HbA1c-how low should we go?
Evidence from recent trials

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Treatment targets for people with diabetes\textsuperscript{1,2}

Blood pressure \textless 130/80

Glycaemic control
- HbA\textsubscript{1c}(\%)\textsuperscript{a} \leq 6.5%

Lipid profile, mmol/L
- Total cholesterol \textless 4.5
- LDL-cholesterol \leq 1.8
- HDL-cholesterol M >1.0 /F >1.2

Triglycerides\textsuperscript{b}
- TC/HDL\textsuperscript{b} <3

Smoking cessation \textbf{Obligatory}

Regular physical activity, mins/day >30–35

Weight control
- BMI, kg/m\textsuperscript{2} <25*
- For overweight, weight reduction, % 10

Waist (optimum, cm)
- Men <94/Women <80

\textsuperscript{a}DCCT-standardised\textsuperscript{3}
\textsuperscript{b}Not recommended for guiding treatment but for metabolic/risk assessment
\textsuperscript{*}Not often achieved; BMI maintenance may more relevant

Glycaemic targets for the management of type 2 diabetes

<table>
<thead>
<tr>
<th>Organisation</th>
<th>HbA$_{1c}$ (%)</th>
<th>FPG (mmol/L)</th>
<th>PPG (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA-EASD$^1$</td>
<td>&lt;7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IDF-Europe$^2$</td>
<td>&lt;6.5</td>
<td>5.5</td>
<td>7.8</td>
</tr>
<tr>
<td>AACE$^3$</td>
<td>≤6.5</td>
<td>6.1</td>
<td>7.8</td>
</tr>
<tr>
<td>NICE$^4$</td>
<td>6.5$^a$</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Meta-analysis of RCTs on macrovascular outcomes and death (1)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Events</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>3071/1549</td>
<td>221/141</td>
<td>21.8%</td>
<td>0.78 (0.62-0.98)</td>
<td>0.83 (0.64-1.06)</td>
</tr>
<tr>
<td>PROActive</td>
<td>2605/2633</td>
<td>119/144</td>
<td>18.0%</td>
<td>0.78 (0.62-0.98)</td>
<td>0.83 (0.64-1.06)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5571/5569</td>
<td>153/156</td>
<td>21.9%</td>
<td>0.98 (0.78-1.23)</td>
<td>0.81 (0.68-1.01)</td>
</tr>
<tr>
<td>VAAT11,12</td>
<td>892/899</td>
<td>64/78</td>
<td>9.4%</td>
<td>0.81 (0.68-1.01)</td>
<td>0.78 (0.64-0.95)</td>
</tr>
<tr>
<td>ACCORD</td>
<td>5128/5123</td>
<td>186/235</td>
<td>28.9%</td>
<td>0.83 (0.75-0.93)</td>
<td>0.83 (0.75-0.93)</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773</td>
<td>743/754</td>
<td>100%</td>
<td>0.83 (0.75-0.93)</td>
<td>0.83 (0.75-0.93)</td>
</tr>
</tbody>
</table>

Figure 1: Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Events</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>3071/1549</td>
<td>426/259</td>
<td>8.6%</td>
<td>0.75 (0.54-1.04)</td>
<td>0.82 (0.68-1.01)</td>
</tr>
<tr>
<td>PROActive</td>
<td>2605/2633</td>
<td>164/202</td>
<td>20.2%</td>
<td>0.82 (0.68-1.01)</td>
<td>0.78 (0.64-1.06)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5571/5569</td>
<td>310/337</td>
<td>36.1%</td>
<td>0.82 (0.68-1.01)</td>
<td>0.78 (0.64-1.06)</td>
</tr>
<tr>
<td>VAAT11,12</td>
<td>892/899</td>
<td>77/90</td>
<td>9.0%</td>
<td>0.82 (0.68-1.01)</td>
<td>0.78 (0.64-1.06)</td>
</tr>
<tr>
<td>ACCORD</td>
<td>5128/5123</td>
<td>205/248</td>
<td>25.7%</td>
<td>0.82 (0.68-1.01)</td>
<td>0.78 (0.64-1.06)</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773</td>
<td>1182/1136</td>
<td>100%</td>
<td>0.82 (0.68-1.01)</td>
<td>0.82 (0.68-1.01)</td>
</tr>
</tbody>
</table>

Figure 2: Probability of events of coronary heart disease with intensive glucose-lowering versus standard treatment

* Included non-fatal myocardial infarction and death from all-cardiac mortality.

