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Reduced Glucose Variability With Glucose-Dependent Versus Glucose-Independent Therapies Despite Similar Glucose Control and Hypoglycemia Rates in a Randomized, Controlled Study of Older Patients With Type 2 Diabetes Mellitus

Richard E. Pratley, MD[1], Julio Rosenstock, MD[2], Simon R. Heller, MD[3], Alan Sinclair, MD[4], Robert J. Heine, MD[5], Jacek Kiljański, MD[6], Cynthia S. Brusko, PharmD[7], Ran Duan, PhD[7], and Andreas Festa, MD[8,9]

Abstract

Background: Few studies have evaluated continuous glucose monitoring (CGM) in older patients with type 2 diabetes mellitus (T2DM) not using injectable therapy. CGM is useful for investigating hypoglycemia and glycemic variability, which is associated with complications in T2DM.

Methods: A CGM substudy of **I**ndividualized treat**M**ent a**P**proach for old**ER** pat**I**ents in a randomized trial in type 2 diabetes **M**ellitus (IMPERIUM)) was conducted. Patients were vulnerable (moderately ill and/or frail) older (≥65 years) individuals with suboptimally controlled T2DM. Strategy A comprised glucose-dependent therapies (n = 26) with a nonsulfonylurea oral antihyperglycemic medication (OAM) and a glucagon-like peptide-1 receptor agonist as the first injectable. Strategy B comprised non-glucose-dependent therapies (n = 21) with sulfonylurea as the preferred OAM and insulin glargine as the first injectable. Primary endpoints were duration and percentage of time spent with blood glucose (BG) ≤70 mg/dL over 24 hours at week 24.

Results: Duration and percentage of time spent with hypoglycemia at ≤70 mg/dL were similar for Strategy A and Strategy B; glycemic control improved similarly in both arms (LSM change in HbA1c at week 24; A = −1.2%, B = −1.4%). Duration and percentage time spent with euglycemia and hyperglycemia were also similar in both arms. However, Strategy A was associated with lower within-day (21.1 ± 1.2 vs 25.1 ± 1.4, P = .046) and between-day (5.4 ± 1.0 vs 9.1 ± 1.3, P = .038) BG variability (coefficient of variance [LSM ± SE]) at week 24.

Conclusions: This CGM substudy in older patients with T2DM showed lower within- and between-day BG variability with glucose-dependent therapies but similar HbA1c reductions and hypoglycemia duration with glucose-independent strategies.

Keywords

continuous glucose monitoring, glycemic control, hypoglycemia, glycemic variability, older, type 2 diabetes

Lowering blood glucose (BG) to a safe but effective range is important in the treatment of type 2 diabetes mellitus (T2DM) but age and functional status should be taken into account when setting treatment goals.[1,2] National and international guidelines now recommend individualized glycemic targets aligned with functional status for people with T2DM.[3-5] The American Geriatric Society and the American Diabetes Association recommend an A1C target of 7.5% to 8.0% for most older adults, and of 8.0% to 9.0% in older adults with multiple comorbidities, poor health, and limited life expectancy.[6,7]

Older individuals are at higher risk of developing hypoglycemia which is often under-recognized in this population and may be associated with severe consequences such as

falls, cognitive impairment, and hospitalization.[8] Recurrent episodes of hypoglycemia can have significant physical and cognitive effects, and lead ultimately to frailty, disability and increased mortality.[9]

Several treatments that exert glucose-dependent action but do not increase hypoglycemia risk[4,10] (eg, dipeptidyl-peptidase-4 [DPP-4] inhibitors, thiazolidinediones, glucagon-like peptide-1 receptor agonists [GLP-1 RA] and sodium-glucose cotransporter-2 [SGLT-2] inhibitors) are available. However, older patients are commonly treated with medications that exert a non-glucose-dependent action, such as sulfonylureas and insulin, which may confer a higher risk of hypoglycaemia.[11-13]

Hypoglycemia can be difficult to diagnose in older adults and can easily be missed by intermittent BG monitoring.[14] Emerging data suggest that all hypoglycemic events may be clinically relevant. For example, both severe hypoglycemia and nocturnal hypoglycemia are associated with an increased risk of cardiac arrhythmias[15,16] Unrecognized hypoglycemic episodes and nocturnal hypoglycemia are of particular concern in older patients with T2DM.[14] Unfortunately, the magnitude of this potential problem is not well characterized in these individuals.

