Continuous Glucose Monitoring

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LifeScience Alley
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Why is continuous glucose monitoring in diabetes so important?

- **Finger stick testing with Meter/strip**
- **Continuous sensing**
- **Continuous sensing with alerts**
Continuous Glucose Monitoring Technologies

Schematic representation of future products. Not approved by FDA.
Measuring Glucose in Interstitial Fluid

• Interstitial fluid (ISF) surrounds the cells in the body tissue
  – Cells receive oxygen and nutrients, including glucose

• ISF is highly comparable to blood glucose
  – ISF is fed by the capillaries
  – Steady-state differences between blood and ISF is compensated for in sensor calibration

Continuous Glucose Monitoring

Glucose Sensor

• Tiny electrode worn up to 3-days
• Measures glucose levels in interstitial fluid where cells get oxygen and nutrients, including glucose
• 288 glucose readings captured every 24 hrs
• Patients use the Sen-serter® to insert the sensor quickly, easily and with virtually no pain

* Investigational device. Not yet approved by the FDA; Bears CE mark in Europe
Sen-serter is a registered trademark of Medtronic MiniMed, Inc.
Plasma versus Sensor Glucose

Observed delay between plasma and sensor glucose = Physiological, sensor related and filtering delay

• Healthcare Professional inserts Sensor & programs Monitor.

• Patient wears CGMS for up to 3 days (readout not visible).

• Patient returns to physician’s office.

• Data is downloaded and a glucose report generated.

• FDA approval granted in 1999.

• Fairly wide spread reimbursement available today
### CGMS® System Gold™ Performance

<table>
<thead>
<tr>
<th>Population ( * )</th>
<th>Sensor Life</th>
<th>MAD/Correlation</th>
<th>CEG†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsored Trial (127/1229)</td>
<td>64.2 hrs</td>
<td>11.3%/0.94</td>
<td>98%</td>
</tr>
<tr>
<td>Clinical Practice (61/1165)</td>
<td>74.3 hrs</td>
<td>11.8%/0.96</td>
<td>97%</td>
</tr>
<tr>
<td>Historical Performance (238/4015)</td>
<td>64.0 hrs</td>
<td>18.4%/0.92</td>
<td>96%</td>
</tr>
</tbody>
</table>

* Number of sensors/ Number of sensor-meter pairs
† Clarke Error Grid Analysis, Zones A & B

Diabetes 2003 52(Suppl. 1):384


Glucose Sensing Helps Achieve Glycemic Control

Mean A1c levels before and after CGMS monitoring and insulin regimen readjustment in adults:

- **Ludvigsson**
  - M. Dur.: 24 weeks
  - n=27, Type 1 diabetes
  - Before CGMS: 7.7%
  - After CGMS: 7.3%

- **Bode BW**
  - M. Dur.: 5 weeks
  - n=9, Type 1 diabetes
  - Before CGMS: 9.9%
  - After CGMS: 8.8%

- **Schaepelynck-Belicar**
  - M. Dur.: 2 months
  - n=12 adolescents, Type 1 diabetes
  - Before CGMS: 10.3%
  - After CGMS: 8.8%

Schaepelynck-Belicar P, et al; Diabetes & Metabolism 2003;29(6)
Ludvigsson J, et al; Pediatrics 2003;111:933-938
Glucose Sensing Helps Reduce Hypoglycemic Risk

Hypoglycemia Events:
Before and after CGMS® System Gold™ use

Therapy adjustments based on CGMS® System Gold™

- 27 children (6-13 yrs), Mean A1C 7.6%, MDI therapy
- Hypoglycemia defined at 55 mg/dl (3 mmol/l)
- Significant reduction in fructosamine levels (p<0.05)

Guardian Real Time Patient Use CGM: Real-time and Historical Analysis

- Displays glucose values every 5 minutes
- Alerts patients to take action when glucose levels become too high or too low
- Patients print trend reports for discussion with HCPs
- System is calibrated twice a day (every 12 hours)
- Adjunct to fingerstick measurements

Real-Time Trend
- Numeric value
- Arrows indicate speed and direction of glucose
- Trend Graph
A randomized, controlled, multi-center (8 International sites), clinical study to assess whether Type 1 diabetic patients in non-optimal glycemic control can improve using the real-time values of the Guardian® RT versus conventional Self-Monitoring Blood Glucose.