Non-fatal MI
-18% for -1% HbA1c

Coronary events

All-cause mortality


Figure 4: Probability of events of all-cause mortality with intensive glucose-lowering versus standard treatment
Meta-analysis of RCTs on macrovascular outcomes and death (2)

<table>
<thead>
<tr>
<th>Trials</th>
<th>Number of events (annual event rate, %)</th>
<th>ΔHbA1c (%)</th>
<th>Favour more intensive</th>
<th>Favour less intensive</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More intensive</td>
<td>Less intensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>ACCORD 198 (1.18)</td>
<td>345 (1.51)</td>
<td>-1.01</td>
<td>0.77 (0.66–0.93)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ADVANCE 310 (1.51)</td>
<td>337 (1.29)</td>
<td>-0.72</td>
<td>0.92 (0.79–1.07)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UKPDS 150 (1.26)</td>
<td>76 (1.40)</td>
<td>-0.66</td>
<td>0.81 (0.62–1.07)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VADT 72 (1.65)</td>
<td>87 (1.99)</td>
<td>-1.16</td>
<td>0.83 (0.61–1.13)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>730</td>
<td>745</td>
<td>-0.88</td>
<td>0.85 (0.76–0.94)</td>
<td>(Q=2.25, p=0.52, I²=0.00%)</td>
</tr>
</tbody>
</table>

**Fatal and non-fatal MI**

<table>
<thead>
<tr>
<th>Trials</th>
<th>Number of events (annual event rate, %)</th>
<th>ΔHbA1c (%)</th>
<th>Favour more intensive</th>
<th>Favour less intensive</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More intensive</td>
<td>Less intensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major cardiovascular events</td>
<td>ACCORD 352 (2.11)</td>
<td>371 (2.29)</td>
<td>-1.01</td>
<td>0.90 (0.78–1.04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ADVANCE 557 (2.15)</td>
<td>590 (2.28)</td>
<td>-0.72</td>
<td>0.94 (0.84–1.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UKPDS 169 (1.36)</td>
<td>87 (1.66)</td>
<td>-0.66</td>
<td>0.80 (0.62–1.04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VADT 116 (2.68)</td>
<td>128 (2.98)</td>
<td>-1.16</td>
<td>0.90 (0.70–1.16)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1,194</td>
<td>1,176</td>
<td>-0.88</td>
<td>0.91 (0.84–0.99)</td>
<td>(Q=1.32, p=0.72, I²=0.00%)</td>
</tr>
</tbody>
</table>

**Major CV events***

*CV Death, Non-Fatal Stroke, Non-Fatal MI

<table>
<thead>
<tr>
<th>Trials</th>
<th>Number of events (annual event rate, %)</th>
<th>ΔHbA1c (%)</th>
<th>Favour more intensive</th>
<th>Favour less intensive</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More intensive</td>
<td>Less intensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>ACCORD 257 (1.41)</td>
<td>203 (1.14)</td>
<td>-1.01</td>
<td>1.22 (1.01–1.46)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ADVANCE 498 (1.86)</td>
<td>533 (1.99)</td>
<td>-0.72</td>
<td>0.93 (0.83–1.06)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UKPDS 123 (0.13)</td>
<td>53 (0.25)</td>
<td>-0.66</td>
<td>0.96 (0.70–1.33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VADT 102 (2.22)</td>
<td>95 (2.06)</td>
<td>-1.16</td>
<td>1.07 (0.81–1.42)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>980</td>
<td>884</td>
<td>-0.88</td>
<td>1.04 (0.90–1.20)</td>
<td>(Q=5.71, p=0.13, I²=47.5%)</td>
</tr>
</tbody>
</table>

