Comprehensive Diabetes Treatment

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Diabetes Treatment Objectives

• Blood glucose control
  » Improve patient wellbeing
  » Prevent acute complications (DKA, infection, etc)
  » Reduce the risk of chronic complications

• Cardiovascular disease risk reduction (lifestyle, lipids, blood pressure, smoking)
  » Reduce risk of CAD, stroke and PVD

• Treat chronic complications

• Diabetes prevention
  » Reduce future disease burden
# Guidelines for Glycemic, BP, & Lipid Control

<table>
<thead>
<tr>
<th></th>
<th>American Diabetes Assoc. Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA(_1c)</strong></td>
<td>(&lt; 7.0% ) <em>(Alternate goal for selected patients)</em></td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td>(&lt; 130/80 \text{ mmHg})*</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
</tr>
<tr>
<td><strong>LDL:</strong></td>
<td>(&lt; 100 \text{ mg/dL (2.59 mmol/l)})</td>
</tr>
<tr>
<td></td>
<td>(&lt; 70 \text{ mg/dL (1.81 mmol/l)} ) <em>(with overt CVD)</em></td>
</tr>
<tr>
<td><strong>HDL:</strong></td>
<td>(&gt; 40 \text{ mg/dL (1.04 mmol/l)} ) <em>Men</em></td>
</tr>
<tr>
<td></td>
<td>(&gt; 50 \text{ mg/dL (1.30 mmol/l)} ) <em>Women</em></td>
</tr>
<tr>
<td><strong>TG:</strong></td>
<td>(&lt; 150 \text{ mg/dL (1.69 mmol/l)} )</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>regardless of baseline lipids for patients with overt CVD or multiple risk factors</td>
</tr>
</tbody>
</table>

### Effects of Early Glycemic Control: Long-Term Follow-up of Intervention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervent. duration</th>
<th>Int. A1c</th>
<th>Observ. duration</th>
<th>Obs. A1c</th>
<th>Microvasc. comps</th>
<th>CV events and death</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td>6.5 yrs</td>
<td>7.4 (I)</td>
<td>9.1 (C)</td>
<td>11 yrs</td>
<td>8.0 (I) 8.2 (C)</td>
<td>53-59% reduction in retinopathy 56% reduction in CV death, MI or CVA</td>
</tr>
<tr>
<td>UKPDS</td>
<td>10.0-10.7 yrs</td>
<td>7.0 (I)</td>
<td>7.9 (C)</td>
<td>10 yrs</td>
<td>7.9 (I) 8.5 (C) 8.4 (I) 8.9 (C)</td>
<td>24% reduction in aggregate microvasc. comps 15% reduction in MI 27% reduction in all-cause death</td>
</tr>
<tr>
<td>STENO 2</td>
<td>7.8 yrs</td>
<td>7.9 (I)</td>
<td>9.0 (C)</td>
<td>5.5 yrs</td>
<td>7.7 (I) 8.0 (C)</td>
<td>13% reduction in CV death 20% reduction in all-cause death</td>
</tr>
</tbody>
</table>

Steno-2 Study: Cardiometabolic Control During Follow-up

Implications of Long-Term Trials

- Early treatment reduces complications
- Beneficial effects of early treatment persist
- Effects of poor metabolic control also persist
- Intensive interventions have risks as well as benefits
A 1% change in HbA$_{1C}$ equals a 29 mg/dl change in average plasma glucose
Glycemic Control Decision Making Elements

Target HbA1C

Lower

Higher

Inzucchi S et al. 2012;
Diabetes Care. 35:1364-1379
Antihyperglycemic Agents: Major Sites of Action

Plasma glucose

- Kidney
  - (+) with SGLT2 inhibitor

- Muscle/Fat
  - (+)

Liver

- (+) with Insulin secretion

Pancreas

- (-)

Carbohydrate Absorption

- (+) with Metformin

Glucose Production

- (+)

Glucose Uptake

- (-)

