Ways to Reduce Hypoglycemia in Type 1 Diabetes

Practical Ways to Achieve Targets in Diabetes Care
July 14, 2012
H. Peter Chase, MD

I) Introduction/Definitions

II) Incidence of Severe Hypoglycemia

III) Causes

IV) Hypoglycemia Prevention NOW

V) Hypoglycemia Prevention in the FUTURE

VI) SUMMARY
I. Hypoglycemia: Introduction/Definitions

1) **ADA**: “A blood glucose level <70 mg/dL (<3.9 mmol/L)”
   (At this level people secrete counter-regulatory hormones to help detect low glucose levels)

2) **True Hypoglycemia**: “A blood glucose level <60 mg/dL (<3.3 mmol/L)”
   (Non-diabetic normal individuals are rarely <60 mg/dL [<3.3 mmol/L])

3) **Clinical definitions of hypoglycemia**
   i) **Mild**: person (parents) can easily treat
   ii) **Moderate**: neuroglycopenic signs but not unconscious or seizure
   iii) **Severe**: unconscious, seizure, neurologic impairment

4) **Delayed Hypoglycemia**: usually 4 to 12 hours after exercise (48%) vs. no exercise (28%)

5) **Hypoglycemia Unawareness**: Two or more episodes per week with BG <70mg/dL (<3.9 mmol/L) and no symptoms. Diagnosis using Hypoglycemia Awareness Questionnaire (HAQ).
   *(Clark et al. Diabetes Care, 18:517,1995)*
1. CGM Glucose Values in People without Diabetes:  
I. Introduction/Definitions

*(JDRF Study Group: Diabetes Care 33:1297, 2010)*

1) 74 subjects, ages 9 to 65 years: 84 hours of CGM per subject

2) Not “prediabetic:” normal fasting and 2hr postprandial glucose levels
   1) No first degree relatives with diabetes
   2) No ICAs
   3) HbA1c <6.0%
   4) BMI 10th to 90th percentile

3) Glucose levels:
   1) 60-69 mg/dL (3.3-3.8 mmol/L) = 1.5% of CGM readings (≈4 readings/day)
   2) <60 mg/dL (<3.3 mmol/L) = <0.1% of CGM readings
I. How Common is Nocturnal Hypoglycemia?

I. Introduction/Definitions

(JDRF-RCT Diabetes Care, 33:1004, 2010)

- **Biochemical:**
  JDRF – Randomized Clinical Trial: 180 subjects with T1D
  Use of Navigator or Paradigm RT Systems: 36,000 nights, 2.4 million CGM readings.

<table>
<thead>
<tr>
<th>Frequency of Nocturnal Hypoglycemia</th>
<th>≤70 mg/dL</th>
<th>≤60 mg/dL</th>
<th>≤50 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(≤3.9 mmol/L)</td>
<td>(≤3.3 mmol/L)</td>
<td>(≤2.8 mmol/L)</td>
</tr>
<tr>
<td>Single value hypoglycemic</td>
<td>25%</td>
<td>15%</td>
<td>7.6%</td>
</tr>
<tr>
<td>2 consecutive values hypoglycemic</td>
<td>23%</td>
<td>13%</td>
<td>6.7%</td>
</tr>
<tr>
<td>20 consecutive minutes hypoglycemic</td>
<td>18%</td>
<td>9.6%</td>
<td>4.5%</td>
</tr>
<tr>
<td>60 consecutive minutes hypoglycemic</td>
<td>9.7%</td>
<td>4.6%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Two predictors:
Lower HbA1c and hypoglycemia on blinded baseline CGM
## II. Incidence of Severe Hypoglycemia: DCCT
(Episodes per 100 patient years)

<table>
<thead>
<tr>
<th></th>
<th>Intensive Treatment</th>
<th>Conventional Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assistance Required</td>
<td>62</td>
<td>19</td>
</tr>
<tr>
<td>Coma or Seizure</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td><strong>All:</strong></td>
<td><strong>62</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>

*NEJM 329:977, 1993*

<table>
<thead>
<tr>
<th></th>
<th>Intensive Treatment</th>
<th>Conventional Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peds:</td>
<td>85.7</td>
<td>27.8</td>
</tr>
<tr>
<td></td>
<td>26.7</td>
<td>9.7</td>
</tr>
</tbody>
</table>