- 162 total patients, 3 months. Both MDI and pumpers, adults and peds.
- Three arm trial comparing 1) Guardian RT worn continuously, to 2) bi-weekly group (wearing sensors every 2 weeks) to 3) Control Group (finger-sticks only)
- Statistically significant reduction in A1c and hypoglycemia with sensor use
- Results met expectations
Results: A1c Total Population (N=162)

Δ of reduction
G1 vs Control:

Continuous G1
Bi-weekly G2
Control

Baseline 1 month 3 months

A1c (%) +/- SE

0.7% P=0.003
0.4% P=0.008

ADA presentation by Jon Bolunder, June 2005
CSII & CGM Integration: “MiniMed Paradigm REAL-Time System”

- World’s first integrated insulin pump system with REAL-Time continuous glucose readings
  - Utilizes a glucose sensor and transmitter
  - Displays glucose values, directional arrows and trend graphs
  - Calculates insulin dosages and keep track of insulin used by the body
  - Alarms when glucose becomes too high or too low
  - Receives glucose values from a dedicated glucose meter via radio frequency (Canada and Germany)

- Adjunct to fingerstick measurements*

* System is calibrated twice a day (every 12 hours)
Paradigm is a registered trademark of Medtronic MiniMed, Inc.
Clinical Feasibility Study #1

To assess the feasibility of the Sensor-Augmented System to provide real-time glucose values

Dr. Fran Kaufman, Children’s Hospital Los Angeles, CA
- 10 subjects <18 yrs old with Type 1 diabetes
- Used non-pumping version of Sensor-augmented pump
- 7 consecutive sensors worn over 30 days at home
- Sensor accuracy measured by comparing to Paradigm Link Blood Glucose Meter
- Safety as measured by the frequency of adverse effects and device complications

Clinical Feasibility Study – Results

• Patient Demographics
  – 10 Children ages 10-18, median age 14.5
  – Mean Diabetes duration: 9.1 +/- 3.3 years
  – 202 Days of User Device Experience

• Sensor Performance vs. Meter
  – Number of Evaluation Points: 1141
  – Mean (Median) Absolute Difference: 19.6% (14.3%)
  – Correlation: 0.86

• Safety
  – One adverse event related to irritation at the sensor insertion site

• Outcomes
  – A1C reduced from 8.1 to 7.8% after only 30 days
  – Average glucose decreased from 167 to 156 mg/dl
"Unstructured" long-term assessment of patients' ability to use the Sensor-Augmented Pump System to provide real-time glucose values.

In-House Clinical Protocol, Northridge, CA

- Up to 10 adults with Type 1 diabetes
- Used non-pumping version of sensor-augmented pump
- Sensors worn at patient’s discretion
- Outcomes measured by quarterly HbA1c
- Safety as measured by the frequency of adverse effects and device complications
HbA1c with the Sensor-Augmented Pump

HbA1c Changes after **600 Days** (+/- 35d) with Sensor-Augmented Pump

<table>
<thead>
<tr>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>9</th>
<th>10</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c Start</td>
<td>9.8</td>
<td>7.3</td>
<td>6.6</td>
<td>7.3</td>
<td>7.8</td>
<td>7.3</td>
<td>7.8</td>
<td>7.7</td>
<td>7.7</td>
</tr>
<tr>
<td>HbA1c End</td>
<td>6.6</td>
<td>6.1</td>
<td>5.0</td>
<td>5.8</td>
<td>6.5</td>
<td>5.7</td>
<td>5.8</td>
<td>6.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Δ HbA1c</td>
<td>-3.2</td>
<td>-1.2</td>
<td>-1.6</td>
<td>-1.5</td>
<td>-1.3</td>
<td>-1.6</td>
<td>-2.0</td>
<td>-1.1</td>
<td>-1.7</td>
</tr>
</tbody>
</table>

Although promising, the results of this study were obtained from a small number of subjects in an uncontrolled study. STAR trials represent our formal RCT’s to evaluate the utility of the Sensor Augmented Pump to improve patient outcomes.
Value of Paradigm REAL-Time System

Value of Paradigm REAL-Time System

Pre-meal BG readings used to aid in meal-time insulin bolus calculation

Low alert, decrease basal rate

High alert, corr. bolus

Glucose - mg/dL

Time Of Day

3:00 AM 6:00 AM 9:00 AM 12:00 PM 3:00 PM 6:00 PM 9:00 PM

0 100 200 300 400

140

80
CareLink Remote Monitoring

**CareLink Personal**
- On-line tool for Paradigm pump users
- Over 30,000 users registered

**CareLink Pro**
- HCP desktop software
- Optional Internet-enabled functionality:
  - Remote access to patient data on CareLink Personal
  - Remote version updates
- Reports optimized for clinical usefulness
Weekly Data

First Week

Second Week

Third Week
An artificial pancreas – or “closed-loop system” – is expected to continually monitor the body’s glucose levels and respond with proper doses of insulin to normalize glucose control.

Medtronic Diabetes leads the industry in total diabetes management: insulin delivery, continuous glucose monitoring, algorithm development and therapy management software.

The company is developing two approaches to an artificial pancreas using external and implantable devices.

* Investigational device. Not yet approved by the FDA or European Health Authorities.