10 mg: \(-0.9\) mmHg (95% CI: \(-1.7\), \(-0.1\)) (n=1096)
  - Control groups: \(-4.4\) mmHg (95% CI: \(-5.3\), \(-3.5\)) (n=949)

- **Diastolic blood pressure**
  - Dapagliflozin 10 mg: \(-2.1\) mmHg (95% CI: \(-2.6\), \(-1.6\)) (n=1096)
  - Control groups: \(-0.5\) mmHg (95% CI: \(-1.0\), 0.0) (n=1096)

\(p\) values not calculated. Background antihypertensive drugs not controlled.

Caution should be exercised in patients for whom a drop in blood pressure induced by dapagliflozin could pose a risk, such as:

- Patients with known cardiovascular disease
- Patients on anti-hypertensive therapy with a history of hypotension
- Elderly patients\textsuperscript{3}

Dapagliflozin is not recommended in patients receiving loop diuretics as it may add to the diuretic effect and may increase the risk of dehydration and hypotension\textsuperscript{3}

\textsuperscript{1} Ptaszynska A et al, Safety of Dapagliflozin in Clinical Trials for T2DM 1011-P. Presented at 72\textsuperscript{nd} Scientific Sessions of the American Diabetes Association, Philadelphia, PA June 8-12, 2012

\textsuperscript{2} SJÖSTRÖM C et al. Pilot analysis of the effect of the SGLT2 inhibitor dapagliflozin on blood pressure: A pooled analysis of placebo-controlled trials. Oral presentation at the European Society of Cardiology, Munich 2012

\textsuperscript{3} FORXIGA Summary of Product Characteristics
SGLT2 inhibition - summary

- Glucose lowering
- Weight loss
- Minimal risk of hypoglycaemia
- Blood pressure reduction
Mechanism of diabetes remission

• Is weight loss alone enough?
  Or
• Is it something else?
Diabetes remission post bariatric surgery

JAMA 2004;292:1724-1737
All of the following procedures have evolved to provide a small pouch of stomach just below the gastro-esophageal junction.

- **Laparoscopic Adjustable Gastric Banding**: 39% world share
- **Roux-en-Y Gastric Bypass**: 37% world share
- **Vertical Banded Gastroplasty**: 3% world share

Significant reduction in hyperglycaemia is often observed within 1 week of surgery.
Glucagon-like peptide 1 (GLP-1) levels post surgery

Mechanism of diabetes remission

• Is weight loss alone enough?
  Or

• Is it GLP-1 levels?
  Or

• Is it something else?
Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol

E. L. Lim · K. G. Hollingsworth · B. S. Aribisala · M. J. Chen · J. C. Mathers · R. Taylor

Received: 22 March 2011 / Accepted: 5 May 2011 / Published online: 9 June 2011
© The Author(s) 2011. This article is published with open access at Springerlink.com

Abstract
Aims/hypothesis Type 2 diabetes is regarded as inevitably progressive. It involves increased insulin resistance and inadequate insulin secretion. We aimed to investigate whether reversal of diabetes can be achieved in a subset of patients with type 2 diabetes. Methods A cohort of 30 patients with type 2 diabetes who were treated with exercise, diet and lifestyle modification only were followed up for 2 years. Results Diabetic remission was achieved in 12 patients after 8 weeks of treatment. These patients had lower HbA1c values (0.62±0.15 nmol min⁻¹ m⁻²; \( p = 0.42 \)). Maximal insulin response became supranormal at 8 weeks (1.37±...
Very low calorie diet ‘reverses’ diabetes by enhancing insulin secretion independent of changes in peripheral insulin resistance

Lim et al, Diabetologia 2009
What were they allowed to eat in a day?
Mechanism of diabetes remission

• Is weight loss alone enough?  
  Or
• Is it GLP-1 levels?  
  Or
• Is it entirely about how much patients eat?  
  Or
• Is it something else?
Overall conclusions

• Prevalence of type 2 diabetes and early onset type 2 diabetes is rising
• Insulin therapy may be necessary in many patients with type 2 diabetes
• Response to insulin therapy is heterogenous
• Further studies to clarify cardiovascular safety of insulin therapy are required
• Novel therapies have focussed on treating hyperglycaemia in the absence of weight gain or hypoglycaemia risk
• VLCD may play an important role in motivated patients
Thank you