*J. Peds 125:177, 1994*
II. Incidence of Severe Hypoglycemia

- The Rate Limiting Factor in Attaining Optimal Glycemic Control
- The number one fear of families with T1D

A) Real Life:
i) General peds diabetes clinic: 19/100 patient years

B) Research Studies:
i) JDRF-RCT (CSII or MDI): 17.9/100 patient years

   ii) Star 3 (CSII + CGM) – 495 patients = 13.3/100 patient years

C) Nocturnal severe hypoglycemia:
   DCCT = 55% (Diabetes Care, 18:1415, 1995)
   Davis, et al ≈ 75% (Diabetes Care, 20:22, 1997)
II. Duration of Nocturnal Hypoglycemia Before Seizures

(Buckingham, et al. Diabetes Care, 31:2110, 2008)

Summary: Shortest time CGM <60 mg/dL before seizure = 2.15 hr.
The rate of severe hypoglycemia (SH) for intensively treated patients in the DCCT was 26.7 and 16 events/100 patient years for adolescents, and for all subjects, respectively.
Mean HbA$_{1c}$ by Age Group
Type 1 Diabetes Exchange Registry (Helmsley)

Age (Years) | HbA$_{1c}$
---|---
<6 | 8.3%
6-12 | 8.3%
13-17 | 8.7%
18-25 | 8.5%
26-49 | 7.7%
≥ 50 | 7.6%

III. Biochemical Causes of Hypoglycemia

1. Increased glucose utilization and insulin sensitivity with exercise
2. Increased insulin levels during exercise
3. Hypoglycemia begets hypoglycemia
4. Impaired counterregulatory hormone responses in T1D (especially during sleep)
5. Insulin inhibition of hepatic glucose output
III. Causes: Hypoglycemia Unawareness (HUN)
(The #1 Known Factor Associated with SH in Adults)

- Adult population showed 23% of patients with T1D to have HUN
  - All patients with HUN had SH in the previous year

- Barbara Davis Center pediatric patients: 14.3% (28/196) as determined by HAQ (Hypoglycemia Awareness Questionnaire)
  - 17.9% with HUN reported Severe Hypoglycemia vs 4.8% without HUN in the previous year (p < 0.01)

- Perth Pediatric Patients: 29% of patients with HUN
  - 33% of those with HUN reported Severe Hypoglycemia (SH) vs 5.2% of subjects without HUN reported SH in the previous year
    *(Ly et al. Diabetes Care, 32:1802, 2009)*
III. Causes: Decreased Epinephrine Responses in Children with T1D

*(DirecNet, Diabetes Care, 32:1954, 2009)*

- **Subjects:**
  - 14 children 4-7 yo; duration 3.3 years
  - 14 adolescents 12-17 yo; duration 6.6 years
- No epinephrine response (>3SD above baseline) to insulin-induced hypoglycemia (<60 mg/dL [<3.3 mmol/L])
  - 9 of 14 young children (average 47 → 82 pg/mL)
  - 8 of 14 adolescents (average 27 → 71 pg/mL)
- 14 nondiabetic adolescents increased from 77 to 582 pg/mL in response to hypoglycemia
- Glucagon levels did not increase with hypoglycemia in young children or adolescent subjects with T1D
III. Causes: Decreased Epinephrine Responses in Children with T1D

(DirecNet, Diabetes Care, 32:1954, 2009)
IV. Hypoglycemia Prevention NOW

What Can We Do NOW?

1. Reduce Intensity of Glycemic Control
2. Use of Insulin Analogs
3. Improved Management of Exercise
4. Use of an Insulin Pump
   • Particularly helpful with/following exercise
5. Use of Continuous Glucose Monitoring (CGM)

V. Hypoglycemia Prevention in the FUTURE

6. Closed Loop (Bionic) Pancreas
   • Low Glucose Suspend (LGS) in Europe (2009)
   • Predicted Low Glucose Suspend (PLGS)
7. Preserving C-Peptide/Insulin Production
IV. Hypoglycemia Prevention NOW

2. Use of Insulin Analogs


<table>
<thead>
<tr>
<th>Year</th>
<th>HbA1c (%)</th>
<th>Severe Hypoglycemia Episodes (subject per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>9.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1994</td>
<td>8.80</td>
<td>0.00</td>
</tr>
<tr>
<td>1995</td>
<td>8.60</td>
<td>0.00</td>
</tr>
<tr>
<td>1996</td>
<td>8.40</td>
<td>0.00</td>
</tr>
<tr>
<td>1997</td>
<td>8.20</td>
<td>0.00</td>
</tr>
<tr>
<td>1998</td>
<td>8.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*P < .001 vs previous year
IV. Hypoglycemic Prevention NOW

