

Continuous Glucose Monitoring-Based Metrics with Fixed-Dose Combination Versus Co-administered Dapagliflozin/Metformin in Chinese Patients with Type 2 Diabetes Mellitus

Xuejie DONG

Beijing Chaoyang Hospital, Capital Medical University

Jia LIU

Beijing Chaoyang Hospital, Capital Medical University

Ying WEI

Beijing Chaoyang Hospital, Capital Medical University

Ping SHI

The People's Hospital of Dingzhou

Ji CHEN

The People's Hospital of Zhuji

Lingling XU

Shenzhen Hospital, Southern Medical University

Yinghong KONG

Affiliated Changshu Hospital of Nantong University

Jun YE

The Second People's Hospital of Hefei

Xueqin WANG

The First People's Hospital of Nantong

Juan XU

The People's Hospital of Jiangyin

Ling WANG

The People's Hospital of Chuxiong Yi Autonomous Prefecture

Li LI

BioPharmaceuticals Medical, AstraZeneca

Guang WANG

wangguangcy@ccmu.edu.cn

Beijing Chaoyang Hospital, Capital Medical University

Research Article

Keywords: Continuous glucose monitoring, Dapagliflozin, Metformin, Sodium-glucose cotransporter-2 inhibitor, Type 2 diabetes

Posted Date: September 29th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11046331/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: Competing interest reported. Li Li is an employee of AstraZeneca China. All other authors declare no potential conflict of interest relevant to this article.

Abstract

Background

Dapagliflozin plus metformin provides effective glycemic control with cardiorenal protection in type 2 diabetes mellitus (T2DM), and fixed-dose combination (FDC) reduces pill burden. This is the first study comparing continuous glucose monitoring (CGM) metrics of dapagliflozin/metformin FDC versus co-administration worldwide.

Methods

In the 24-week, multicenter, randomized EFFICIENT study, Chinese adults with newly diagnosed T2DM received dapagliflozin/metformin FDC or co-administration. CGM metrics were collected at Week 12, including percentage of time in tight range (TITR), time in range (TIR), time above range (TAR), time below range (TBR), mean amplitude of glycemic excursion (MAGE) and standard deviation of blood glucose (SDBG).

Results

The CGM analysis included 305 patients. Among those with sufficient evaluable traces (FDC: 149; co-administration: 144), the median TITR was 71.5% versus 75.0% (difference: -3.07%; 95% CI [- 7.16%, 0.81%]; nominal $p = 0.13$). Median TIR, TAR, and TBR were 90.7% versus 93.4%, 7.5% versus 6.3%, and 0.0% versus 0.0%, respectively. Median MAGE and SDBG were 2.7 mmol/L and 1.6 mmol/L, respectively, for both groups.

Conclusions

This study provided the first CGM data of dapagliflozin/metformin FDC worldwide, demonstrating glycemic control well above recommended targets. FDC had comparable efficacy to co-administration while reducing pill burden, providing an effective and simplified alternative for T2DM.

Trial registration:

ClinicalTrials.gov, NCT06327815

1 BACKGROUND

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic disorders in China. By 2023, age-standardized prevalence had climbed to 13.7%, nearly double the 7.5% recorded in 2005, and it

continues to rise across all age groups.[1] Despite the availability of multiple antidiabetic agents, cross-sectional studies in China showed that fewer than half of treated adults with diabetes achieved the guideline-recommended glycemic target of hemoglobin A1c (HbA1c) < 7%, and poor glycemic control is associated with increased cardiorenal morbidity and mortality.[2–4] Compared with the general population, Chinese patients with diabetes experience approximately twice the incidence of major adverse cardiovascular events and more than four times the risk of chronic kidney disease.[5, 6]

Early and intensive glycemic control is crucial for the preservation of β -cell function and the improvement of long-term clinical outcomes. As such, initial combination therapy with complementary mechanisms of action, included fixed dose combination (FDC), is recommended for patients with high HbA1c ($\geq 1.5\%$ above target) at diagnosis.[7, 8] Metformin is a classic glucose-lowering agent with robust efficacy and extensive clinical use, and exerts its effect through improving insulin sensitivity.[8, 9] Dapagliflozin, a highly stable and selective sodium-glucose cotransporter-2 inhibitor (SGLT2i), lowers glucose independently of insulin and confers additional cardiovascular and renal benefits [10, 11]. The combination of metformin plus SGLT2i has shown adequate efficacy and favorable safety, with additional cardiorenal benefits in high-risk patients,[12–16] and is recommended by contemporary guidelines as a preferred combination therapy.[8, 17, 18] A once-daily FDC of dapagliflozin 10 mg and extended-release metformin 1000 mg was first approved by the US Food and Drug Administration and the European Medicines Agency in 2014, and has been approved in a growing number of countries, including China (in 2023). FDC reduces pill burden compared with free co-administration. In a meta-analysis of 61 studies across a range of chronic diseases, FDCs significantly improved treatment adherence compared with free-equivalent combination therapy.[19]