Continuous glucose monitoring (CGM) devices record interstitial glucose values frequently and are therefore particularly useful for identification of asymptomatic and nocturnal hypoglycemic episodes.[17] In addition, CGM is a useful tool for investigating glycemic variability (GV), which has been associated with the development of microvascular complications in T2DM.[18]

The **I**ndividualized treat**M**ent a**P**proach for old**ER** pat**I**ents in a randomized trial in type 2 diabetes **M**ellitus (IMPERIUM) study compared the efficacy and safety of 2 antihyperglycemic treatment strategies in vulnerable (moderately ill and/or frail) older (≥65 years) individuals with suboptimally controlled T2DM.[19] Strategy A used oral and injectable therapies that do not stimulate insulin secretion when BG reaches normal/low values (a glucose-dependent mode of action). GLP-1 RA was a preferred first-line injectable. Sulfonylureas and insulin were excluded. Strategy B used treatments that exert their glucose-lowering effect irrespective of prevailing glycemia; sulfonylureas were the preferred oral antihyperglycemic medication (OAM) and insulin the preferred first-line injectable therapy (non-glucose-dependent agents). The study results showed similar proportions of older, vulnerable patients with T2DM achieved/maintained glycemic treatment goals without clinically significant hypoglycemia with Strategy A or Strategy B. However, glucose-dependent therapies as expected, resulted in lower risk of total, documented symptomatic and asymptomatic hypoglycemia.

This CGM substudy of IMPERIUM was conducted to better characterize the duration and percentage of time spent in hypoglycemia for the 2 treatment strategies evaluated in the main study.

Methods

Study Design

A detailed description of the main study design and results has been reported.[19] In brief, this randomized, multinational, open-label, in-label, active-controlled, parallel group study involved moderately ill and/or frail older patients. This study compared the efficacy of 2 treatment strategies in achieving/maintaining glycemic control without "clinically significant hypoglycemia," defined as severe hypoglycemia or repeated hypoglycemia causing interruption of patients' activities or BG <54 mg/dL.

The primary objective of this CGM substudy was to compare the impact of the 2 treatment strategies (A and B) studied in the IMPERIUM trial on duration of time (in minutes) and percentage of time spent with a BG ≤70 mg/dL during the 24-hour period. The secondary objectives were to compare the impact of the 2 treatment strategies on the following outcome measures: (1) duration and percentage of time spent during a 24-hour period for hypoglycemia (BG ≤70 mg/dL or ≤54 mg/dL), euglycemia (BG ≥71 to ≤180 mg/dL) and hyperglycemia (BG >180 mg/dL); (2) duration and percentage of time spent with hypoglycemia (BG ≤70 mg/dL and ≤54 mg/dL) during the nocturnal period (midnight to 0600 hours); (3) mean glucose level during a 24-hour period; (4) BG level variability during a 24-hour period.

The study was conducted according to the ethical principles of the Declaration of Helsinki and Council for International Organizations of Medical Science International Ethical Guidelines, the International Conference on Harmonization Good Clinical Practice Guidelines, and applicable laws and regulations.

CGM was offered to a subgroup of patients in the IMPERIUM study at multiple study sites. All patients participating in the CGM substudy had to meet the inclusion criteria for the main

[1]Florida Hospital and Sanford Burnham Prebys Translational Research Institute, Orlando, FL, USA
[2]Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX, USA
[3]University of Sheffield, Sheffield, UK
[4]Foundation for Diabetes Research in Older People, Diabetes Frail Limited, Worcestershire, UK
[5]Eli Lilly and Company, Indianapolis, IN, USA
[6]Eli Lilly & Company, Warsaw, Poland
[7]Lilly USA, LLC, Indianapolis, IN, USA
[8]Eli Lilly & Company, Vienna, Austria
[9]1st Medical Department, LK Stockerau, Niederösterreich, Austria

Corresponding Author:
Richard E. Pratley, MD, Florida Hospital Translational Research Institute, 301 Princeton Ave, Orlando, FL 32804, USA.
Email: Richard.Pratley@flhosp.org

IMPERIUM study listed below. In addition, patients were required to be willing to wear a CGM device without interruption for ≥72 hours and have a normal wake/sleep pattern. Patients participating in the CGM substudy signed a CGM substudy-specific informed consent form at visit 1.

Patients (male or female) eligible for the IMPERIUM study were ≥65 years with T2DM, HbA1c >7.3% and <10.9% and ≥0.4% higher than the upper limit of the individualized target range set at screening. Patients were assessed according to established frailty scales (Clinical Frailty Scale [CFS])[20] and comorbidities (Total Illness Burden Index [TIBI])[21] and were required to have a CFS score ≥4 and/or a TIBI score ≥5. Patients could enroll if before study entry they were treated with diet and exercise (only if metformin contraindicated) or for ≥3 months received OAMs, as monotherapy/dual combination: sulfonylurea (any dose); maximally tolerated/effective doses of metformin (≥1500 mg/day), DPP-4 inhibitor (any marketed dose), thiazolidinedione (≥30 mg/day of pioglitazone/≥4 mg/day of rosiglitazone), or acarbose (≥75 mg/day).