*(Dixon, Chase et al., Ped Diab, 6:150-154, 2005)*

2. Use of Insulin Analogs

<table>
<thead>
<tr>
<th></th>
<th>Pre-study – 6 mo.</th>
<th>Study - 6 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total SH</strong></td>
<td><strong>Total SH</strong></td>
<td></td>
</tr>
<tr>
<td>A. Lantus</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>B. NPH</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th><strong>Nighttime SH</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Lantus</td>
<td>12</td>
</tr>
<tr>
<td>B. NPH</td>
<td>1</td>
</tr>
</tbody>
</table>

128 Preschoolers (<6yo): 64 began glargine insulin
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3. Improved Management of Exercise

(The #1 Known Factor Associated with SH in Youth)

DirectNet Exercise Protocol

Treadmill

- Exercise
- Exercise
- Exercise
- Exercise

Five minute rest periods

0 15 20 35 40 55 60 75

TIME (minutes)

Exercise at 55% maximum effort (VO2max): (HR = 140/min)

Three studies using this protocol:
Mean Glucose Levels on Two Study Days
(Study A: Same 50 Youth/CSII or Lantus)

Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus.

Exercise Period
4:00 – 5:15 PM

Sedentary
mean BG 154 mg/dL
28% had lows (<60 mg/dL [<3.3 mmol/L]) during the night

Exercise
mean BG 131 mg/dL
48% had lows (<60 mg/dL [<3.3 mmol/L]) during the night
IV. Hypoglycemia Prevention NOW
to Prevent Exercise-Related Hypoglycemia
3. Improved Management of Exercise

B) DirecNet Exercise Study #2: CSII only
During 1 hr intense exercise: < 70 mg/dL (<3.9 mmol/L) (50 youth)
i) With insulin = 43%
ii) CSII discontinued with exercise = 16%
   *(DirecNet: Diabetes Care 29:2200, 2006)*

C) Barbara Davis Center Exercise Study
Discontinuing CSII with exercise plus 80% temporary basal rate: 9 p.m. to 3 a.m.:
   Lows during the night:
   <70 mg/dL (<3.9 mmol/L) = 1 of 16 youth
   <60 mg/dL (<3.3 mmol/L) = 0 of 16 youth
IV. Hypoglycemia Prevention NOW

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IV. Hypoglycemia Prevention NOW

4. Use of an Insulin Pump

Meta-analysis of Severe Hypoglycemia in CSII vs MDI


<table>
<thead>
<tr>
<th>Study</th>
<th>Rate ratio (95%) % weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bode (poor control)</td>
<td>5.55 (3.57, 8.61) 5.84</td>
</tr>
<tr>
<td>Bode (good control)</td>
<td>10.50 (4.24, 26.01) 4.66</td>
</tr>
<tr>
<td>Kaderman</td>
<td>6.47 (3.09, 13.55) 5.11</td>
</tr>
<tr>
<td>Maniatis</td>
<td>1.29 (0.31, 5.42) 3.34</td>
</tr>
<tr>
<td>Rizvi</td>
<td>8.00 (1.84, 34.79) 3.26</td>
</tr>
<tr>
<td>Litton</td>
<td>5.75 (0.72, 45.97) 2.19</td>
</tr>
<tr>
<td>Linkschova</td>
<td>13.92 (6.95, 27.86) 5.23</td>
</tr>
<tr>
<td>Bruttomesso</td>
<td>3.44 (1.62, 7.33) 5.07</td>
</tr>
<tr>
<td>Rudolph, Hirsch</td>
<td>3.81 (2.49, 5.84) 5.87</td>
</tr>
<tr>
<td>Plotnick</td>
<td>2.18 (1.05, 4.52) 5.13</td>
</tr>
<tr>
<td>Cohen</td>
<td>4.69 (0.52, 41.98) 2.04</td>
</tr>
<tr>
<td>Hunger-Dathe</td>
<td>3.62 (2.23, 5.85) 5.75</td>
</tr>
<tr>
<td>Weintrob</td>
<td>3.00 (0.62, 14.44) 3.04</td>
</tr>
<tr>
<td>Weinzimer</td>
<td>2.11 (1.50, 2.96) 6.03</td>
</tr>
<tr>
<td>McMahon</td>
<td>2.89 (1.67, 4.98) 5.60</td>
</tr>
<tr>
<td>Siegel-Czarkowski</td>
<td>7.07 (0.87, 57.46) 2.17</td>
</tr>
<tr>
<td>Alemzadeh</td>
<td>2.51 (0.67, 9.47) 3.58</td>
</tr>
<tr>
<td>Mack-Fogg</td>
<td>2.09 (1.12, 3.92) 5.40</td>
</tr>
<tr>
<td>Sciaffini</td>
<td>1.25 (0.34, 4.65) 3.61</td>
</tr>
<tr>
<td>Rodrigues</td>
<td>35.41 (29.94, 57.15) 5.75</td>
</tr>
<tr>
<td>Lepore</td>
<td>3.50 (2.04, 6.01) 5.61</td>
</tr>
<tr>
<td>Hoogma</td>
<td>2.50 (1.53, 4.08) 5.73</td>
</tr>
<tr>
<td>Overall ($I^2$ = 84.2%, $P = 0.00$)</td>
<td>4.19 (2.86, 6.13) 100.00</td>
</tr>
</tbody>
</table>
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5. Use of Continuous Glucose Monitoring (CGM)