Insulin

GLP-1 agonist

DPP-4 inhibitor

(+)

Sulfonylureas, Meglitinides, Nateglinide

(-)
Glucose-Lowering Therapy in Type 2 Diabetes (1)

Inzucchi S et al. 2012; Diabetes Care. 35:1364-1379
Glucose-Lowering Therapy in Type 2 Diabetes (2)

Inzucchi S et al. 2012; Diabetes Care. 35:1364-1379
Insulin Therapy
Intensive Insulin Therapy in Type 1 Diabetes

- Goal: Mimic endogenous insulin secretion in order to maintain fasting and post-prandial blood glucose within normal ranges
Physiologic Insulin Secretion

- **Insulin** (µU/mL) vs. **Time of Day**
  - Peaks at A.M. and P.M.
  - Concentration decreases through the day.

- **Glucose** (mg/dL) vs. **Time of Day**
  - Peaks at A.M. and P.M.
  - Concentration decreases through the day.

**Breakfast**
- 8 A.M.

**Lunch**
- 12 P.M.

**Supper**
- 6 P.M.

Graph indicates insulin secretion peaks coincide with meals.
# Insulin Pharmacodynamics

<table>
<thead>
<tr>
<th>Classification</th>
<th>Generic Names</th>
<th>Onset of Action</th>
<th>Peak Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting analog</td>
<td>Lispro Aspart</td>
<td>5-15 min</td>
<td>0.5-2 hours</td>
</tr>
<tr>
<td></td>
<td>Glulisine</td>
<td></td>
<td>3-5 hours</td>
</tr>
<tr>
<td>Short-acting</td>
<td>Regular</td>
<td>30-60 min</td>
<td>2-4 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-8 hours</td>
</tr>
<tr>
<td>Intermediate</td>
<td>NPH</td>
<td>1-3 hours</td>
<td>4-10 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10-20 hours</td>
</tr>
<tr>
<td>Long-acting</td>
<td>Glargine Detemir</td>
<td>2-4 hours</td>
<td>Broad “peakless”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16-24 hours</td>
</tr>
</tbody>
</table>
Insulins: Brand and Generic Names

• “Basal” formulations
  » Lantus          glargine
  » Levemir         detemir
  » Humulin N, Novolin N  NPH

• “Bolus” formulations
  » Humalog         lispro
  » Novolog         aspart
  » Apidra          glulisine
  » Humulin R, Novolin R  regular

• Pre-mixed
  » NPH – regular (“70 – 30”)  70% NPH/30% reg
  » Novolog mix (“75/25”)  75% int/25% aspart
  » Humalog mix (“70/30”)  70% int/30% lispro
Implementation of Basal Bolus Therapy

NPH at AM and HS
+ Aspart AC

Glargine HS or AM
+ Aspart AC
Insulin Therapy in Type 2 Diabetes

- Effective...can lower hyperglycemia by a greater amount than any other therapeutic option
- For recently diagnosed patients, insulin sensitivity and endogenous insulin secretion may improve as a result of reduced glucotoxicity.
- UKPDS: Cardiovascular risk declines with HbA$_{1c}$. CV risk in insulin treatment group not worsened.
- May be less expensive and simpler than multi-drug combination therapy
Insulin Therapy in Type 2 Diabetes

- Who should be started on insulin?
- When should insulin therapy be initiated?
- What are the barriers to using insulin?
- How should insulin be initiated and titrated?
- How can initial insulin therapy be intensified?
- What are the safety considerations in using insulin?
Fear of self-injection
Perception that insulin use represents a personal failure
Fear that insulin will cause diabetic complications

Hypoglycemia
Weight gain
Cost

Lack of resources and support for patient education
Lack of knowledge about appropriate insulin use
Perception of complexity in initiation and dose titration
Concerns about long-term consequences of insulin therapy
Indications for Insulin in Type 2 Diabetes

