Glycemic variability and iatrogenic hypoglycemia: how to resolve

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Abstract:

The attempt to lower plasma glucose to near normal levels without consideration of the within-day glycemic variability is a potential risk factor for iatrogenic hypoglycemia in persons with insulin-treated diabetes. It is therefore crucial to address this issue in parallel to the development of newer technologies of insulin delivery. Recent analysis has revealed that the percentage of time spent with plasma glucose levels below 70 mg/dL (TBR <70mg/dL) and the coefficient of variation for glucose (%CV glucose) in individuals treated with SAP (Sensor Augmented Pump) or AID (Automated Insulin Delivery) are positively and significantly correlated. A mean reduction of 2.0 % in the %CV glucose is reflected in a mean decrease in TBR <70 mg/dL of approximately 0.50 %. In addition, the risk for hypoglycemia becomes negligible or eventually eliminated according to whether the %CV glucose is brought down below 27 or 19 %, respectively, which correspond to the upper limit or the averaged value of %CV glucose, respectively, in non-diabetic people. These goals remain currently out of reach in type 1 diabetes even with the most sophisticated systems of insulin delivery. Consequently, further improvements are needed to achieve the ultimate objective of normal glucose homeostasis combining both normal mean glucose and glycemic variability as observed in healthy non-diabetic subjects.

Key words: Iatrogenic hypoglycemia; glycemic variability; new insulin delivery systems

Introduction

The pathophysiological common denominator of iatrogenic hypoglycemia in individuals living with type 1 diabetes is always a consequence of an imbalance between excess exogenous insulin and compromised endogenous hormonal responses of the glucose counter-regulatory system, as frequently encountered in diabetes [1]. This imbalance is usually associated with excessive daily glucose fluctuations from peaks to nadirs, which reflect the within-day glycemic variability and are potent predictive risk factors for hypoglycemic episodes with a bidirectional relationship between the two disorders [2-12]. In addition, this risk of hypoglycemia can be amplified when mean glucose concentrations are brought into normal or near normal ranges [13]. This predicted view is displayed in figure 1 by considering the 4 following theoretical scenarios in individuals with type 1 diabetes on insulin therapy.

The theory: Where does it lead us?

The first scenario: when there is unsatisfactory glycemic control in terms of total glucose exposure (mean glucose concentration 190 mg/dL, 10.5 mmol/L), i.e., a level that approximates to an HbA1c of 7.8% [14-16], with high glycemic variability reflecting a state of labile diabetes with a %CV

glucose > 36% [17,18]. The %CV glucose (coefficient of variation for glucose) represents the daily dispersion of plasma glucose values relative to the mean glucose concentration and is calculated as follows: [(Standard Deviation around the mean glucose value)/(Mean glucose)] x 100 [19-21]. In this situation, the risk for observing a glucose value below 70 mg/dL , and thus experiencing a hypoglycemic episode [22] is markedly elevated. This risk can be quantified from the assessment of the percentage of time spent with glucose level below 70 mg/dL (3.9 mmol/L), i.e. a metric described by the acronym TBR < 70 mg/dL. The latter is considered to be abnormally high and out of range of the usual international recommendations when its value is above 4% [23].

The second scenario is when the total glucose exposure is identical to the above, but with medium glycemic variability (< 36%) [17,18]. For this situation the risk for hypoglycemia is lower than in the preceding situation with a TBR < 70mg/dL within the recommended range, i.e. below 4% [23].

The third scenario corresponds to a situation where the daily mean glucose concentration is near normal (110 mg/dL, 6.1 mmol/L) but with a medium level of glycemic variability (<36%) [17,18]. Therefore, as the daily mean glucose concentration is 110 mg/dL, the probability of experiencing a hypoglycemic event remains high with a TBR < 70 mg/dL above 4% [23].

The fourth scenario corresponds to near normal chronic glucose exposure and a glucose variability within a low to medium range (< 36%) [17,18]. In this situation with a TBR <70mg/dL below 4% [20], the risk of incurring hypoglycemia is markedly diminished. These targets are recommended by international organizations such as the ADA (American Diabetes Association) to prevent or at least to minimize the risk for both acute and chronic diabetes complications [22,23].