All-cause mortality

Turnbull, et al. Diabetologia 2009; Epub August 5
### Review of recent studies investigating intensive glycaemic control

<table>
<thead>
<tr>
<th>Variable</th>
<th>VADT (n=1,700)</th>
<th>ACCORD (n=10,250)</th>
<th>ADVANCE (n=11,140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.4 vs 6.9</td>
<td>7.5 vs 6.4</td>
<td>7.3 vs 6.5</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>MI, stroke, death from CV causes, new or worsening CHF, revascularisation&lt;sup&gt;b&lt;/sup&gt; and inoperable CAD, amputation for ischaemic gangrene</td>
<td>Non-fatal MI, non-fatal stroke, CVD death</td>
<td>Non-fatal MI, non-fatal stroke, CVD death</td>
</tr>
<tr>
<td>HR (95% CI) for primary outcome</td>
<td>0.87 (0.730–1.04)</td>
<td>0.90 (0.78–1.04)</td>
<td>0.94 (0.84–1.06)</td>
</tr>
<tr>
<td>HR (95% CI) for mortality</td>
<td>1.065 (0.801–1.416)</td>
<td>1.22 (1.01–1.46)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.93 (0.83–1.06)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conventional vs intensive

<sup>b</sup> p=0.04

CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; MI, myocardial infarction
No significant difference in time to death from cardiovascular causes or death from any cause

- Mortality Rate for Intensive vs Standard Tx: Death From Any Cause

22% relative increase in mortality for intensive Tx over standard Tx

**ACCORD**

- Mortality Rate for Intensive vs Standard Tx: Death From CV Events

![Graph showing mortality rates for Intensive and Standard therapy over years.](image)

**Conclusions**
- Intensive glucose lowering can be *harmful* in patients at high CV risk

Possible causes of increased mortality during intensified therapy

Specific medication

Weight gain

Hypoglycaemia
Severe hypoglycaemia in the three recent trials of intensive glucose control in Type 2 diabetes

- **VADT**
- **ACCORD**
- **ADVANCE**
ACCORD: Higher Mortality in Participants who Experienced Severe Hypoglycaemia (SH)

Overall mortality rate

Never experienced SH: 1.2%
Experienced SH: 3.3%
Potential Mechanisms of Hypoglycaemia Induced Mortality

- Cardiac arrhythmias due to abnormal cardiac repolarization in high-risk patients (IHD, cardiac autonomic neuropathy)
- Increased thrombotic tendency/decreased thrombolysis
- Cardiovascular changes induced by catecholamines
  - *Increased heart rate*
  - *Silent myocardial ischaemia*
  - *Angina and myocardial infarction*
Effect of experimental hypoglycaemia on QT interval

5.0mM

A

QTc = 456 ms
HR = 66 bpm

B

QTc = 610 ms
HR = 61 bpm

2.5mM
The ACCORD Study

- Intensive therapy to lower HbA1c to normal target levels for 3.5 years was associated with higher mortality but with no significant reduction of major cardiovascular events.

- The cause of the increased mortality could not be proven; severe hypoglycaemia was implicated.

- This study demonstrated the potential harm of using intensive treatment to lower glucose in high-risk patients with Type 2 diabetes.

- The outcome raises questions about targets for glycaemic control in type 2 diabetes and how they should be achieved.

