Evaluation of the Impact of CGM Analytical Performance Differences on Relevant Clinical Outcomes by Simulation Testing

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Background
This in-silico study evaluates the impact of the analytical performance of real-time continuous glucose monitoring (CGM) systems on clinical outcomes under various conditions similar to daily life.

Study Purpose & Methods

Background and Purpose:
The analytical performance of continuous glucose monitoring (CGM) sensors is crucial for their usefulness and acceptance by people with diabetes. A Roche prototype CGM sensor demonstrated improved accuracy, particularly in the hypoglycemic range and during periods of rapid glucose fluctuation in a small clinical study. This in-silico study examined the impact of superior CGM performance on clinical outcomes under a variety of simulated conditions similar to those experienced in daily life with diabetes.

Methods:
Using the UVa/Padova T1DM Metabolic Simulator (1) T1DMS) we compared the prototype sensor with two competitor sensors in an in-silico environment with 100 virtual adult subjects with Type 1 Diabetes Mellitus (T1DM). The T1DMS is a computer model that simulates the glucose-insulin dynamics of human metabolism characteristic of T1DM, with a virtual population that is influenced by carbohydrate and insulin dosing at the individual level. The Roche prototype sensor and competitor sensor were modeled (CGM1 and CGM2) using CGM blood glucose (BG) measurement traces collected during clinical studies where frequent (every 15 minute) finger-stick measures and reference measures were also collected for correlation. The Roche CGM and competitor sensor models were then used to monitor the virtual subjects’ BG levels during seven clinical scenario protocols which simulated real-life situations for people with diabetes. The scenarios were designed to induce glucose levels that would be seen under best control as well as situations that are known to occur with patient self-management.

Statistical Analysis:
The accuracy and precision of the sensors were examined and compared during each of these simulated conditions using the Mean Absolute Relative Difference (MARD), Precision Absolute Relative Difference (PARD). Additionally, the impact of the rate of correctly detected, missed, or falsely detected hypoglycemic events as well as a delay in detection of hypoglycemia onset and recovery detection were analyzed and compared among the sensors. Data from 100 adult in-silico subjects were collected over 50 repeated simulations to obtain robust datasets for analyses of infrequent events.

Clinical Protocol Scenarios
The clinical protocols were designed to reflect usual daily life experiences of people with T1DM. The study simulations began at 6 a.m. and ended at 8 p.m. for all scenarios except the nocturnal hypoglycemia, (6 p.m. to 8 a.m.). Breakfast meals consisted of 60g carbohydrates (CHO), lunch was 60 or 90g CHO, and dinner was 90g CHO. Target BG range was defined as 70–180 mg/dL (3.8–10.0 mmol/L). Hyperglycemia is defined as BG > 200 mg/dL (11.0 mmol/L) and > 240 mg/dL (13.4 mmol/L). Hypoglycemia is defined as BG < 70 mg/dL (3.8 mmol/L) and BG < 55 mg/dL (3.0 mmol/L). Meals and insulin dosing combinations were chosen to produce usual and extreme plasma glucose levels for examination of the CGM performance in situations known to occur in diabetes disease management. Some of these extreme situations which would be unethical and dangerous in human studies can be safely simulated and studied in a virtual environment.

Protocol 1. Optimal glucose control
Protocol 2. Hyperglycemia
Protocol 3. Hypoglycemia
Protocol 4. Exercise hypoglycemia (not shown)
Protocol 5. Insulin stacking (not shown)
Protocol 6. Nocturnal hypoglycemia (not shown)
Protocol 7. Rapid glycemic excursions

During Protocols 3 and 5, Rescue CHO (16g glucose tablets) were given when BG levels measured ≤ 50 mg/dL (2.8 mmol/L) to simulate a “person-in-the-loop.” This was repeated until the subject BG recovered to > 70 mg/dL.

Table 1: MARD, PARD, Misses and Delays

<table>
<thead>
<tr>
<th>Sensor</th>
<th>MARD (%)</th>
<th>PARD %</th>
<th>Misses</th>
<th>Delays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche</td>
<td>4.8</td>
<td>5.6</td>
<td>0.1</td>
<td>0.15</td>
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<tr>
<td>CGM 1</td>
<td>5.9</td>
<td>6.4</td>
<td>0.2</td>
<td>0.17</td>
</tr>
<tr>
<td>CGM 2</td>
<td>6.6</td>
<td>7.1</td>
<td>0.3</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Figure 1: Comparison of probability of missing hypoglycemia onset

The Roche sensor had the lowest probability of missing a hypoglycemic event of all the sensors. [Examples of simulated individuals shown]

Figure 2: Comparative simulation of Roche CGM sensor and two competitor sensors shows superior real-time accuracy in all glycemic zones

Figure 3: The Roche CGM sensor accurately detected nocturnal hypoglycemia when it occurred

Figure 4: The Roche CGM sensor tracked rapid glycemic excursions into hypoglycemia most accurately

Conclusion
- In this simulation study, the Roche prototype CGM sensor showed superior analytical performance across all glycemic ranges, and particularly during all levels of hypoglycemia.
- Under rigorous in-silico examination of hypoglycemia-detection characteristics, the Roche prototype sensor showed superior accuracy, and was the first to detect the onset of hypoglycemia with the lowest probability of missing an event or showing hypoglycemia that did not exist.
- The Roche prototype sensor demonstrated minimal delay (lag) during rapid glycemic excursions, and was most accurate of the sensors tested.