Individualized treatment targets (HbA1c 7.5% to 7.9%, 7.0% to 7.4%, or <7%) were chosen before randomization (at screening) and based primarily on life expectancy, hypoglycemic burden/risk, comorbidities, and cognitive/functional status. These guidelines are described in more detail in the IMPERIUM study manuscript.[19]

Marketed OAMs and injectable glucose-lowering treatments were used across different lines of treatment in each strategy, beginning with a single OAM and progressing to 3 OAMs, and/or first-line injectable therapy. Patients randomized to Strategy A (Supplementary Figure 1) were excluded from sulfonylurea and insulin therapy. If OAMs were not effective and injectable treatment was indicated, Strategy A patients commenced available GLP-1 RA therapy (exenatide twice-daily, exenatide once-weekly, or liraglutide at the discretion of the investigator). Patients randomized to Strategy B (Supplementary Figure 1) were treated with glimepiride as part of any OAM treatment (monotherapy, dual, or triple combination) and insulin glargine (Lantus®) as first-line injectable treatment. Treatments were titrated throughout the study until the maximally tolerated and/or approved doses or preset, individualized HbA1c target were reached. If maximally tolerated and/or approved doses were reached but individualized HbA1c targets were not met, next-line therapy was initiated by adding another treatment. The treatment strategies are described in more detail in the IMPERIUM study manuscript.[19]

Enrollment in the IMPERIUM study began in February 2014, and the last patient completed/data cutoff in October 2015. The CGM substudy was conducted during the first 24 weeks of the IMPERIUM study. Patients were asked to perform CGM on 2 occasions, for 72 hours per occasion, within 10 days prior to randomization (Visit 2) and 24 weeks of treatment (Visit 6) (Supplementary Figure 1). A Medtronic iPro 2 CGM system (Northridge, CA) was used. Trained investigative staff inserted the CGM device according to the product directions for use. Patients were trained on the use of the CGM device and the requirements for CGM, including the need to maintain a diary and collect self-monitoring blood glucose readings. Patients were blinded to the CGM results during the study. All patients who were enrolled in this addendum and received at least 1 dose of study drug and had CGM results from at least 1 collection time point were included in these analyses.

Table 1. Patient Characteristics.

	Glucose-dependent Strategy A (N = 26)	Glucose-independent Strategy B (N = 21)
Male, % of patients	61.5	61.9
Age, years	69.2 ± 4.3	71.0 ± 4.6
Race, % of patients		
Caucasian	88.5	71.4
BMI, kg/m^2	29.4 ± 4.9	29.2 ± 4.8
HbA1c, %	8.5 ± 1.0	8.3 ± 0.7
FBG, mg/dL	158 ± 38	160 ± 38
TIBI[a]	4.0 ± 2.0	3.8 ± 2.9
CFS[a]	4.0 ± 0.2	4.1 ± 0.2
Prior OAM, n (%)		
1 OAM	6 (23.1)	9 (42.9)
2 OAMs	18 (69.2)	12 (57.1)
3 OAMs	2 (7.7)	0 (0)
Prior SU use, n (%)	16 (61.5)	12 (57.1)
eGFR group, n (%)		
≥30 to <60 mL/min/1.73 m^2	6 (23.1)	3 (14.3)
≥60 to <90 mL/min/1.73 m^2	11 (42.3)	9 (42.9)
≥90 mL/min/1.73 m^2	9 (34.6)	9 (42.9)

Data are presented as mean ± standard deviation unless otherwise indicated. No statistically significant differences between treatment strategies for all parameters except TIBI and CFS (the means for TIBI and CFS were not compared).
[a]n = 20 for glucose-independent arm.

Statistical Analyses

All endpoints were prespecified. A total of 40 patients (54 randomized) with valid CGM measurements were required to provide 80% power to detect a difference between treatment groups of 130 minutes of hypoglycemia ≤70 mg/dL, assuming a standard deviation of 140 minutes and a two-sided type I error of .05. Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were applied to treatment-arm comparisons of duration (in minutes) and percentage of time spent in prespecified glycemic ranges before randomization (baseline) and week 24. Covariates included treatment strategy, treatment target, country, prestudy OAM, and prestudy sulfonylurea use. BG variability was assessed using within-day standard deviation, and within-day and between-day coefficient of variance. ANOVA and ANCOVA were applied to treatment-arm comparisons of mean BG and BG variability at baseline and week 24.

Results

A total of 47 patients were included in the CGM substudy of IMPERIUM (Strategy A, n = 26; Strategy B, n = 21). Baseline characteristics for patients in each strategy were well balanced (Table 1). Patients were from Puerto Rico

Table 2. Study Treatment.