The four aforementioned theoretical situations beg the questions as to whether they are validated in clinical practice and consequently what recommendations in terms of glucose variability are necessary to minimize or eradicate the risk for hypoglycemic events when near normal 24-h mean plasma glucose concentrations is achieved with the more advanced systems of insulin delivery [24-30].

The contribution of scientific evidence to clinical practice

Consideration of the following observations, based on scientific research and clinical trials, may provide further recommendations to prevent hypoglycemia.

1) First observation: Reduction in mean blood glucose level (HbA1c) increases the risk for hypoglycemia

1.a Studies in type 1 diabetes

In a large cohort of patients with type 1 diabetes followed for several years, the investigators of the Diabetes Control and Complications Trial (DCCT) have demonstrated that the rate of severe hypoglycemia was threefold greater in the group assigned to intensive insulin therapy (mean HbA1c around 7.0%) compared to the group exposed to a conventional insulin regimen (mean HbA1c around 9.0%) [31]. In addition, the risk for severe hypoglycemia increased continuously with lower monthly HbA1c values. These results were further confirmed when the relationships between hypoglycemic and glycemic control were revisited [13] using the data from the Juvenile

Diabetes Research Foundation Continuous Glucose Monitoring Study Group (JFR CGM study) [32] in which the efficacy and safety of insulin treatments were assessed in populations of adults and children with type 1 who were randomly assigned to either continuous or standard glucose monitoring. The retrospective analysis of these data has shown that lower HbA1C values were associated with increased hypoglycemia risk at least in the control group even though this relationship was markedly flattened in CGM users [13], thus favoring the wear of GGM devices in type 1 diabetes [33]. In addition, the analysis of the longer-term DCCT/EDIC (Diabetes Control Complications Trial/Epidemiology of Diabetes Interventions and Complications) trial has shown that the rates of severe hypoglycemia remained high in those individuals who exhibited the lower HbA1c levels [34,35] even though the inverse relationship between the rates of hypoglycemic events and HbA1c levels had a tendency lessen over time.

1.b Studies in type 2 diabetes

In a large population of type 2 diabetes, the investigators of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) have established that the use of intensive glucose lowering therapies to target normal HbA1c levels were associated to a higher frequency of level 3 hypoglycemia requiring clinical assistance [36]. In addition, by using CGM systems in a blinded fashion with retrospective glucose readings, we have been able to demonstrate that the risk for hypoglycemia became more frequent as soon as the daily mean glucose concentrations were lowered below 7.8 mmol/L (140 mg/dL) (figure 2) [37].

There is, therefore, a broad spectrum of evidence for stating that all reductions of ambient hyperglycemia, especially when the target is near normal glucose levels, are strongly associated with an increased frequency of hypoglycemic events.

2) Second observation: Reduction in mean glucose concentrations associated with increased glycemic variability can lead to an increased risk for hypoglycemia

Reverting to the results of our aforementioned study using blinded CGM systems in type 2 diabetes receiving insulin or non-insulin glucose lowering agents, we observed that the risk for experiencing hypoglycemic events depends not only on reductions of the ambient hyperglycemia and achievements of tight glycemic goals, but also on excess within-day glycemic fluctuations [37]. The relationship between the number of hypoglycemic events (symptomatic and silent with interstitial glucose value < 3.1 mmol/L (56 mg/dL) plotted as dependent variable (on the vertical axis) and the two potential explanatory variables, i.e. the daily mean glucose value (x-axis) and the glucose variability (y-axis) is represented in figure 2. We found that the risk for hypoglycemia tended to be eradicated, at least in type 2 diabetes, when the %CV glucose and mean glucose concentrations were both below 28% and above 7.8 mmol/L (140 mg/dL), simultaneously and respectively. However, this cross tabulation also indicates that the %CV glucose < 28 % is not sufficient to eradicate the risk of hypoglycemia. For instance, some patients who were in the lower tertile of mean glucose concentrations (<7.8 mmol/L) retained a significant risk for hypoglycemia even when their %CV glucose was <28 %. From these observations it might be interpreted that the glycemic variability and mean glucose concentrations have opposite impacts on the risk for hypoglycemia. However this implication may not apply currently due to the availability of glucose like peptide -1 (GLP-1) receptor agonists and sodium-glucose co-transporter (SGLT2i) inhibitors for treating type 2 diabetes [38,39]. It is now possible with the help of real-time unblinded Continuous Glucose Monitoring (rt-CGM) devices to simultaneously achieve reductions in both