“Bad Glycaemic Legacy”

- Before entering VADT intensive treatment arm
- After entering VADT intensive treatment arm

Generation of a ‘bad glycaemic legacy’

Drives risk of complications

HbA1c (%) vs. Time since diagnosis (years)
Microvascular Disease Hazard Ratio
(photocoagulation, vitreous haemorrhage, renal failure)

Intensive (SU/Ins) vs. Conventional glucose control

All-cause Mortality Hazard Ratio

Intensive (SU/Ins) vs. Conventional glucose control

All-cause mortality
HR = 0.94
p = 0.44

HR = 0.87
p = 0.006

Hazard ratio

Number of events

Con: 213 267 330 400 460 537
Int: 489 610 737 868 1028 1163

1997 1999 2001 2003 2005 2007
Myocardial Infarction Hazard Ratio
(fatal or non-fatal myocardial infarction or sudden death)

Intensive (SU/Ins) vs. Conventional glucose control

Myocardial Infarction Hazard Ratio
(fatal or non-fatal myocardial infarction or sudden death)

Intensive (metformin) vs. Conventional glucose control

Conclusions from UKPDS
10 years post-trial follow-up

Despite an early loss of glycaemic differences there was a continued reduction in microvascular risk and emergent risk reductions for MI and death from any cause during 10 years of post-trial follow-up.

Continued benefit after metformin among overweight patients.

GOOD GLYCAEMIC CONTROL IN THE EARLY YEARS OF DIABETES IS VITAL TO REDUCE VASCULAR EVENTS AND MORTALITY LONGTERM.
“... within the timeframe of the intensive treatment period of recent trials, there is less opportunity to influence the development and/or progression of complications in individuals with longstanding diabetes. Conversely, in both type 1 and type 2 diabetic patients, early strict glycaemic control generates a legacy that may confer protection against, or delay, long term diabetic complications”

“... no form of mild diabetes exists, and no excuse exists to postpone appropriate and effective treatment”

S. Del Prato  Diabetologia 2009;52:1219-1226
Overall conclusions from recent trials

- Tight diabetes control in the early years after diagnosis associated with significant reduction in total and CV mortality and vascular events.

- Caution re “too tight” and “too rapid tightening of” control in longer duration, high risk patients possibly because of increased chance of hypoglycaemia precipitating arrhythmias/CV events and death.
HYPOGLYCAEMIA

A major limiting factor to achieving intensive glycaemic control for people with type 2 diabetes

Briscoe VJ et al Clin Diab 2006;24:115-121
Hypoglycaemia in type 2 diabetes

• Hypoglycaemia symptoms common in type 2 diabetes – 38% of patients\(^1\)

• Associated with reduced –
  
  quality of Life
  
  treatment satisfaction
  
  therapy adherence

More common at HbA1c < 7%

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Rates of Hypoglycemia Increase as A1C Levels Decrease in type2 diabetes patients

Reproduced with permission of Elsevier, Inc., from Wright et al. J Diabetes Complications. 2006;20:395–401; permission conveyed through Copyright Clearance Center, Inc.
Frequency of Hypoglycemic Symptoms Among Patients With Type 2 Diabetes

Other studies in Asia and Europe report similar prevalence of hypoglycemia in patients with type 2 diabetes treated with oral agents.2,3

Awareness of hypoglycaemia

- Recognition of warning symptoms fundamental for self-treatment and prevent progression to severe hypo\(^1\)

- Even mild hypoglycaemia induces defects in counterregulatory responses and impaired awareness\(^2\)

- Impaired awareness predisposes to six-fold increase in the frequency of severe hypoglycaemia\(^3\)

- Only 15% of type 2 diabetes patients who experienced a hypoglycaemic event reported the incident to their doctor\(^1,4\)

Normal physiological response to hypoglycaemia

- Blood glucose (mM)
- Start of brain dysfunction
- Confusion/loss of concentration
- Adrenaline release
- Sweating, tremor
- Coma/seizure
- Brain damage
Impaired physiological responses and unawareness

- Adrenaline release
- Sweating, tremor
- Start of brain dysfunction
- Confusion/loss of concentration
- Coma/seizure

Blood glucose (mM)
Lessons from UKPDS: better control means fewer complications

EVERY 1% reduction in HbA$_{1c}$

Deaths from diabetes: 21%
Heart attacks: 14%
Microvascular complications: 37%
Peripheral vascular disorders: 43%

