Hypoglycemia: A Complication When Targeting Type 2 Diabetes

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Diabetes is the Epidemic of Our Time

- 24 million Americans have diabetes
- 7.8% of adults have diabetes
- 213,000 people die each year from diabetes
- >60 million people have pre-diabetes

Diabetes increased 70% among people age 30-39 in approximately the last decade
Case Conversation
A 63 year old male is treated for T2DM for 16 years. Comorbidities include hypertension and hyperlipidemia. Medications include analogue basal insulin, metformin, ACE inhibitor, and statin.

His Hgb A1C is 8.6%.

Because of the risk of hypoglycemia and CVD risk he is concerned about trying to achieve an Hgb A1C of 6.5%.

Please discuss.
Risk Factors and Consequences of Hypoglycemia in Type 2 Diabetes

- **Risk factors**
  - Use of insulin secretagogues and insulin therapy
  - Missed or irregular meals
  - Advanced age
  - Duration of diabetes
  - Impaired awareness of hypoglycemia

- **Consequences**
  - Suboptimal glycemic control
  - Other health effects?

OUTLINE

1. Dangers: Blunted hormonal response to hypoglycemia
   (glucagon stimulation, antecedant hypoglycemia)

2. Hypoglycemia evaluation in outcome and targeted trials: UKPDS, ACCORD, VADT, 4 - T, Currie trial

3. Targeting Hgb A1C for tighter control
Characteristics of Patients at an Increased Risk of Hypoglycemia

- Are older\(^1\)
- Have a long duration of diabetes\(^1\)
- Regularly miss meals\(^2\)
- Exercise\(^2\)
- Take greater than the prescribed dose of their medication\(^2\)

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The Glucagon Response to Hypoglycemia is Reduced in “More Advanced” Type 2 Diabetes

Glucagon response at plasma glucose 2.5mM

Effect of One Episode of Antecedent Hypoglycemia

Responses measured 1 day apart

Effect of Two Episodes of Antecedent Hypoglycemia in 15 patients with Type 2 diabetes (HbA1c 10.2%)

Adrenaline (pg/mL) at 3.3 mM

Responses Measured 1 Day Apart

Symptom Score at 3.3 mM

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Hypoglycemic Episodes per Annum - UKPDS

37% of patients had 2 episodes of hypoglycemia per year

UKPDS = United Kingdom Prospective Diabetes Study Group.
## The Three Current Trials

### Glycemia

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Standard</td>
<td>Intensive</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.1%</td>
<td>7.5%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Final</td>
<td>6.4%</td>
<td>7.5%</td>
<td>6.4%</td>
</tr>
</tbody>
</table>
ACCORD Outcomes

ADA 2009

- **Baseline mortality predictors:** $A_1c > 8.5\%$, ASA use, neuropathy hx
- **20\%↑ risk of death for every 1\%↑ $A_1c > 6\%$**
  - 1\%↓ $HbA1c$ associated with 56\%↓ adjusted mortality in intensive therapy group ($P=0.0001$); but 1\%↓ $HbA_{1c}$ ↓ risk 14\% in standard therapy group ($P=0.17$)
- **$A_1c <7\%$ did not explain excess deaths or predict mortality risk**
- **Greater ↓ $A_1c$ associated with reduced mortality; higher mortality with $A_1c >7\%$**
- **Of 451 deaths, 1 severe hypo, but glucose measures n/a near times of deaths for others**

ACCORD Definition of a Severe Hypoglycemic Episode

- Hypoglycemia requiring medical or paramedical attention, AND
  - Documented blood glucose < 50 mg/dl (2.8 mmol/L), or
  - Prompt recovery with administration of oral CHO, IV glucose, or subcutaneous glucagon

Each participant’s ‘Glucose Diary’ was reviewed at each clinic visit to identify the occurrence of one of these hypoglycemic events

What is Already Known on this Topic

- Intensive glycaemia control results in increased rates of severe hypoglycemia

- The intensive glycaemia control intervention used in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was associated with increased mortality (hypoglycemia?)

BMJ 2010;340:b4909
## Adverse Outcomes:

<table>
<thead>
<tr>
<th>Intensive vs Std</th>
<th>ACCORD*</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypoglycemia (% per yr)</td>
<td>3.0 vs 1.0</td>
<td>0.7 vs 0.4</td>
<td>-</td>
</tr>
<tr>
<td>Hypoglycemia requiring assistance (% per year)</td>
<td>4.6 vs 1.5</td>
<td>1.8 vs 0.6</td>
<td>2.3 vs 1.1</td>
</tr>
<tr>
<td>Weight gain &gt;10 Kg</td>
<td>27.8 % vs 14.1%</td>
<td>0.0 vs -1.0</td>
<td>-</td>
</tr>
<tr>
<td>Weight gain (Kg) Intensive group</td>
<td>3.5</td>
<td>0.7</td>
<td>6.8</td>
</tr>
</tbody>
</table>

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; VADT = Veterans Affairs Diabetes Trial.


VADT Study Results. ADA Scientific Session; San Francisco, CA; 2008.