ambient hyperglycemia and glycemic variability without increasing the risk for hypoglycemia. Additionally, most observations that are reported in type 2 diabetes cannot be extrapolated to type 1 diabetes, because the averaged %CV glucose of approximately 27% observed in type 2 diabetes [17] even when such patients are treated with automated insulin delivery [40] is markedly lower when compared with that commonly observed in studies conducted in type 1 diabetes (mean %CV glucose approximately ranging from 29 to 42%) [5,17,30,41-58].

3) Third observation: The glycemic variability exerts a strong impact upon the risk of hypoglycemia in people with type 1 diabetes treated with advanced systems of insulin delivery

3.a Defining a threshold of glycemic variability below which hypoglycemia can or could be eradicated

By combining the results from 38 randomized controlled trials (RCTs) in type 1 diabetes were treated with AID (Automated Insulin Delivery) and/or SAP (Sensor Augmented Pump) [59] we established that the TBR < 70 mg/dL was positively correlated with the glycemic variability (%CV glucose) (figure 3). The regression equation was computed as follows: TBR < 70 mg/dL (percentage points) = 0.26 x [%CV glucose] – 6.92 (R^2 = 0.334; P < 0.001). In order to weigh up the respective impact of the 38 different studies on the regression equation, weight adjustments were made using the square root of each study's sample size. The intercept of the regression line with the abscissa axis for a TBR < 70 mg/dL = 0 (considered the threshold of %CV glucose below which either the risk for hypoglycemia < 70 mg/dL can be eradicated or reduced to the minimal value) occurred when the %CV glucose was equal to 26.5% (figure 3). However, there remains the question as to whether this threshold determined as ranging between 26 and 27%, when AID and SAP groups were pooled, is applicable regardless of the modality of insulin delivery. To address this issue, we have analyzed separately the data of the SAP and AID groups, to calculate in each group the linear dependences of the TBR<70mg/dL on the %CV glucose and to estimate the respective intercept values with the abscissa axis (%CV glucose) when the TBR<70 mg/dL is equal to zero. These computations have demonstrated that the regression equations had somewhat different formulations according to the use of SAP (i.e. when adjustment of insulin delivery remained under human intervention) or AID (i.e. in users of controller algorithms that can be either intermittent at mealtimes and/or during physical activity with hybrid closed-loop systems or continuous with full closed -loop systems). The relationships for the TBR <70 mg/dL as a function of the %CV glucose were described by the following equations: TBR < 70 mg/dL = 0.46 x [%CV glucose] – 13.8 (R^2 = 0.405; p = 0.008) in the SAP group versus TBR < 70 mg/dL = 0.12 x [%CV glucose] – 2.38 (R^2 = 0.304, p = 0.008) in the AID group (figure 3). Consequently, the values of %CV glucose for a TBR < 70 mg/dL = 0, at intercepts of regression lines with the abscissa axis were found to differ between the SAP (30.1%) and AID (18.9 %) groups. It should be noted that the management using AID systems resulted in better control of the daily overall glucose exposure (averaged daily mean glucose concentrations = 8.69 mmol/L, 156 mg/dL; averaged HbA1c = 7.37%) than those using SAP (averaged mean glucose concentrations = 9.26 mmol/L, 167 mg/dL; averaged HbA1c = 7.13%). Therefore, it can be stated that the eradication of hypoglycemia requires a more pronounced reduction in the within-day glycemic variability when the control of the glucose homeostasis is reinforced to target a near normal glycemic status in terms of daily mean glucose levels.

The current evidence therefore suggests that any attempt to achieve near normal glucose homeostasis will require a near normal glycemic variability (%CV glucose) of 19%, similar to that observed in healthy non-diabetic people (%CV glucose = 17%; IC 99.9% = 7 to 27%]) [60].

