Clinical Practice Guidelines: 
Management of 
Type 2 Diabetes Mellitus 
2015

Topic :
Targets for Individualised Control
Causes of Death in People With Diabetes

65% of Diabetic Patients Deaths are from CV Causes

UKPDS and myocardial infarction

![Graph showing the percentage of patients with MI over years after randomisation. The graph compares conventional and intensive treatment groups, with the intensive group showing a lower percentage of MI cases. The risk reduction is 16% (CI 95%: 0-29%).](UKPDS_33_Lancet_1998_352_837-853)
Improved Glycemic Control and Diabetes Complications from UKPDS

According to the United Kingdom Prospective Diabetes Study (UKPDS) 35, Every 1% Decrease in A1C Resulted in:

- 21% Decrease in risk of any diabetes-related end point ($P<.0001$)
- 14% Decrease in risk of MI ($P<.0001$)
- 12% Decrease in risk of stroke ($P=.04$)
- 37% Decrease in risk of microvascular complications ($P<.0001$)

Post-Trial Changes in HbA$_{1c}$

UKPDS results presented

Mean (95% CI)
Any Diabetes-related Endpoint

Intervention Trial
Median follow-up 10.0 years

RR=0.88 (0.79-0.99)
P=0.029

Conventional
Sulfonylurea/Insulin

Intervention Trial + Post-trial monitoring
Median follow-up 16.8 years

RR=0.91 (0.83-0.99)
p=0.040

Time from randomisation (years)
Myocardial Infarction Hazard Ratio
(fatal or non-fatal myocardial infarction or sudden death)

Intensive (SU/Ins) vs. Conventional glucose control

HR (95%CI)

Myocardial infarction
HR=0.84
p=0.052

HR=0.85
p=0.014

Number of events
Con: 186 212 239 271 296 319
Int: 387 450 513 573 636 678

1997 1999 2001 2003 2005 2007

HR (95%CI)
All-cause Mortality Hazard Ratio

Intensive (SU/Ins) vs. Conventional glucose control

**HR (95%CI)**

- Intensive: HR = 0.94, p = 0.44
- Conventional: HR = 0.87, p = 0.006
## UKPDS: 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>
</tr>
</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><strong>0.040</strong></td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>$RRR$: 25%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>$P$: <strong>0.0099</strong></td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>$RRR$: 16%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>$P$: 0.052</td>
<td><strong>0.014</strong></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><strong>0.007</strong></td>
</tr>
</tbody>
</table>

$RRR = Relative\ Risk\ Reduction, \ P = Log\ Rank$

N Eng J Med 2008
1. The presence of a legacy effect argues for early intensive glucose lowering

2. Target HbA$_{1c}$ to 6.5% except where this requires complex treatment regimens or life expectancy is less than 5 years
Questions addressed in RCT of Type 2 diabetes treatment

Question 1:
Does treatment-directed lowering HbA1c (below 6.0 to 6.5%) reduce CV endpoints

After nearly 10 years of follow-up, patients with type 2 diabetes who had been randomly assigned to intensive glucose control for 5.6 years had 8.6 fewer major cardiovascular events per 1000 person-years than those assigned to standard therapy, but no improvement was seen in the rate of overall survival.


P, primary prevention;  S, secondary prevention
# Early vs Late Glycemic Intervention

<table>
<thead>
<tr>
<th></th>
<th>UKPDS(^a) (N=3867)</th>
<th>ADVANCE(^b) (N=11,140)</th>
<th>ACCORD(^c) (N=10,251)</th>
<th>VADT(^d) (N=1791)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of diabetes, y</strong></td>
<td>0*</td>
<td>8</td>
<td>10</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>Mean age, y</strong></td>
<td>53</td>
<td>66</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td><strong>Mean baseline HbA(_{1c}), %</strong></td>
<td>7.1</td>
<td>7.5</td>
<td>8.3</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>Mean baseline FPG, mmol/L</strong></td>
<td>8.0</td>
<td>8.5</td>
<td>9.7</td>
<td>11.4</td>
</tr>
<tr>
<td><strong>ΔHbA(_{1c}), %</strong></td>
<td><strong>0.9</strong></td>
<td><strong>0.7</strong></td>
<td><strong>1.1</strong></td>
<td><strong>1.5</strong></td>
</tr>
<tr>
<td><strong>CVD</strong></td>
<td>↔↓</td>
<td>↔</td>
<td>↔</td>
<td>↔↓</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>↔↓</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
</tr>
</tbody>
</table>

*Newly diagnosed patients with no previous history of CVD.*


Impact of Intensive vs Conventional Glycemic-Lowering Strategies on Risk of CV Outcomes Is Unclear

<table>
<thead>
<tr>
<th>Study</th>
<th>Diabetes Duration (mean)</th>
<th>Antihyperglycemic Medicationa</th>
<th>Follow-up (median)</th>
<th>A₁c: Baseline, Between-arm Difference</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE³</td>
<td>8 years</td>
<td>Intensive glucose control including gliclazide vs standard treatment</td>
<td>5 years</td>
<td>7.5% (both arms)b, –0.8%d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD⁴,⁵</td>
<td>10 years</td>
<td>Multiple drugs in both arms</td>
<td>3.4 years</td>
<td>8.1% (both arms)e, –1.1%c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VADT⁶</td>
<td>11.5 years</td>
<td>Multiple drugs in both arms</td>
<td>5.6 years</td>
<td>9.4% (both arms)b, –1.5%d</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aMedian between-arm difference; bMean between-arm difference; cMedian baseline HbA₁c.
Glycated Hemoglobin Measurement and Prediction of Cardiovascular Disease