Risk of severe hypoglycemia: Intensive glucose control vs standard treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Events/Total (n/n)</th>
<th>Risk difference (95% CI)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Conventional</td>
<td></td>
</tr>
<tr>
<td>Early trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UKPDS 33</td>
<td>397/2729</td>
<td>80/1138</td>
<td></td>
</tr>
<tr>
<td>UKPDS 34</td>
<td>22/342</td>
<td>31/411</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>419/3071</td>
<td>111/1549</td>
<td>1.37 (0.58 to 3.27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16 (-26 to 58)</td>
</tr>
<tr>
<td>Recent trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>538/5128</td>
<td>179/5123</td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>150/5571</td>
<td>81/5569</td>
<td></td>
</tr>
<tr>
<td>VADT</td>
<td>76/892</td>
<td>28/899</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>764/11,591</td>
<td>288/11,591</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>1183/14,662</td>
<td>399/13,140</td>
<td>2.48 (1.78 to 3.47)</td>
</tr>
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<td></td>
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<td>54 (-6 to 115)</td>
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<tr>
<td>Heterogeneity P &lt; 0.001; I² = 85.4%</td>
<td></td>
<td></td>
<td>2.03 (1.46 to 2.81)</td>
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<td></td>
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<td>39 (7 to 71)</td>
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# The Three Current Trials

*Glycemia*

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<td>7.5%</td>
<td>6.4%</td>
<td>7.0%</td>
<td>6.9%</td>
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</table>
Percent of Patients Experiencing at Least 1 Episode of Hypoglycemia In T2DM Intensification Trials

Mortality and episodes of hypoglycaemia among all participants and by study arm

<table>
<thead>
<tr>
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<th>All Participants</th>
<th>Standard Group</th>
<th>Intensive Group</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>451/10194 (4.40%)</td>
<td>197/5088 (3.87%)</td>
<td>254/5106 (4.97%)</td>
</tr>
<tr>
<td>Hypoglycaemic Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>requiring any assistance,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medical or non medical (</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HA)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No events</td>
<td>377/9122 (4.13%)</td>
<td>176/4832 (3.64%)</td>
<td>201/4090 (4.69%)</td>
</tr>
<tr>
<td>At least one hypoglycaemic event</td>
<td>74/1072 (6.90%)</td>
<td>21/256 (8.20%)</td>
<td>53/816 (6.49%)</td>
</tr>
</tbody>
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Bonds BMJ 2010;340:b4909
History of Symptomatic, Severe Hypoglycemia Increases Mortality Risk

Mortality Rate

- Intensive Therapy
- Standard Therapy

Previous Symptomatic Severe Hypoglycemic Episodes (No.)

None  At Least 1

$P = 0.076$ between history of hypoglycemia and glycemia intervention
Severe Hypoglycemia Frequency

Intensive vs Standard Treatment

Baseline HbA1c

Graph showing the frequency of severe hypoglycemia for Intensive and Standard treatment groups.
Tight Glycemic Control
Controversies

Patients with lower baseline glycemia may require less glucose lowering agents—resulting in hypoglycemia—You are already close to goal.
What This Study Adds

- Patients with type 2 diabetes who experience symptomatic, severe hypoglycaemia are at increased risk of death regardless of the intensity of glucose control regardless of STD or INT groups.

- The increased risk of death seen in the ACCORD trial among participants in the intensive glycaemia control arm cannot be attributed to the increased rate of severe hypoglycaemia in intensive arm participants (Mortality greater with history of previous hypoglycemia in the STD arm over INT arm)

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Symptomatic Severe Hypoglycemia

Tip of the Iceberg?

Symptomatic Severe

Symptomatic Non-severe

Asymptomatic Non-severe

Asymptomatic severe

Coronary Artery Disease
Arrhythmias
Autonomic neuropathy

Myocardial Ischemia
Oxidative stress
Vasoactive cytokines
1. Dangers: Blunted hormonal response to hypoglycemia
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1. Dangers: Blunted hormonal response to hypoglycemia
   (glucagon stimulation, antecedant hypoglycemia)
2. Hypoglycemia in context with the UKPDS and ACCORD trials
3. Targeting Hgb A1C for tighter control
Regimens “had similar glycemic efficacy for patients with baseline $A_1c<8.5\%$, but differed significantly for patient values above this level”

Treating to Target in Type 2 Diabetes

(4-T) – 3 year results

Treating to Target in Type 2 Diabetes

(4-T) – 3 year results

Treating to Target in Type 2 Diabetes

(4-T) – 3 year results

• Adverse Events

• “During the study period, 19 patients died (7 in the biphasic group, 9 in the prandial group, and 3 in the basal group; \(P=0.23\)); of these patients, 14 died from cardiovascular disease (4 in the biphasic group, 9 in the prandial group, and 1 in the basal group; \(P=0.002\)). The proportion of patients with any type of serious adverse event differed among the groups, with the highest proportion in the biphasic group (\(P=0.01\)).”

Adverse effect of metformin-SU combination, intensification from oral monotherapy, mortality risk vs $A_1c$, n=27,965

Adverse effect of insulin intensification from oral monotherapy, mortality risk vs $A_1c$, $n=20,005$

Hypoglycemia and Other Adverse Consequences of Glucose-lowering Therapies in the Trials

- ACCORD, ADVANCE, VADT: suggestion of relationship between adverse outcome and overtreatment/hypoglycemia
- Corroborative studies: suggestion of relationship between hypoglycemia and adverse outcome
- "new" paradigm: Improve glycemia without causing hypo-glycemia