(JDRF CGM Study Group, Diabetes Care 32:1378, 2009)

- 129 (of 451) subjects 8-69 yo on CSII or MDI with HbA1c < 7.0% (49% = 8-24 yo)
- Randomized to CGM (67) or Control (62) x 6 mo (2 group analyses)
- Primary outcome: change in time per day with glucose < 70 mg/dL (< 3.9 mmol/L) (using blinded CMG at start vs. 26 wk)
Results: Primary Endpoint:
- CGM group = ↓ from 91 min/d to 54 min/d < 70 mg/dL (< 3.9 mmol/L) (p < 0.002)
- Control group = ↓ from 96 to 91 min/d (p = 0.43) (p = 0.16 between groups)

Secondary Endpoints:
- CGM group = Less time < 60 (< 3.3 mmol/L) or < 50 mg/dL (<2.8 mmol/L); more time @ 70-180 mg/dL
- HbA1c better at 6 mo; 6.4% for CGM group vs. 6.8% for controls (comparison between groups; p < 0.001)

CONCLUSION:
- Lower HbA1c values in well controlled subjects using CGM with a decrease in time spent in hypoglycemia
4, 5. Use of CSII and CGM to Prevent Hypoglycemia NOW
STAR-3 Improved HbA1c with NO increase in Hypoglycemia
(Bergenstal, et al. NEJM, 363, 311, 2010)

**MDI + SMBG vs CSII + CGM (SAP)**

<table>
<thead>
<tr>
<th>Mean 1-Year Change in A1C</th>
<th>SAP</th>
<th>MDI</th>
<th>Difference (ΔA1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (Δ A1C)</td>
<td>8.3 → 7.5% (↓0.8)</td>
<td>8.3 → 8.1% (↓0.2)</td>
<td>-0.6*</td>
</tr>
<tr>
<td>(485)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults ≥ 19 yrs (Δ A1C)</td>
<td>8.3 → 7.3% (↓1.0)</td>
<td>8.3 → 7.9% (↓0.4)</td>
<td>-0.6*</td>
</tr>
<tr>
<td>(329)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatrics 7–18 yrs (Δ A1C)</td>
<td>8.3 → 7.9% (↓0.4)</td>
<td>8.3 → 8.5% (↑0.2)</td>
<td>-0.6*</td>
</tr>
<tr>
<td>(156)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) p < 0.001
2) SH: 13% in each group (< 2 SH in previous 12 mos)
3) DKA: 3 patients vs. 2 patients
4) HbA1c: 44% (vs. 20%) pediatric patients in ADA ranges
V. Hypoglycemia Prevention in the FUTURE

A) Low Glucose Suspend (LGS)
   (partial bionic pancreas)

B) Predicted Low Glucose Suspend (PLGS)
   (partial bionic pancreas)

C) Preserving C-Peptide/Insulin Production
V. Hypoglycemia Prevention in the FUTURE

A) A Commercial Semi-Closed-Loop System:

System with Low Glucose Suspend (LGS)