*p<0.0001

UKPDS 35. BMJ 2000;321:405-12
Progressively Declining Beta-cell Function in T2DM—"waiting for failure"

# Anti-Diabetes Agents

<table>
<thead>
<tr>
<th>Insulin Secretion</th>
<th>Insulin Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas</td>
<td>Thiazolidinediones (Glitazones)</td>
</tr>
<tr>
<td>Insulin secretagogues (rapid)</td>
<td>Metformin</td>
</tr>
<tr>
<td>Incretin-mimetics</td>
<td></td>
</tr>
<tr>
<td>DPP4 - inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

**Glucose Absorption**
Alpha-glucosidase inhibitors
UKPDS: benefit of metformin in overweight Type 2 diabetes patients*

*Compared to conventional treatment group

Most current therapies result in weight gain

UKPDS: up to 8 kg in 12 years
- Insulin
- Glibenclamide
- Metformin

ADOPT: up to 4.8 kg in 5 years
- Rosiglitazone
- Metformin
- Glibenclamide

Conventional treatment; diet initially then sulphonylureas, insulin and/or metformin if FPG >15 mmol/L

Obstructive Sleep Apnoea (OSA), type 2 diabetes and obesity

- In the US, ~17% of adults 30–69 years have OSA\(^1\)
- Excess weight is an important factor for OSA\(^1\)
- About 86% of obese people with type 2 diabetes have OSA\(^2\)
- OSA is an independent marker of type 2 diabetes\(^1\)
- OSA is a significant risk factor for CV disease and mortality\(^1\)

Pooled hypoglycaemia results for randomized trials, by drug comparison

UK Hypoglycaemia Group Study

Multicentre study funded by Dept for Transport

Determine the frequency of hypoglycaemia in type 2 diabetes treated with SUs and insulin for differing duration

Compare frequencies with type 1 diabetes

Prospective study over 9-12 months of patients with good glycaemic control

Documented severe and mild hypoglycaemia prospectively, supplemented with CGM x 2
Hypoglycaemia in Type 2 DM: Sulphonylureas vs Insulin

In patients treated for < 2 years, no difference in the proportion of patients experiencing:
- severe hypoglycaemia (7% v 7%)
- mild symptomatic (39% v 51%)
- interstitial glucose < 2.2 mol/L (22% v 20%)

Clinical consequences

• Hospital admissions:
  – Prospective study\(^1\) of well-controlled elderly T2D patients- 25% of hospital admissions for diabetes for severe hypo

• Increased mortality:
  – 9% in a study\(^2\) of severe SU-associated hypoglycaemia

• Road accidents caused by hypos\(^3\):
  – 45 serious events per month

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1. *Diab Nutr Metab* 2004; 17:23–26
3. *BMJ* 2006; 332: 812
Drug-induced hypoglycaemic coma is more common in elderly people with type 2 diabetes—yet this is the group told not to monitor!

Retrospective medical record review of individuals with diabetes who were admitted with DIHC or developed DIHC during hospitalisation.

Lack of awareness and education

- Patient receive little information on the adverse events of oral medication, including hypos:
  - In a UK survey, only 10% of people treated with an SU knew that it could cause hypos.\(^1\)

- GPs and practice nurses may not be aware of the prevalence of hypos with SUs

\(^1\) Diabet Med 2000; 17:528–531
SUs and severe hypoglycaemia in the UK

• >5000 patients pa on SUs experience at least one severe hypo requiring hospital admission

Newer agents for blood glucose control in type 2 diabetes

NICE guideline overview
Publication date: 27 May 2009
Current targets recommended by NICE\textsuperscript{1}

- HbA\textsubscript{1c} 6.5% - for first 2 treatment steps
- HbA\textsubscript{1c} 7.5% - beyond this