	Glucose-dependent Strategy A (N = 26)	Glucose-independent Strategy B (N = 20)	*P* value
Maximum line of treatment			
Biguanides: metformin	24 (92.3)	17 (85.0)	.640
DPP-4 inhibitors	23 (88.5)	11 (55.0)	.010
Sitagliptin	13 (50.0)	7 (35.0)	.309
Linagliptin	10 (38.5)	4 (20.0)	.177
SU: glimepiride	0 (0.0)	19 (95.0)	<.001
TZD: pioglitazone	19 (73.1)	2 (10.0)	<.001
GLP-1 RA: exenatide QW	4 (15.4)	0 (0.0)	.121
Insulin glargine	0 (0.0)	2 (10.0)	.184

Data are presented as n (%).

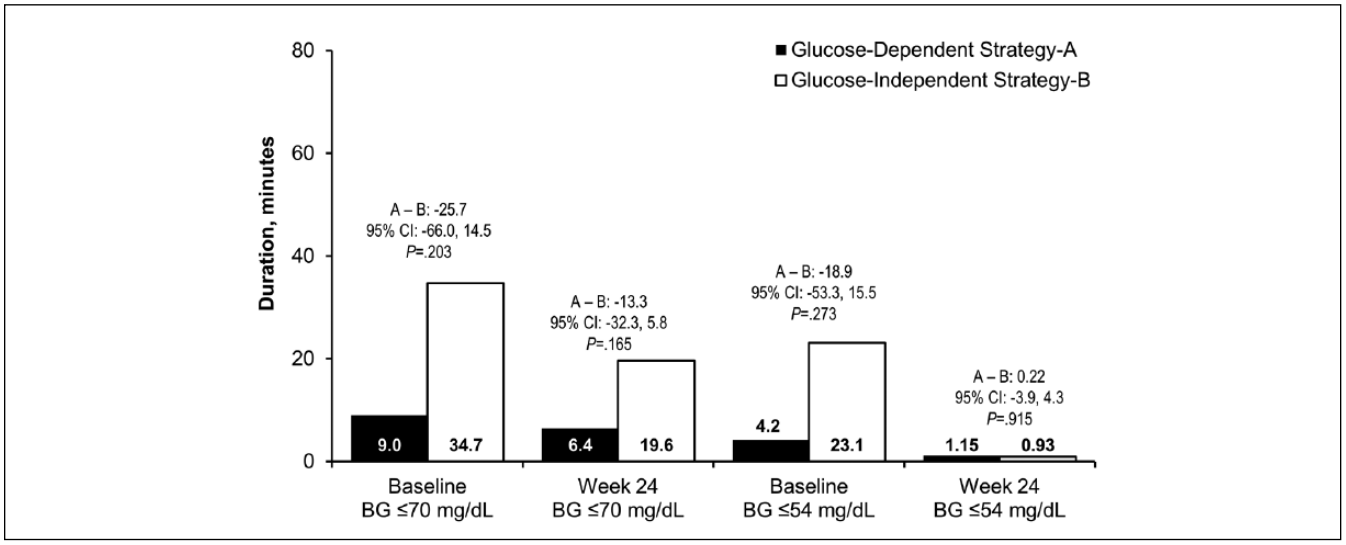

Figure 1A. Duration of hypoglycemia during a 24-hour period at baseline and week 24. Data are presented as least squares mean.

(Strategy A, n = 23; Strategy B, n = 16) or the United States (Strategy A, n = 3; Strategy B, n = 5). Predominant study treatments were metformin (92.3%), DPP-4 inhibitors (88.5%), and thiazolidinediones (pioglitazone, 73.1%) in Strategy A, and glimepiride (95.0%), metformin (85.0%), and DPP-4 inhibitors (55.0%) in Strategy B (Table 2).

A small number of patients spent time with BG ≤70 mg/dL at baseline (Strategy A, n = 3; Strategy B, n = 5) and 24 weeks (Strategy A, n = 4; Strategy B, n = 6) and with BG ≤54 mg/dL at baseline (Strategy A, n = 1; Strategy B, n = 3) and 24 weeks (Strategy A, n = 1; Strategy B, n = 1). Durations of hypoglycemia (BG ≤70 mg/dL and ≤54 mg/dL), euglycemia (BG ≥71 mg/dL to ≤180 mg/dL), and hyperglycemia (>180 mg/dL) during a 24-hour period were similar between Strategy A and Strategy B at baseline and at week 24 (Figure 1A, Supplementary Table 1). Similarly, percentage of time spent with hypoglycemia (BG ≤70 mg/dL and ≤54 mg/dL), euglycemia (BG ≥71 to ≤180 mg/dL), and hyperglycemia (>180 mg/dL) during 24-hour period were similar between Strategy A and Strategy B at baseline and at week 24 (Figure 1B, Supplementary Table 1).