The Paradigm Veo™*

- Integrated sensor
- Glucose trends/values every 5 min
- Alarms
  - Lows and highs
  - Predictive
- Hypoglycemia suspend at set level
  - Suspend for up to 2 hours
  - Re-suspend after 4 hours if needed

* Limited by U.S. law to investigational use.
V. Hypoglycemia Prevention in the Future

A) Veo: Daily Summary Report:
LGS (Low Glucose Suspend) for 2 Hours

Keenan et al, Ped Endo Rev, 7, 445, 2010
V. Hypoglycemia Prevention in the FUTURE
A) Use of Low Glucose Suspend (LGS) with Sensor-Augmented Pump (SAP)

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients/ Methods</th>
<th>Results</th>
</tr>
</thead>
</table>
| Danne, T. et al., Diab. Tech. Ther. 13, 1129, 2011 | 21 youth with T1D from 3 centers in Germany 2 wks=SAP 4 wks=SAP with LGS | \textit{SAP with LGS=}
1) No SH or DKA
2) Decrease time spent (and decrease number of episodes) <70mg/dL
3) Positive device satisfaction |
| Choudhary, P. et al., Diabetes Care 34, 2023, 2011 | 31 adults with T1D in . 2 wks=SAP 3 wks= SAP with LGS | \textit{SAP with LGS=}
1-) No deterioration of glucose control
2) ↓ time of nocturnal hypoglycemia in those with highest quartile of hypoglycemia at baseline
3) All subjects found LGS “useful” and 93%= (more secure at night) |
| Agrawal, P. et al., J. Diab. Sci Tech. 5, 1137, 2011 | 935 patients 28,401 pt days/278 pts. > 3mos LGS feature in “Real World” | 1) Sensor glucose @ 2 hours=150±69 mg/dL
2) Significant reduction in BG values < 50 mg/dL when LGS in use (p < 0.001). |

In summary, time spent in hypoglycemia is reduced as a result of the use of the LGS feature.
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   - Predicted Low Glucose Suspend (PLGS)
7. Preserving C-Peptide/Insulin Production
V. Hypoglycemia Prevention in the FUTURE

B) Predicted Low Glucose Suspend (PLGS)

(First Admission)
V. Hypoglycemia Prevention in the FUTURE

B) Predicted Low Glucose Suspend (PLGS)


(Second Admission)
V. Hypoglycemia Prevention in the FUTURE

B) Home Use: Predicted Low Glucose Suspend (PLGS) and Prevention of Hypoglycemia
V. Hypoglycemia Prevention in the FUTURE

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C. Preserving C-Peptide/Insulin Production

Use of CLP in 72 newly diagnosed subjects to prevent glucotoxicity and to preserve islets (and prevent severe hypoglycemia)
VI. Summary

The Prevention of Hypoglycemia:

1. **WE HAVE MADE PROGRESS!**
   - The use of insulin analogs, better management of exercise (youth), and increased insulin pump use have all helped.
   - The use of CGM with alarms for lows has been helpful for adults (especially with HUN) and for youth when consistently used.

2. **THERE IS A NEED FOR CONTINUED PROGRESS!**
   - The “Bionic” pancreas will develop gradually, with the LGS and PLGS the first components. Studies from other countries show a reduction in low glucose levels as a result of using the LGS.

3. **THE BALANCING OF SAFETY AND MOVING AHEAD MUST REMAIN A HIGH PRIORITY.**

THANK YOU
Treatment: Hypoglycemia Unawareness (HUN)

1. Reduce intensity of glycemic control
   (Fanelli et al. Diabetes, 42:1683, 1993)

2. Use of an insulin pump
   (Giménez et al. Diabetes Tech & Ther: 12:517, 2010)

   • Use of continuous glucose monitoring
     (Cobry E and Chase HP. Infusystems, 3:25, 2006)

4. Pancreatic/Islet Transplant

5. Closed Loop Pancreas
   (The future)
Results: Primary Endpoint:
• CGM group = ↓ from 91 min/d to 54 min/d < 70 mg/dL (< 3.9 mmol/L) (p < 0.002)
• Control group = ↓ from 96 to 91 min/d (p = 0.43)
  (p = 0.16 between groups)

Secondary Endpoints:
• CGM group = Less time < 60 (< 3.3 mmol/L) or < 50 mg/dL (< 2.8 mmol/L); more time @ 70-180 mg/dL
• HbA1c better at 6 mo; 6.4% for CGM group vs. 6.8% for controls (comparison between groups; p < 0.001)