3b. Determining the relationship between the reduction in the risk for hypoglycemia and the decrements in glycemic variability

The response is provided by the formula of the regression equation between the TBR < 70 mg/dL and the %CV glucose in the pooled SAP and AID groups: TBR < 70 mg/dL (expressed as percentage points) = 0.26 x [%CV glucose] – 6.92 (figure 3) [59]. This equation indicates that for a reduction of 2% in the %CV glucose the expected diminution in the TBR<70 mg/dL (ΔTBR) should be approximately – 0.50%. Such a reduction is not negligible when a 2% reduction in the %CV glucose can be achieved when switching from SAP to AID treatments [59].

3c. Determining the contribution of the glycemic variability as predictor of hypoglycemia

As the coefficient of determination for the regression equation between the TBR < 70 mg/dL and the %CV glucose is equal to 0.334, (figure 3), one can estimate that approximately one third of the total variation in the TBR < 70 mg/dL is attributable to the %CV glucose and that the residual two thirds is due to other factors. Even though this may differ from one study to another, the significant role played by other contributory factors to the risk of hypoglycemia is supported by the fact that AID systems can improve the TBR < 70 mg/dL when compared with SAP, independently of any change in the %CV glucose. When the %CV glucose is set at 36%, the recommended threshold in type 1 diabetes for separating stable and labile glucose homeostasis [17,18], the mean difference in TBR < 70 mg/dL between SAP and AID groups was equal to 0.86% (percentage points) in favor of AID systems, independently of any change/improvement in glycemic variability (figure 3).

At this time, it is therefore highly likely that beyond the improvement in glycemic variability, the list of other factors involved in the reduction of hypoglycemia in users of the newer technologies of insulin delivery encompasses a better education and empowerment of patients who, more specifically, take benefit from the wear of a CGM with real-time readings [2-5]. For instance, this tool allows the detection of rapid falls in blood glucose and permits to prevent hypoglycemia before it occurs or, at least, reduces the time spent in hypoglycemia if this event has still happened. However it must be noted that despite the use of advanced diabetes technologies many patients with type 1 diabetes continue to experience severe hypoglycemic episodes [41,61]. One of these studies has reported that the mean %CV glucose decreased only by 2.9% when open-loop therapy (mean %CV glucose = 38.3%) was switched to closed- loop insulin delivery (mean %CV glucose = 35.4%) [41]. These findings indicate that such reductions remain largely insufficient to achieve a near normal glycemic variability, which is as mentioned above the prerequisite to eliminate the risk for hypoglycemic events. Even with the concomitant implementation of current advanced technologies and appropriate educational measures it appears that this goal cannot be met. Therefore, there is a need for the development of improved technologies and algorithms to better accommodate the rapid changes in blood glucose. These novel technologies should likely include bihormonal AID systems [62] and/or beta-cell replacement [63,64].

Conclusions

Several conclusions can be drawn at both individual and population levels, the latter concerning trials mainly designed to test the efficacy, safety and delivery of future glucose lowering preparations.

At an individual level:

• Excessive glycemic variability accounts for 30% of the factors contributing to iatrogenic hypoglycemia in type 1 diabetes.

• A 2% - reduction in the coefficient of variation for glucose (%CV glucose) diminishes by approximately 0.50% the time spent with glucose below 70 mg/dL.

• The figure 4 attempts to illustrate the risk for hypoglycemia as a function of the degree of glycemic variability. This risk is elevated when the %CV glucose is above 36%, the threshold that separates labile from stable glucose homeostasis. This risk is still present when the % CV glucose ranges between 27 and 36%, with a progressive lessening when the %CV glucose approaches 27%. However, it should be noted that this value is somewhat difficult to achieve, even with the implementation of a Neuronal-Net Artificial Pancreas (NAP) after encoding AID algorithms into a neuronal network [65]. The risk for hypoglycemia really becomes small or very small below 27%. Presently, the full eradication of hypoglycemia is a goal that remains unattainable because it would mean that we have to bring down the glycemic variability the %CV glucose below 19%, a level which is currently observed as within the normal range in non-diabetic healthy people [60].

At population levels:

In randomized controlled trials, glycemic variability should be included in the study design when assessing the risk for hypoglycemia. Its absence is regrettable in recent phase 3 randomized trials investigating the efficacy and safety of once-weekly insulins (icodec or efsitora) in type 1 diabetes (ONWARDS 6 [66] and QWINT-5 trials [67]). In these two interventional trials, the incidence rates of hypoglycemia were higher with the once-weekly formulations versus the once-daily insulin degludec. Therefore, it would have been important to see whether such significant differences could be associated or not with increased glycemic variability in the participants assigned to once-weekly insulins.