• Severe insulin deficiency (ex DKA)
• Symptomatic hyperglycemia
• Uncontrolled hyperglycemia despite oral agents
  » Fasting glucose >250 mg/dl or random glucose frequently >300 mg/dl
  » Hb A₁C ≥10%
• Inadequately controlled glucose (Hb A₁C target) on non-insulin therapy
EASIE: Addition of Glargine Insulin or Sitagliptin in Patients Not Controlled on Metformin

- 6 month, randomized open label trial
- 515 patients randomized to glargine insulin or sitagliptin
- Insulin dose titrated twice weekly to achieve fasting glucose target range of 95-140 mg/dl

EASIE Study: HbA$_{1c}$ Results

Initiation of Insulin in Type 2 Diabetes

• Basal insulin only
  » Glargine or detemir insulin: QD
  » Intermediate insulin: HS or BID
• Intermediate/short-acting premix
  » 70/30 or 75/25: BID
• Mealtime rapid-acting insulin
Starting With Basal Insulin

- 1 injection with no mixing
- Slow, safe, and simple titration
- Low dosage
- Limited weight gain
- Does not alter pre- to post-prandial glucose increment
Basal Insulin in Type 2 Diabetes

• Start with basal insulin
  » Glargine
  » Detemir
  » NPH hs

• Initial dose:
  » 10 units
  » 0.2-0.3 units/kg

• Titrate based on fasting blood glucose

• Add premeal short-acting insulin if necessary
## Basal Insulin Titration

*Adjust weekly based on average fasting glucose*

<table>
<thead>
<tr>
<th>Fasting blood glucose</th>
<th>Basal insulin increment</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 - 119 mg/dl</td>
<td>2 units</td>
</tr>
<tr>
<td>120 – 139 mg/dl</td>
<td>4 units</td>
</tr>
<tr>
<td>140 – 179 mg/dl</td>
<td>6 units</td>
</tr>
<tr>
<td>180 mg/dl or higher</td>
<td>8 units</td>
</tr>
</tbody>
</table>
Treat to Target Study: Glargine or NPH Insulin Added to Oral Therapy

Patients inadequately controlled on OHAs

A1C 7.5%–10%

Continue OHAs +
Insulin glargine at bedtime

24-wk treatment

Continue OHAs +
NPH insulin at bedtime

Target FPG ≤100 mg/dL

Treat to Target Study
Mean A1C Levels During Study

By week 18, the percentage of patients with HbA1c < 7.0% increased from 2.5% to 66.2%.

Treat to Target Study: Risk of Hypoglycemia
Treat to Target Study

Risk of Hypoglycemia

Proportion of patients with hypoglycemia ≤ 72 mg/dL (4.0 mM)

Events per patient exposure year (≤ 72 mg/dL, 4.0 mM)

Basal Insulin Titration

Patient Instructions

- Increase glargine insulin dose by 2 units if fasting blood glucose is >120 mg/dl (6.6 mM)
- Adjust insulin dose no more often than every 3-4 days
- Decrease insulin dose if nocturnal hypoglycemic reactions occur
Comparison of Clinic-Directed Basal Insulin Dose Algorithm with Patient-Directed Algorithm
Comparison of Clinic-Directed Basal Insulin Dose Algorithm with Patient-Directed Algorithm

Hypoglycemia
Comparison of Glargine with Once or Twice Daily Detemir

HbA$_1^C$

Pre- and Post-meal glucose

Initiation of Pre-Mixed Insulin

• May be advantageous in patients with post-prandial hyperglycemia
• Increased risk of hypoglycemia if patient takes insulin dose and does not eat usual meal
• Formulations:
  » 70% NPH + 30% Regular
  » 75% NPL + 30% Lyspro
  » 70% Protamine-Aspart + 30% Aspart
• Initial dose: 10 units bid before breakfast and dinner
Adjustment of Pre-Mixed Insulin