CONCLUSION:
• Lower HbA1c values in well controlled subjects using CGM with no increase in hypoglycemia

(Diabetes Care 32,1378,2009)
C. Sensor Augmented Pump Therapy

1) **European Guard Control Trial** – Guardian system
   *Diess et al, Diabetes Care 29: 2730, 2006*
   
   - 156 T1D subjects (pediatric and adult)
   - CSII or MDI: \( \text{HbA1c} \geq 8.1\% \)
   - 50% = ↓ HbA1c by ≥ 1%

2) **Star 1**
   *Hirsch et al, Diabetes Tech & Ther 10:377, 2008*
   
   - 146 pediatric and adult T1D subjects using MDI
   - Paradigm Real Time (PRT) System or CSII
   - HbA1c > 7.5%: both groups lower after 6 mos
   - More use (> 60%) = lower HbA1c
C. Sensor Augmented Pump Therapy

3) **JDRF – RCT**  
*NEJM 359, 1464, 2008*  
- 322 subjects using CSII or MDI  
- Randomized to CGM or SMBG  
- HbA1c lower in subjects ≥ 25 yo

4) **Real Trend Study**  
*Raccah et al, Diabetes Care: 32, 2245, 2009*  
- 115 peds and adult T1D subjects using MDI → PRT vs CSII  
- HbA1c ≥ 8.0% → both groups improved  
- > 70% time CGM wear = PRT group greater improvement

5) **Star 3 Study**  
*Bergenstal, NEJM, 363, 311, 2010*  
- 485 TID subjects on MDI (pediatric and adult)  
- Randomized to SAP or remain on MDI  
- Significant reduction of HbA1c in SAP group only
V. Hypoglycemia Prevention In the FUTURE

CSII/CGM

(Buckingham, et al. Study in Progress)

- Preserving insulin production
  - CLP x72 hrs; then CSII/CGM
3 year study, subjects on treatment for 2 years
- 78 new onset type 1 subjects
  - Age range 3 – 45 years with staggered enrollment
  - 2/3rds to treatment arm, 1/3 to standard treatment arm
  - Randomized within 7 days of starting insulin
- 3 centers: Stanford, Yale, UCO
  - 24 patients studied to date (16 on intensive treatment/8 controls)
  - NIH sponsored via TrialNet and DirecNet
VI. SUMMARY

The FUTURE: The Next Decade(s)

1) CGM devices will become more “user friendly”

2) CGM glucose values will become more accurate (especially low glucose levels).

3) Insulin dosing will be permitted by FDA based on CGM values.

4) The need for BG calibrations will be reduced.

5) The first part of the “bionic” pancreas, ie: turning off a pump when a CGM value is low, or predicted to become low, will be approved by the FDA.

6) The second part of the “bionic pancreas” will likely be closed loop control during sleep.

7) Episodes of severe hypoglycemia will be greatly reduced.
### IV. Hypoglycemia Prevention NOW

**STAR-3 Hypoglycemia: All Patients (AUC- from CGM)**

<table>
<thead>
<tr>
<th></th>
<th>SAP</th>
<th>Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(247)</td>
<td>(248)</td>
</tr>
<tr>
<td>&lt;70 mg/dL:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline:</td>
<td>0.27</td>
<td>0.29</td>
</tr>
<tr>
<td>At 1 year:</td>
<td>0.24</td>
<td>0.28</td>
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<tr>
<td>&lt;50 mg/dL:</td>
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<td></td>
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<tr>
<td>Baseline:</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>At 1 year:</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Summary:** Lower HbA1c with no increase in hypoglycemia
V. Hypoglycemia Prevention in the FUTURE
C) Preserving C-peptide Production in T1D Prediction (PLGS) and Prevention

• Does improved metabolic control at the onset of diabetes induce a longer remission (honeymoon)?
  

• DCCT clearly showed that individuals with T1D and continued C-peptide production had reduced episodes of severe hypoglycemia *(DCCT: Diabetes Care. 26:832, 2003)*

• Preservation of C-peptide production may be an important way to prevent acute and chronic complications

• TrialNet/DirecNet, et al: CLP x 72 hrs in first week post-dx
  Then CSII/CGM x 2 years (see presentation at this meeting)

• TrialNet: Multiple immunosuppression protocols to try to preserve insulin production in new onsets