Hazard ratios for incident CVD by baseline levels of glycemia measures

73 prospective studies involving 294,998 participants without a known history of diabetes mellitus or CVD at the baseline, adjusted for several conventional cardiovascular risk factors, there was an approximately J-shaped association between HbA1c and CVD risk.
A1c Targets

<table>
<thead>
<tr>
<th>Individualised A1c Targets and Patients’ Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tight (6.0 – 6.5%)</strong></td>
</tr>
<tr>
<td>• Newly diagnosed</td>
</tr>
<tr>
<td>• Younger age</td>
</tr>
<tr>
<td>• Healthier</td>
</tr>
<tr>
<td>• (long life expectancy,</td>
</tr>
<tr>
<td>• Low risk of</td>
</tr>
<tr>
<td>hypoglycaemia</td>
</tr>
</tbody>
</table>
Treatment Strategies: Glucose Triad

- Treatment strategy should target all 3 components

![Diagram showing HbA1c, FPG, and PPG in a triangle]

As Patients Get Closer to A1C Goal, the Need to Manage PPG Significantly Increases

Adapted from Monnier L, Lapinski H, Collette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of Type 2 diabetic patients: variations with increasing levels of HBA(1c). Diabetes Care. 2003;26:881-885.
Contribution of FPG and PPG to A1c

- Landmark study using 4-point glucose measurement (290 T2DM subjects)

- PPG accounted for ~70% overall glycaemic exposure when A1c is low (<7.3%)

- Contribution from the fasting hyperglycaemia increasing as A1c increases

- With A1c >10.2%, contributions reversed; PPG contributed ~30% and FPG ~70%

Steno-2 Study

Patients Reaching Intensive-Treatment Goals at Mean 7.8 y, (%)

- Glycosylated haemoglobin <6.5%
P = 0.06
- Cholesterol <3.8 mmol/l
  - Intensive Therapy: P < 0.001
  - Conventional Therapy: P = 0.19
- Triglycerides <1.7 mmol/l
  - Intensive Therapy: P = 0.001
  - Conventional Therapy: P = 0.21
- Systolic BP <130 mm Hg
- Diastolic BP <80 mm Hg

Steno-2 follow up primary endpoint

Steno-2 primary outcome

P = 0.007

Hazard ratio = 0.47 (95% CI, 0.24–0.73; P = 0.008)

Steno-2 Follow up

Steno-2 follow up secondary endpoint

# Treating the ABCs Reduces Diabetic Complications

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Complication</th>
<th>Reduction of Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose control</td>
<td>Heart attack</td>
<td>↓ 37%&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular disease</td>
<td>↓ 51%&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>Heart failure</td>
<td>↓ 56%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>↓ 44%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Diabetes-related deaths</td>
<td>↓ 32%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease mortality</td>
<td>↓ 35%&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lipid control</td>
<td>Major coronary heart disease event</td>
<td>↓ 55%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Any atherosclerotic event</td>
<td>↓ 37%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease event</td>
<td>↓ 53%&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Glucose lowering – waste of time?

- Glucose lowering, started early, may have long term cardiovascular benefits

- Multifactorial risk reduction is imperative
**Self-monitoring of Blood Glucose (SMBG)**

**Noninsulin Users**
- Introduce at diagnosis
- Personalize frequency of testing
- Use SMBG results to inform decisions about whether to target FPG or PPG for any individual patient

**Insulin Users**
- All patients using insulin should test glucose
  - ≥2 times daily
  - Before any injection of insulin
- More frequent SMBG (after meals or in the middle of the night) may be required
  - Frequent hypoglycemia
  - Not at A1C target

Testing positively affects glycemia in T2D when the results are used to:
- Modify behavior
- Modify pharmacologic treatment

SMBG, self-monitoring of blood glucose.
When and how should glucose monitoring be used?

SMBG Frequency vs A1C

# Targets for Control

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycaemic control*</td>
<td>Pasting or pre-prandial 4.4 – 7.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Post-prandial** 4.4 – 8.5 mmol/L</td>
</tr>
<tr>
<td></td>
<td>A1c** ≤6.5%</td>
</tr>
<tr>
<td>Lipids</td>
<td>Triglycerides ≤1.7 mmol/L</td>
</tr>
<tr>
<td></td>
<td>HDL-cholesterol &gt;1.0 mmol/L (male)</td>
</tr>
<tr>
<td></td>
<td>&gt;1.2 mmol/L (female)</td>
</tr>
<tr>
<td></td>
<td>LDL-cholesterol ≤2.6 mmol/L#</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≤135/75 mmHg$</td>
</tr>
<tr>
<td>Exercise</td>
<td>150 minutes/week</td>
</tr>
<tr>
<td>Body weight</td>
<td>If overweight or obese, aim for 5-10%weight loss in 6 months</td>
</tr>
</tbody>
</table>