- Adjust once or twice weekly
  - Adjust pre-breakfast dose based on pre-dinner capillary blood glucose
  - Adjust pre-dinner dose based on pre-breakfast capillary blood glucose
  - 2 hour post-meal glucose levels can also be used to adjust

<table>
<thead>
<tr>
<th>3 day average glucose (mg/dl)</th>
<th>Insulin dose adjustment (change in units of insulin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80</td>
<td>- 2</td>
</tr>
<tr>
<td>80-109</td>
<td>No Change</td>
</tr>
<tr>
<td>110-139</td>
<td>+ 2</td>
</tr>
<tr>
<td>140-179</td>
<td>+ 4</td>
</tr>
<tr>
<td>≥180</td>
<td>+ 6</td>
</tr>
</tbody>
</table>
Comparison of basal only with pre-mix

- Comparable efficacy
- Greater risk of hypoglycemia with pre-mix
- Slightly greater weight gain with pre-mix
- Intensification of therapy may be more cumbersome if starting with pre-mix
Should Oral Agents Be Continued When Insulin is Started?

- Metformin: Yes
  » Better glucose control
  » Less weight gain
- DPP4 Inhibitor: ?
  » Better post-prandial glucose control
- Pioglitazone: ?
  » May result in lower insulin dose requirement
  » Fluid retention
  » Weight gain
- Sulfonylurea: ?
  » More weight gain
  » Higher risk of hypoglycemia
Initial dose of insulin glargine should equal approximately 80% of the total daily dose of intermediate acting insulin.

For example if patient was on NPH 40 units am and 50 units pm...the total dose is 90 units and estimated initial dose of glargine is 65 - 75 units to control nocturnal and fasting hyperglycemia.
Insulin "Pen"
Weight Gain with Insulin Treatment

- In controlled studies, weight gain attributable to insulin therapy is generally modest.
- In patients with poorly controlled diabetes, weight gain may be due to re-establishment of usual basal weight.
- Recurrent hypoglycemia may exacerbate weight gain because of additional calories consumed to treat hypoglycemia.
- Weight gain can be minimized by concurrent use of metformin.
Insulin Safety Concerns

- Hypoglycemia
- Cardiovascular disease risk
- Cancer
Risk Factors for Hypoglycemia in Basal-Insulin Treated Patients

- Lower HbA$_{1C}$ target
- Concomitant use of sulfonylurea
- Renal or hepatic impairment
- Advanced age
- NPH or pre-mix insulin before evening meal
- Hypoglycemic unawareness
- Missed meals (especially if basal insulin dose is too high)
Diabetes and Cancer

• Epidemiologic studies suggest diabetes may be associated with increased risk of certain cancers
  » Pancreas (pooled OR 1.8)
  » Liver
  » Colorectal (pooled RR 1.3)
  » Breast (pooled RR 1.2)
  » Bladder (pooled RR 1.2)
  » Endometrium (pooled RR 2.1)

• It is not known to what extent this association is due to common risk factors (diet, activity, etc) or to a causal link (insulin signaling, etc.)
Insulin Treatment and Cancer

• Recently, a series of epidemiologic studies reported a possible association between glargine insulin use and increased risk of cancer.

• These studies have been extensively debated. Potential confounding variables such as duration of diabetes, comorbidities and other confounders may not have been fully controlled.

• Additional retrospective epidemiologic analyses have yielded conflicting results.

• Large, randomized, prospective trials, have not found evidence that glargine insulin is associated with increased cancer risk.