Glycemic control improved similarly in both arms; mean change in HbA1c from baseline to week 24 was similar between Strategy A and Strategy B with reductions of −1.2% and −1.4% ($P = .405$), respectively (Figure 2).

Duration of nocturnal hypoglycemia was similar between Strategy A and Strategy B at baseline (≤70 mg/dL [LSM ± SE, minutes]: A = 5.3 ± 4.3 vs B = 13.9 ± 4.9, $P = .200$) and at week 24 (≤70 mg/dL [LSM ± SE, minutes]: A = 3.7 ± 3.3 vs B = 11.2 ± 3.7, $P = .156$) (Figure 3A, Supplementary Table 2). Similarly, percentage of time spent with nocturnal hypoglycemia was similar between Strategy A and Strategy B at baseline (≤70 mg/dL [LSM ± SE]: A = 1.5 ± 1.2 vs B = 3.9 ± 1.4, $P = .200$) and at week 24 (≤70 mg/dL [LSM ± SE]: A = 1.0 ± 0.9 vs B = 3.1 ± 1.0, $P = .200$) (Figure 3B, Supplementary Table 2).

At baseline, glycemic variability over a 24-hour period was similar between Strategy A and Strategy B (Figure 4, Supplementary Table 3). At week 24, Strategy A was

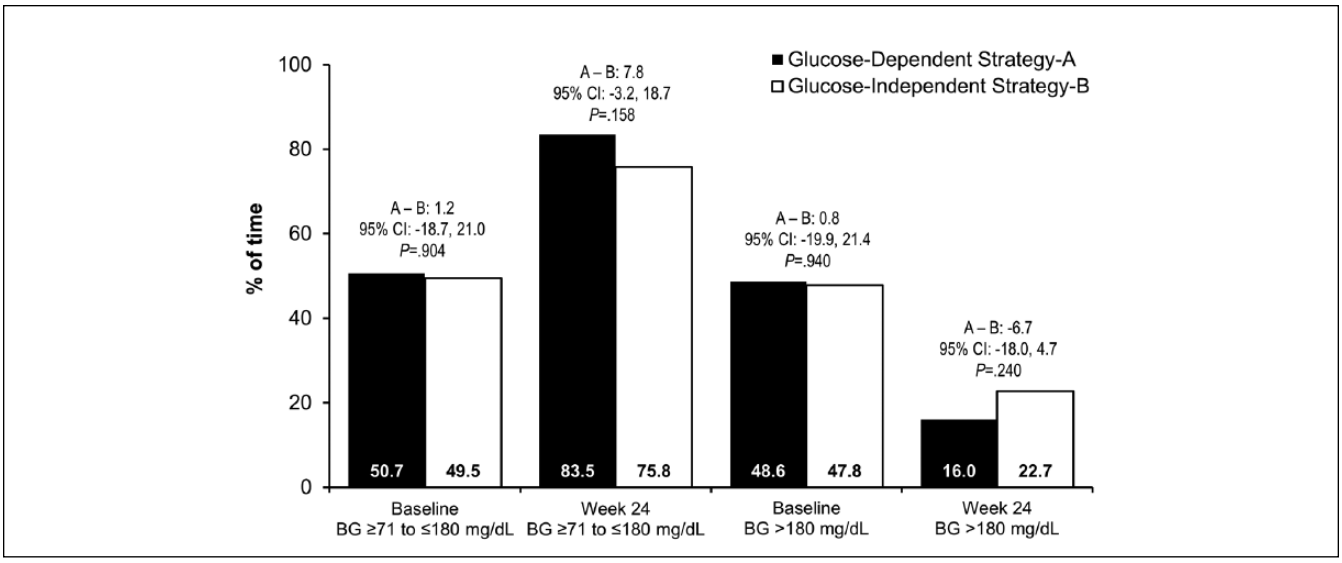

Figure 1B. Percentage of time spent in euglycemia and hyperglycemia during a 24-hour period at baseline and week 24. Data are presented as least squares mean.

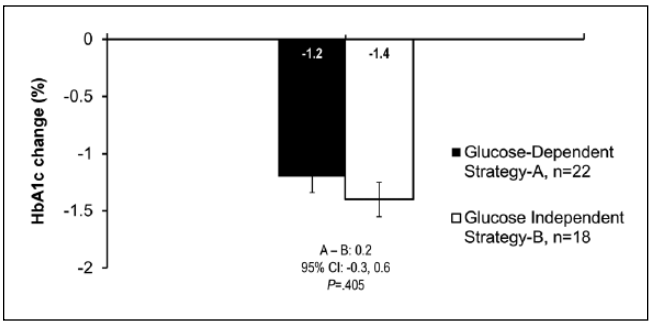

Figure 2. Change in HbA1c from baseline to week 24. Data are presented as least squares mean ± standard error.

associated with lower within-day (21.1 ± 1.2 vs 25.1 ± 1.4, P = .046) and between-day (5.4 ± 1.0 vs 9.1 ± 1.3, P = .038) BG variability (coefficient of variance [LSM ± SE]) (Figure 4, Supplementary Table 3).