Declaration of competing interest

L Monnier, C Colette, S Aouinti, N Molinari and D Owens declare that they have no conflict of interest relevant to this review article; E Renard has received consulting and speaker fees from A.Menarini Diagnostics, Abbott, Air Liquide SI, Astra Zeneca, Beckton-Dickinson, Boehringer-Ingelheim, Cellnovo, Dexcom Inc , Insulet Inc., Johnson & Johnson, Medtronic, Medirio, Novo-Nordisk, Roche, Sanofi-Aventis and research support from Abbott, Dexcom Inc., Insulet Inc., Roche,Tandem Diabetes Care; P-Y Benhamou has received speaker fees from Abbott, Eli Lilly, Novo-Nordisk , served on advisory board panels for Abbott, Insulet, Eli Lilly, Novo-Nordisk and is chief medical officer for Diabeloop.

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All authors were responsible for drafting the article, and for critical review and intellectual content. All authors were equally involved and provided final approval for the version to be published.

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Legends of figures

Figure 1: Progression of the TBR < 70 mg/dL (Time Below Range) plotted as a function of the glycemic variability and mean plasma glucose concentration in 4 theoretical situations that are normally encountered in clinical practice. Two situations (a and c) are associated with a TBR > 4% while the two others (b and d) are associated with a TBR < 4%, the latter corresponding to the recommendation of international organizations.

Figure 2: Cross tabulation analysis of hypoglycemic events (dependent variable) as a function of tertiles of mean glucose concentrations and tertiles of SD for glucose (explanatory variables). [from reference 37]. The %CV glucose of 28% was obtained from the following ratio: [2.2 mmol/L (threshold of SD for glucose below which the risk for hypoglycemia is equal to zero)] divided by [7.8 mmol/L (threshold of mean glucose concentration above which the risk for hypoglycemia is equal to zero)].

Figure 3: Relationships between the time spent below 70 mg/dL (TBR < 70 mg/dL, Y axis) and the coefficient of variation for glucose (%CV glucose, X axis). The regression equations were calculated in the population considered as a whole (AID pooled with SAP, 38 studies) or separately: AID alone (22 studies) and SAP alone (16 studies). The intensity of relationships between the two variables is quantified using the coefficient of determination (R^2). The intercepts of the regression lines with the abscissas for a TBR < 70 mg/dL equal to zero (eradication of the risk for hypoglycemia) are observed for the following values of %CV glucose: 26.5% (pooled studies SAP + AID); 30.1% (SAP alone) and 18.9 (AID alone) [from reference 59].