• “Cancer risk should not be a major factor when choosing between available diabetes therapies…”

ADA/ACS Consensus Report
ORIGIN Trial

- Randomized trial, compared titrated basal insulin with standard care in patients with diabetes, impaired glucose tolerance or impaired fasting glucose
- 12,537 study subjects followed for median 6.2 years
- Co-primary outcomes:
  » Cardiovascular death, nonfatal MI, nonfatal stroke
  » Above plus revascularization or hospitalization for heart failure

### ORIGIN Trial Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Insulin Glargine (N=6264)</th>
<th>Standard Care (N=6273)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td>no./100 patient-yr</td>
<td>no. (%)</td>
<td>no./100 patient-yr</td>
</tr>
<tr>
<td>First coprimary outcome</td>
<td>1041 (16.6)</td>
<td>2.94</td>
<td>1013 (16.1)</td>
<td>2.85</td>
</tr>
<tr>
<td>Second coprimary outcome</td>
<td>1792 (28.6)</td>
<td>5.52</td>
<td>1727 (27.5)</td>
<td>5.28</td>
</tr>
<tr>
<td>Microvascular outcomes</td>
<td>1323 (21.1)</td>
<td>3.87</td>
<td>1363 (21.7)</td>
<td>3.99</td>
</tr>
<tr>
<td>Total mortality</td>
<td>951 (15.2)</td>
<td>2.57</td>
<td>965 (15.4)</td>
<td>2.60</td>
</tr>
<tr>
<td>Total myocardial infarctions</td>
<td>335 (5.4)</td>
<td>0.93</td>
<td>326 (5.2)</td>
<td>0.90</td>
</tr>
<tr>
<td>Total strokes</td>
<td>331 (5.3)</td>
<td>0.91</td>
<td>319 (5.1)</td>
<td>0.88</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>580 (9.3)</td>
<td>1.57</td>
<td>576 (9.2)</td>
<td>1.55</td>
</tr>
<tr>
<td>Hospitalization for congestive heart failure</td>
<td>310 (4.9)</td>
<td>0.85</td>
<td>343 (5.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Revascularization</td>
<td>908 (14.5)</td>
<td>2.69</td>
<td>860 (13.7)</td>
<td>2.52</td>
</tr>
<tr>
<td>Angina</td>
<td>709 (11.3)</td>
<td>2.07</td>
<td>743 (11.8)</td>
<td>2.17</td>
</tr>
<tr>
<td>Unstable</td>
<td>238 (3.8)</td>
<td>0.66</td>
<td>261 (4.2)</td>
<td>0.72</td>
</tr>
<tr>
<td>New</td>
<td>100 (1.6)</td>
<td>0.27</td>
<td>138 (2.2)</td>
<td>0.38</td>
</tr>
<tr>
<td>Worsening</td>
<td>455 (7.3)</td>
<td>1.29</td>
<td>446 (7.1)</td>
<td>1.26</td>
</tr>
<tr>
<td>Limb or digit amputation</td>
<td>47 (0.8)</td>
<td>0.13</td>
<td>53 (0.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiovascular hospitalization</td>
<td>2083 (33.2)</td>
<td>6.98</td>
<td>2071 (33.0)</td>
<td>6.91</td>
</tr>
<tr>
<td>Noncardiovascular hospitalization</td>
<td>2338 (37.3)</td>
<td>7.50</td>
<td>2349 (37.4)</td>
<td>7.53</td>
</tr>
<tr>
<td>Any cancer</td>
<td>476 (7.6)</td>
<td>1.32</td>
<td>477 (7.6)</td>
<td>1.32</td>
</tr>
<tr>
<td>Death from cancer</td>
<td>189 (3.0)</td>
<td>0.51</td>
<td>201 (3.2)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

1. The worldwide prevalence of diabetes is projected to continue increasing, especially in regions undergoing rapid socioeconomic change and development.

2. Early intensive glycemic control is associated with reduced long-term risk of microvascular and cardiovascular complications.

3. Target HbA$_1$c should be individualized based on multiple factors including diabetes duration, presence of cardiovascular complications, risk of hypoglycemia, etc.
4. Insulin treatment in type 2 diabetes is highly effective in improving glycemic control.

5. When starting a patient on basal insulin, a program to titrate the insulin dose to therapeutic goal should be followed.

6. Large prospective trials have shown that glargine insulin use is not associated with increased cardiovascular or cancer risks.