Discussion

We describe the first report on glucose variability utilizing CGM in a specific population of vulnerable (moderately ill and/or frail) older (≥65 years) individuals with suboptimally controlled T2DM. This IMPERIUM substudy showed similar duration and percentage of time spent with hypoglycemia at ≤70 mg/dL for newer glucose-dependent versus traditional non-glucose-dependent treatment strategies. Glycemic control improved similarly in both arms, and duration and percentage time spent with euglycemia and hyperglycemia were also similar in both arms. However, the glucose-dependent strategy was associated with lower within- and between-day BG variability.

The use of CGM, including real-time CGM, has been reported to reduce episodes of severe hypoglycemia and improve quality of life in older patients.[22] However, most studies to date have evaluated use of CGM in older patients with type 1 diabetes mellitus (T1DM). There have been very few studies on CGM use in older patients with T2DM who do not use injectable therapy. In addition, a significant barrier for many patients, especially older patients who may be on a fixed income, is lack of insurance coverage for CGM in patients with T2DM. A recent CGM study showed that HbA1c levels are not associated with hypoglycemia risk in older patients with T2DM on insulin therapy, and that higher HbA1c goals do not protect against hypoglycemia.[23] These findings are consistent with a post hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial which showed an increased risk of hypoglycemia in patients with poorer glycemic control.[24] In the current study, at baseline, there were large differences between patients in daily glucose control and in time spent in hypoglycemia. These differences could not have been appreciated without the use of CGM.

One of the benefits of CGM is the ability to characterize GV. GV increases with age[25] and is thought to be a predictor of complications.[25] A recent systematic literature review suggests that in patients with T2DM, GV is associated with increased risk of microvascular complications (eg, retinopathy) and with an increased risk of cardiovascular complications (eg, coronary artery disease).[18] Severe hypoglycemia is associated with higher GV, but not lower HbA1c or mean glucose levels, in older patients with T1DM.[26] In older patients with T2DM, impairment of cognitive performance is associated with higher GV independent of HbA1c and glucose levels.[27] A recent subanalysis of the Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients with Type 2 Diabetes

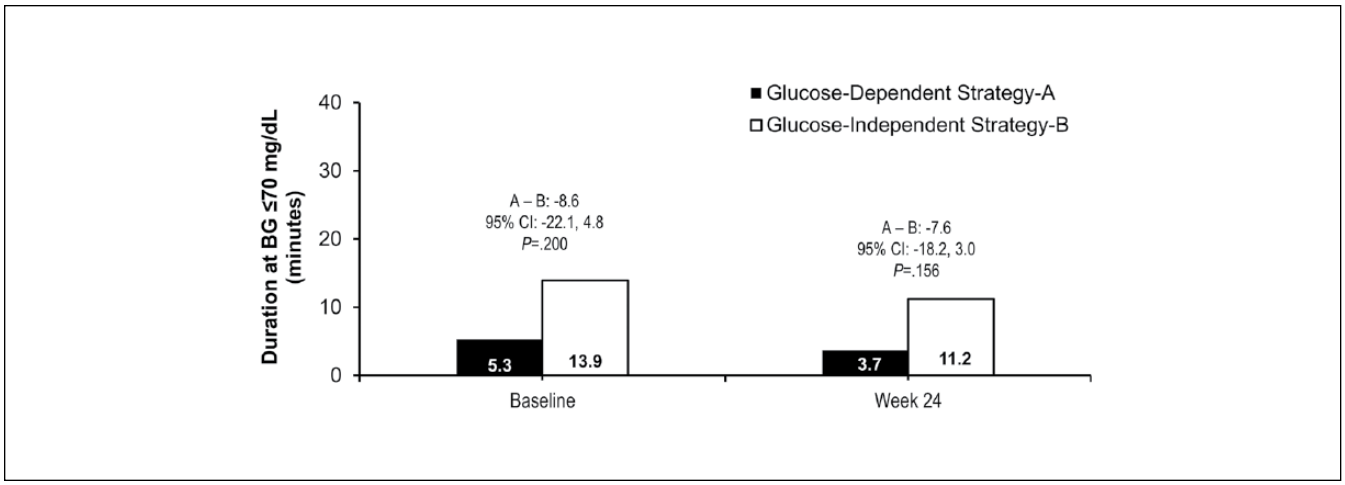

Figure 3A. Duration of hypoglycemia during nocturnal period (midnight to 0600 hours). Data are presented as least squares mean.