Figure 4: Ordinal increasing scale for the risk of hypoglycemia

Figure 1

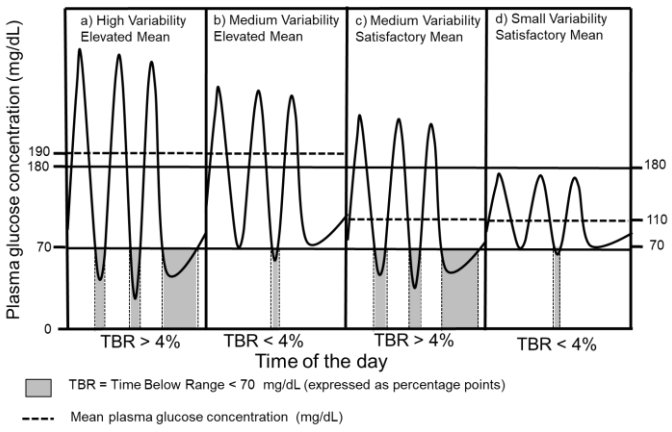


Figure 2

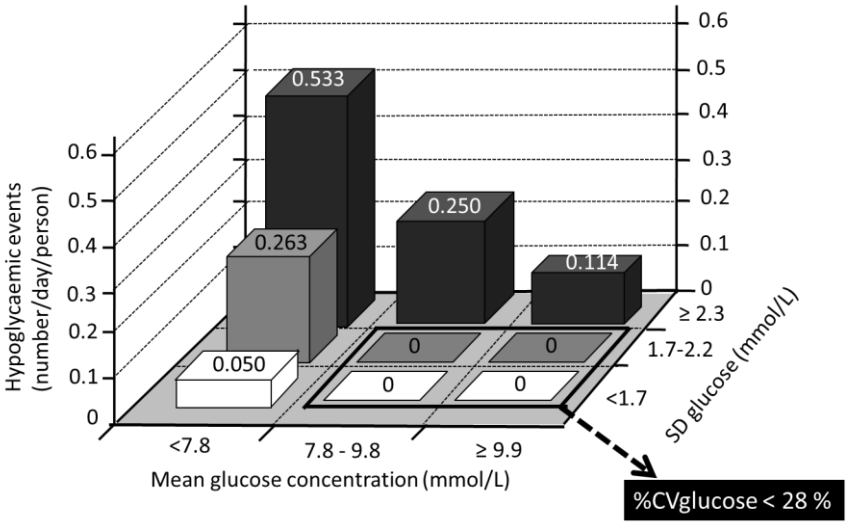


Figure 3

SAP + AID : TBR = 0.26 x [%CV glucose] - 6.92 (R^2 = 0.334, *P < 0.001*)
SAP alone : TBR = 0.46 x [%CV glucose] - 13.8 (R^2 = 0.405, *P = 0.008*)
AID alone :TBR = 0.12 x [%CV glucose] - 2.38 (R^2 = 0.304, *P = 0.008*)

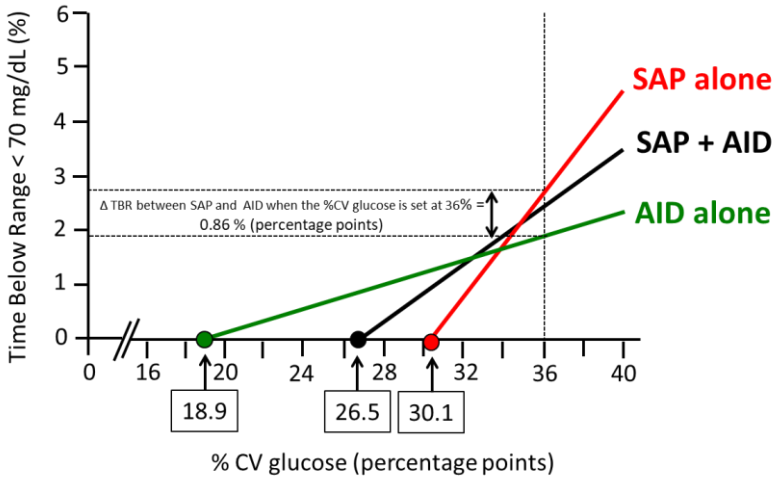
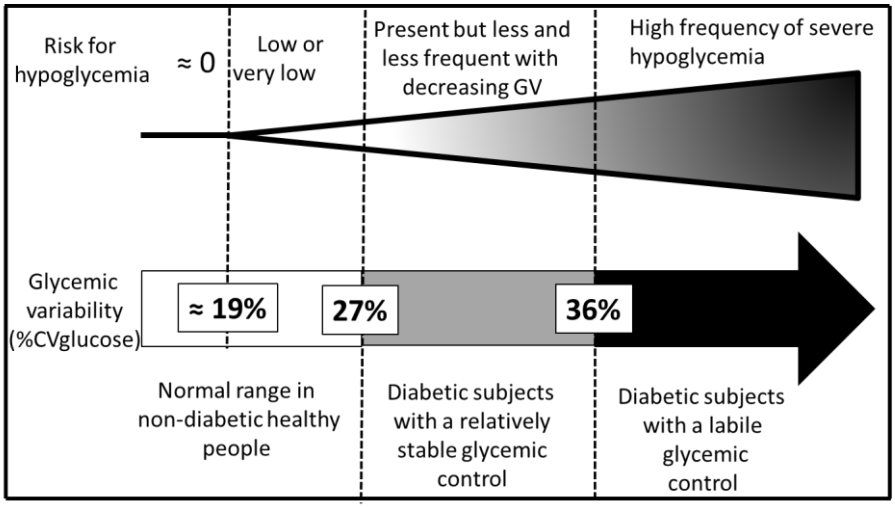


Figure 4



Graphical Abstract