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# How well do glucose variability measures predict patient glycaemic outcomes during treatment intensification in type 2 diabetes?

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ABSTRACT

*Aim:* Despite links to clinical outcomes in patients with type 2 diabetes mellitus (T2DM), the clinical utility of glycaemic variability (GV) measures is unknown. We evaluated the correlation between baseline GV, and glycated haemoglobin (HbA1c) attainment and hypoglycaemic events during treatment intensification in a large group of patients.

*Methods:* Patient-level data from six 24-week clinical trials of T2DM patients undergoing treatment intensification with basal insulin or comparators (N = 1699) were pooled. Baseline GV measures included standard deviation (SD), mean amplitude of glycaemic excursions (MAGE), mean absolute glucose (MAG), coefficient of variation (CV), high blood glucose index (HBGI), and low blood glucose index (LBGI) and were correlated with HbA1c change and hypoglycaemic events.

*Results:* All mean GV measures, excluding CV which worsened, improved significantly from baseline to Week 24, with the largest proportional reduction obtained for HBGI (−65.5%). When assessed as mean individual percentage changes, only HBGI improved significantly. Baseline GV correlated positively with Week 24 HbA1c for SD, MAGE, and HBGI. Baseline HBGI and CV correlated negatively and positively, respectively, with Week 24 HbA1c change. Correlations also existed between most baseline GV measures and age, body mass index, Week 24 fasting plasma glucose, Week 24 postprandial plasma glucose, and hypoglycaemic events; statistical significance depended on the specific measure.

*Conclusions:* Pre-treatment GV is associated with glycaemic outcomes in T2DM patients undergoing treatment intensification over 24 weeks. HBGI might be the most robust predictor, warranting validation in dedicated prospective studies or randomized trials to assess the predictive value of measuring GV.



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## 1. Introduction

A central treatment aim in patients with type 2 diabetes mellitus (T2DM) is to lower blood glucose (BG) levels while avoiding hypoglycaemia [1]. Glycaemic control in T2DM patients is usually assessed with glycated haemoglobin (HbA1c) levels, which provide an average of basal and postprandial hyperglycaemia over the 3 months prior to the measurement [2,3]. It is well recognized, however, that significant excursions in BG – both upward and downward – might not be adequately reflected in HbA1c [4]. T2DM patients with similar HbA1c values, for example, can have markedly different daily glucose profiles, with variations in both the frequency and duration of glucose excursions [5,6]. The clinical utility of measuring glucose variability (GV) in clinical practice is still hotly debated [7,8], owing to uncertainties about its overall clinical impact and also the lack of any randomized controlled trials demonstrating a clinical benefit from therapeutic strategies that specifically target GV [6]. It also remains unclear which method for measuring GV is most robust for predicting outcomes. The most widely used metrics to quantify GV include standard deviation (SD) and mean amplitude of glycaemic excursions (MAGE), but these measures might fail to capture extremes of the glycaemic spectrum (i.e. hyper- and hypoglycaemia) [6,9]. Another method for quantifying GV is the change in mean absolute glucose (MAG). The MAG takes into account glycaemic swings to a larger extent and, in the intensive care setting, has shown a stronger association with mortality than SD [10]. The coefficient of variation (CV) takes into account mean change in blood glucose and has been shown to correlate well with rate of hypoglycaemia [11]. However, reductions in variation may be masked by larger reductions in mean HbA1c. The high blood glucose index (HBGI) is a measure of the frequency and extent of hyperglycaemic excursions [12], which can be viewed as a 'one-sided' measure of GV, specifically designed to be sensitive to the hyperglycaemic range and to ignore any BG fluctuations in the hypoglycaemic range. As such, the HBGI could help to predict treatment success associated with treatment intensification, especially when it is associated with a reduction in postprandial glucose excursions [12]. In contrast, the low blood glucose index (LBGI) is a measure of the frequency and extent of hypoglycaemic excursions [12], which can also be viewed as another 'one-sided' GV measure. It is specifically designed to be sensitive to the hypoglycaemic range and to ignore any BG fluctuations in the hyperglycaemic range. As such, the LBGI could be a potential candidate for predicting the risk of future hypoglycaemia with intensification of therapy.

Few studies have tested the utility of pre-treatment measures of GV to predict glycaemic responses to treatment intensification in a large cohort of T2DM patients. Such information might assist in treatment decisions and help to optimize the management of patients by predicting treatment success as measured by improvements in HbA1c and by assessing the risk of hypoglycaemia typically associated with intensifying therapy.

The primary objective of this analysis was to utilize pooled patient-level data from a large clinical trial database of T2DM patients undergoing treatment intensification with basal insulin (glargine) or comparators for 24 weeks to evaluate if baseline SD, MAGE, MAG, and HBGI correlate with HbA1c after 24 weeks, and with changes in HbA1c from baseline to Week 24. Secondary objectives were to assess correlations between the baseline GV measure and age, body mass index (BMI), fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) contribution at Week 24, and hypoglycaemic events during trial participation. We also sought to determine the correlation between LBGI and hypoglycaemic events.

## 2. Material and methods

### 2.1. Data source

In total, 63 clinical studies evaluating insulin glargine have been conducted by Sanofi, or its predecessor companies, between 1997 and 2007. For inclusion in this analysis, studies were required to be at least phase 3, prospective, randomized, controlled, and conducted in adult (age >18 years) patients with T2DM. Insulin glargine was the only insulin formulation and no other basal or prandial insulin was permitted as part of the insulin regimen (with the exception of short courses of regular insulin therapy for emergency medical purposes).

Seventeen studies met the selection criteria. Patients in these studies were treated with basal insulin glargine or a comparator. Of these, 3 studies provided predefined insulin titration algorithms as an option, but generally left the approach of insulin dose-adjustments at the discretion of the investigator and were, therefore, excluded from the analysis. An additional 2 studies did not meet accepted Good Clinical Practice standards. The remaining 12 studies utilized strict, predefined insulin titration algorithms with insulin dose adjustments varying from every 1 to 3 days to every week to achieve fasting glucose concentrations of ≤5.6 mmol/L. Of these, 7 studies collected multiple-point BG profile data, one of which was excluded because the classic 7-point BG profile (3× pre-meal, 3× post-meal, and 1× bedtime) was not performed.

The pooled analysis was conducted on the remaining 6 published studies in adults with T2DM who completed a 24-week treatment regimen with basal insulin glargine, a comparator (oral antidiabetes drugs, neutral protamine Hagedron [NPH] insulin, 70/30 NPH insulin, and insulin lispro), or insulin glargine plus glimepiride in the morning versus bedtime, and for whom complete 7-point BG profiles were available (Table 1) [13–18]. Data were available for 1699 patients from the 6 studies, who completed 24 weeks of treatment. Overall, 60.4% of patients (1026 of 1699) were treated with insulin glargine and 39.6% (673 of 1699) were treated with comparators. The analysis was performed on the pooled group of patients on insulin glargine and patients on comparators.

### 2.2. Outcomes

Baseline GV was assessed using patient 7-point BG profiles, calculated as follows:

$$\mathrm{SD} = \sqrt{\frac{\sum (x_i - \bar{x})^2}{k-1}},$$