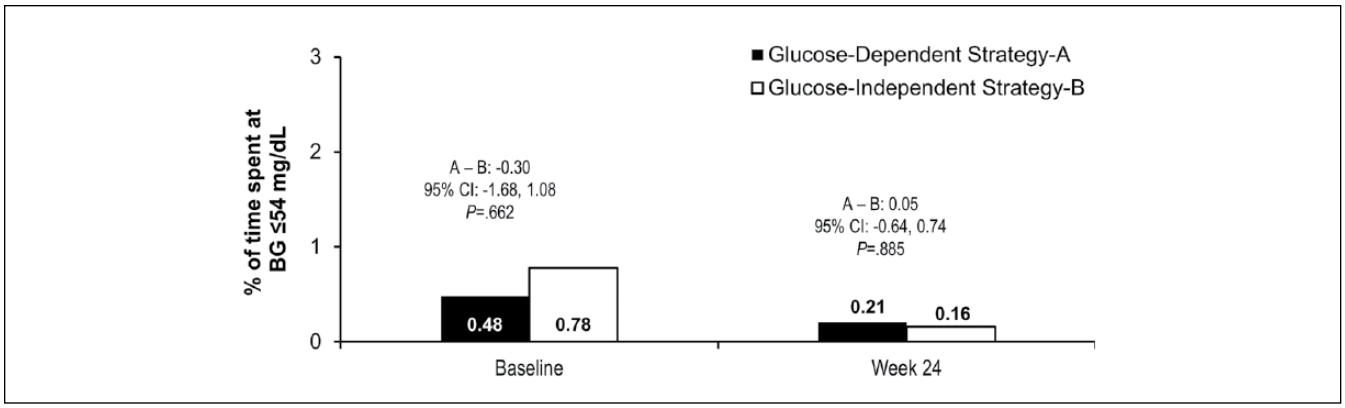

Figure 3B. Percentage of time spent with hypoglycemia during nocturnal period (midnight to 0600 hours). Data are presented as least squares mean.

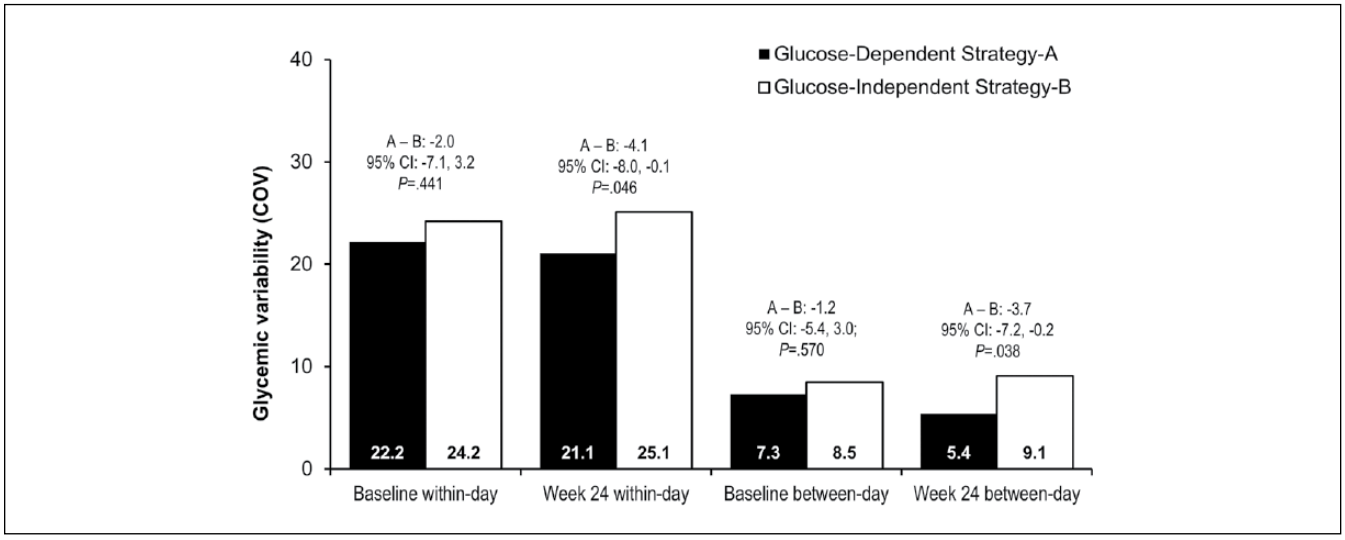

Figure 4. Glycemic variability over 24-hour period.