**DPP-4 inhibitors**

**Recommendation 1.1.1**

- Consider adding a DPP-4 inhibitor second-line instead of SU when blood glucose control inadequate (HbA\textsubscript{1c} ≥6.5%) with metformin if:
  - **Significant risk of hypoglycaemia.** This may include older people and those in certain occupations (eg working at heights or with heavy machinery) or those in certain social circumstances (eg living alone)
  - SU not tolerated or contraindicated

\textsuperscript{1} National Institute for Health and Clinical Excellence. *Type 2 diabetes newer agents*. Clinical guideline. London; May 2009
GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins

GLP-1 secreted upon the ingestion of food

Promotes satiety and reduces appetite

Beta cells: Enhances glucose-dependent insulin secretion

Alpha cells: ↓ Postprandial glucagon secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

GLP-1 Infusion Has Beneficial Effects in T2DM

* p<0.05; (n=10); data presented as mean ± SEM.
DPP-4 Inhibitors: Rationale

DPP-IV = dipeptidyl peptidase IV
Vildagliptin: as effective as glimepiride when added to metformin at 52 weeks

Add-on treatment to metformin (~1.9 g mean daily)

- Vildagliptin 50 mg bid + metformin
- Glimepiride up to 6 mg qd + metformin

Mean HbA1c (%)

Per protocol population.
Data on file, Novartis Pharmaceuticals, LAF237A2308 52-week interim analysis.
Vildagliptin: no weight gain

Add-on treatment to metformin (~1.9 g mean daily)

Per protocol population.
Data on file, Novartis Pharmaceuticals, LAF237A2308 52-week interim analysis.
Vildagliptin vs glimepiride: hypoglycaemic events in add-on to metformin treatment

Patients with ≥1 hypos (%)

<table>
<thead>
<tr>
<th>Glimepiride up to 6 mg qd + metformin</th>
<th>Vildagliptin 50 mg bid + metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1389</td>
<td>1383</td>
</tr>
</tbody>
</table>

Number of hypoglycaemic events

<table>
<thead>
<tr>
<th>Glimepiride up to 6 mg qd + metformin</th>
<th>Vildagliptin 50 mg bid + metformin</th>
</tr>
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<td>1389</td>
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Severe events (grade 2 and suspected grade 2)

<table>
<thead>
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<th>Vildagliptin 50 mg bid + metformin</th>
</tr>
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Safety population.
Data on file, Novartis Pharmaceuticals, LAF237A2308 52-week interim analysis.
### Pooled placebo-controlled safety population: Hypoglycaemia

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<thead>
<tr>
<th>Short-term period (excludes RT)</th>
<th>Percentage</th>
<th>SAXA 2.5 mg</th>
<th>SAXA 5 mg</th>
<th>SAXA 10 mg</th>
<th>Saxagliptin All</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled Monotherapy (-011, -038)</strong></td>
<td><strong>Reported</strong></td>
<td>4.0</td>
<td>5.6</td>
<td>8.2</td>
<td>5.4</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Confirmed</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Add-on Combination + MET (-014)</strong></td>
<td><strong>Reported</strong></td>
<td>7.8</td>
<td>5.2</td>
<td>3.9</td>
<td>5.7</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Confirmed</strong></td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.5</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>+ SU (-040)</strong></td>
<td><strong>Reported</strong></td>
<td>13.3</td>
<td>14.6</td>
<td>–</td>
<td>14.0</td>
<td>10.1</td>
</tr>
<tr>
<td><strong>Confirmed</strong></td>
<td>2.4</td>
<td>0.8</td>
<td>–</td>
<td>1.6</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>+ TZD (-013)</strong></td>
<td><strong>Reported</strong></td>
<td>4.1</td>
<td>2.7</td>
<td>–</td>
<td>3.4</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Confirmed</strong></td>
<td>0.5</td>
<td>0</td>
<td>–</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Placebo-controlled pooled population</strong></td>
<td><strong>Reported</strong></td>
<td>7.6</td>
<td>7.8</td>
<td>5.4</td>
<td>7.4</td>
<td>6.8</td>
</tr>
<tr>
<td><strong>Confirmed</strong></td>
<td>0.8</td>
<td>0.5</td>
<td>0.4</td>
<td>0.6</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td><strong>Initial combination with MET (-39)</strong></td>
<td><strong>Reported</strong></td>
<td>3.4</td>
<td>5.0</td>
<td>1.5</td>
<td>3.3</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Confirmed</strong></td>
<td>0</td>
<td>0.6</td>
<td>0</td>
<td>0.2</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

**Saxagliptina** es un producto en investigación clínica. No está aún comercializado para uso clínico.

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm149225.htm
Accessed: 14 Nov, 09
### Pivotal phase 3 studies/ST period excluding RT
Change from baseline in weight (saxagliptin 5 mg)

<table>
<thead>
<tr>
<th>Short-term Period</th>
<th>n - SAXA 5mg</th>
<th>Weight (kg)</th>
<th>n - PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-011)</td>
<td>105</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>(-038)</td>
<td>71</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td><strong>Add-on therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ MET</td>
<td>191</td>
<td>177</td>
<td></td>
</tr>
<tr>
<td>(-014)</td>
<td>(-038)</td>
<td>(-040)</td>
<td></td>
</tr>
<tr>
<td>+ SU</td>
<td>253</td>
<td>265</td>
<td></td>
</tr>
<tr>
<td>(-040)</td>
<td>(-014)</td>
<td>(-013)</td>
<td></td>
</tr>
<tr>
<td>+ TZD</td>
<td>185</td>
<td>182</td>
<td></td>
</tr>
<tr>
<td>(-013)</td>
<td>(-040)</td>
<td>(-040)</td>
<td></td>
</tr>
<tr>
<td><strong>SAXA 5 + MET</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>318</td>
<td>322</td>
<td></td>
</tr>
<tr>
<td>(-039)</td>
<td>(-013)</td>
<td>(-039)</td>
<td></td>
</tr>
</tbody>
</table>

Data represent point estimate and 95% CI.

[Saxagliptina es un producto en investigación clínica. No está aún comercializado para uso clínico.](http://www.fda.gov/ohrms/dockets/ac/cder09)
DPP-4 Inhibitors

- Effective as mono- and combination therapy
- Oral dosing
- Low risk of hypoglycaemia
- Weight neutral
- Well tolerated
- Theoretical possibility that they could preserve and even reverse progressive loss of insulin secretory capacity
<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>SU</th>
<th>Glitazone</th>
<th>Insulin</th>
<th>GLP-1 agonist</th>
<th>Gliptins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Influence Disease Progression</strong></td>
<td>No</td>
<td>No</td>
<td>(?)</td>
<td>No</td>
<td>(?)</td>
<td>(?)</td>
</tr>
<tr>
<td><strong>Outcome Studies</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Tolerability</strong></td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Excellent</td>
</tr>
<tr>
<td><strong>Weight gain</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Weight loss</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hypos</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>(No?)</td>
<td>No</td>
</tr>
</tbody>
</table>
Personalised Care is Paramount

• When dealing with a complex chronic disease such as type 2 diabetes:
  . . . “the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drug they are considering”

NICE clinical guidelines for the management of type 2 diabetes, May 2009
The Health Professional MUST agree with the individual patient both their glycaemic target and how best to achieve this.

Guidelines are guidelines NOT absolutes!
Need for Personalised Care:  
The Benefits vs. Risks of Diabetes Therapy Must be Assessed for Each Patient
Conclusions

• Tight diabetes control in the early years after diagnosis associated with significant reduction in total and CV mortality and vascular events.

• Caution re “too tight” and “too rapid tightening of” control in longstanding, high risk patients possibly because of increased chance of hypoglycaemia precipitating arrhythmias/CV events and death

• Individualisation of targets and therapies vital

• New drugs, including incretin based therapies, have the potential to improve glycaemic control with low risk of hypoglycaemia and weight gain