at High Risk of Cardiovascular Events (DEVOTE), showed that higher day-to-day fasting GV is associated with increased risks of severe hypoglycemia and all-cause mortality.[28] It has been suggested that minimizing GV may be equally as important as preventing hypoglycemia in older patients.[29] Some have suggested that GV may be as important as traditional measures of glycemic control, such as HbA1c and BG, for optimal glycemic control.[30] Recent recommendations suggest that variables other than HbA1c such as GV, be used to adequately describe glucose control and to tailor individualized approaches for patients.[31,32] The findings of reduced GV (within-day and between-day types) with Strategy A compared with Strategy B in the current study are of interest because of the aforementioned associations of GV with complications. In the main IMPERIUM study,[19] the low overall risk of severe hypoglycemia, driven by conservative use of therapies and also because patients were less prone to developing hypoglycemia than originally assumed, may explain why the reduced GV findings were not reflected in the severe hypoglycemia findings. A treatment strategy which reduces GV may be particularly beneficial in older patients with T2DM, who are often vulnerable because of comorbid conditions and/or frailty.[33,34] However, the clinical significance of these findings needs to be assessed in future studies which should include more thorough CGM evaluations in larger patient groups.

While our study is the first of its kind in this population of older adults, we acknowledge several limitations which include the small sample size that contributed to the large numerical variations within arms and the large numerical differences between arms, especially for baseline hypoglycemia duration. An additional limitation, which was also acknowledged in the main IMPERIUM study,[19] is that enrolled patients were generally younger and less frail than anticipated for Strategies-A and B (mean CFS, 4.0 and 4.1; mean TIBI, 4.0 and 3.8, respectively), and findings may not be reflective of those in very frail and/or very old patients. In addition, two-thirds of patients were taking sulfonylureas at baseline which meant that we presumably selected for patients who did not develop severe/symptomatic hypoglycemia on sulfonylureas. Finally, our study demonstrates that in a randomized controlled trial setting, and in the hands of experienced investigators, despite treatment intensification for 24 weeks (HbA1c reduction of −1.2% and −1.4% for Strategy A and Strategy B, respectively) time spent in hypoglycemia remained low (6 minutes and 20 minutes/24 hours, BG ≤70 mg/dl for Strategy A and Strategy B, respectively) irrespective of the treatment strategy.

Conclusion

This CGM substudy in older patients with T2DM showed lower within- and between-day BG variability for glucose-dependent strategies, but similar HbA1c reductions and hypoglycemia duration with glucose-independent strategies. These results provide a platform for a more detailed inquiry of GV in older people with T2DM, where achieving suitable glycemic control is balanced with protection from hypoglycemia.

Abbreviations

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ANCOVA, analysis of covariance; ANOVA, analysis of variance; BG, blood glucose; BMI, body mass index; CFS, Clinical Frailty Scale; CGM, continuous glucose monitoring; CI, confidence interval; COV, coefficient of variance; DEVOTE, Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; DPP-4, dipeptidyl-peptidase-4; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonists; GV, glycemic variability; IMPERIUM, individualized treatment approach for older patients in a randomized trial in type 2 diabetes mellitus; OAM, oral antihyperglycemic medication; QW, once weekly; SGLT-2, sodium-glucose cotransporter-2; SU, sulfonylurea; TIBI, Total Illness Burden Index; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus, TZD, thiazolidinedione.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: REP has consulted for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Hanmi Pharmaceutical Co, Janssen Pharmaceuticals, Ligand Pharmaceuticals, Eli Lilly and Company, Merck, Novo-Nordisk, and Takeda. He has received research support from Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Takeda and has spoken on behalf of AstraZeneca and Novo Nordisk. All honoraria and fees from these activities have been directed to a nonprofit. REP does not receive any direct or indirect compensation for these services. JR has served on scientific advisory boards and received honorarium or consulting fees from Eli Lilly, Novo Nordisk, Sanofi, Merck, Daiichi Sankyo, Janssen, Boehringer Ingelheim, AstraZeneca and Intarcia. He has received grants/research support from Merck, Pfizer, Sanofi, Novo Nordisk, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Takeda, AstraZeneca, Hanmi, Janssen, Daiichi Sankyo, Asahi, MannKind, Boehringer Ingelheim, Intarcia, and Lexicon. SRH has undertaken consultancy for Novo Nordisk, Eli Lilly and Company, Sanofi, Boehringer Ingelheim, Merck Sharp & Dohme, and Takeda. He has received research support from Medtronic and has been a member of speaker bureaus for Novo Nordisk, Eli Lilly and Company, Sanofi, Takeda, and Merck Sharp & Dohme. AS has received consultancy fees from Merck, Takeda, Novartis, and Eli Lilly and Company. RJH, JK, CSB, RD, and AF and are full-time employees and minor stockholders of Eli Lilly and Company.

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Supplemental Material

Supplemental material for this article is available online.

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