While HbA1c remains the cornerstone for population-level risk stratification, day-to-day glycemic variability is increasingly recognized as an independent predictor of cardiovascular outcomes.[20, 21] Continuous glucose-monitoring (CGM) provides time-resolved metrics, such as time in range (TIR), time above range (TAR) and time below range (TBR), and measures of glycemic excursions such as mean amplitude of glycemic excursions (MAGE) and standard deviation of blood glucose (SDBG). These metrics complement HbA1c and offer additional prognostic value. Time in tight range (TITR) extends this framework by focusing on a stricter glycemic window and captures glycemic variability more sensitively than conventional TIR.[22] A higher TITR signifies more stable daily glycemic control, which may translate into improved microvascular and cardiorenal risk profiles.[23] The 2025 American Diabetes Association (ADA) Standards of Care recommend initiating CGM at the diagnosis of insulin-requiring diabetes and designate TIR as a core treatment target.[24, 25] The Chinese Diabetes Society's 2024 guidance echoes these recommendations, emphasizing CGM as a critical component of therapeutic decision-making.[8, 26] However, most randomized evidence for CGM derives from insulin-treated populations, and CGM data in patients receiving oral glucose-lowering agents, particularly SGLT2i FDCs, remain scarce.[27]

EFFICIENT is a 24-week, multicenter, open-label, phase 4 study designed to address this evidence gap. It represents the first randomized clinical evaluation of the dapagliflozin/metformin FDC, comparing its

efficacy in HbA1c reduction with free co-administration of the same agents in Chinese patients newly diagnosed with T2DM. The current analysis is a prespecified exploratory CGM sub-study, constituting the first assessment of CGM-derived glycemic variability with an SGLT2i FDC worldwide. This sub-study aimed to describe and compare glycemic variability in patients receiving the dapagliflozin/metformin FDC versus those receiving free co-administration.

2 METHODS

2.1 The EFFICIENT Study

EFFICIENT (NCT06327815) was a multicenter, randomized, parallel-group, open-label, non-inferiority study conducted at 35 hospitals in mainland China. Eligible participants were adults aged 18–80 years who had newly diagnosed T2DM (≤ 1 year), with an HbA1c of 7.5–10.0%, a body-mass index (BMI) of 19–40 kg/m², and no prior exposure to glucose-lowering therapy. Key exclusion criteria were New York Heart Association (NYHA) class III–IV heart failure, major cardiovascular events within the past 6 months, estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m², clinically apparent hepatic disease, recent metabolic decompensation, pregnancy or lactation, and participation in another interventional trial within 3 months. Demographic and clinical characteristics, medical history, and concomitant medications were collected at enrollment. Participants were randomized 1:1 to receive either a once-daily FDC tablet containing dapagliflozin 10 mg and metformin extended-release 1000 mg (DAPA/MET FDC) or free co-administration of dapagliflozin 10 mg plus metformin extended release 1000 mg (DAPA + MET) for 24 weeks. The primary endpoint of the parental EFFICIENT study was the change in HbA1c from baseline to Week 24.

2.2 Exploratory CGM Sub-study

This pre-specified CGM sub-study was an exploratory study of glycemic profiles within EFFICIENT. Enrolment was restricted to the first approximately 179 participants randomized to each treatment group who also consented to participate in this sub-study, which was conducted under the same ethical approvals and site-monitoring procedures as the main study.

At Week 12, a real-time CGM system (M8; Beijing Synapsor Artificial Intelligence Co., Ltd., Beijing, China) was placed after all scheduled assessments for participants enrolled into this sub-study. Participants wore the sensor for approximately five consecutive days while maintaining usual activities and a normal sleep–wake cycle (midnight to 06:00 am defined as the nocturnal period), and were instructed not to remove the sensor during this monitoring period. Sensors were removed at the study site one to two days after the monitoring period; if an in-clinic removal was not feasible, participants were instructed to self-remove the sensor and return the CGM device to the study site in person or by shipment at the earliest opportunity. The CGM analysis set comprised all participants who had received at least one dose of study medication before placing the CGM sensor and contributed evaluable Week 12 CGM traces.

2.3 Endpoints

The primary exploratory endpoint of the CGM sub-study was TITR, defined as the proportion of sensor readings with blood glucose levels within the tight target range (3.9–7.8 mmol/L) during the five-day monitoring period beginning at Week 12.

Secondary exploratory endpoints included TIR (range: 3.9–10.0 mmol/L), TBR (< 3.9 mmol/L), TAR (> 10.0 mmol/L), as well as MAGE and SDBG. MAGE was defined as the mean of blood glucose values that exceeded one within-day standard deviation of the 24-hour mean blood glucose. SDBG was defined as the 24-hour standard deviation of all valid CGM readings. All endpoints excluded data recorded after initiation of rescue therapy or permanent discontinuation of study medication.

2.4 Statistical Analysis

All analysis in this CGM sub-study followed the pre-specified Statistical Analysis Plan and were conducted in the CGM analysis set. The primary exploratory hypothesis was that the TITR at Week 12 would differ between the FDC and co-administration groups. A prespecified sample size of 143 participants per group was determined a priori for exploratory superiority testing, providing 80% power to detect a between-group difference of 10 percentage points in TITR (assuming a standard deviation of 30%) at a two-sided alpha level of 0.05. Allowing for up to 20% drop-out rate, 358 participants were planned for enrolment.

CGM data processing excluded the first day of wearing the sensor to mitigate signal instability. CGM data were considered missing and excluded from analysis for any of the following reasons: receiving rescue medication prior to the Week 12 CGM assessment, permanently discontinuing study intervention prior to the Week 12 CGM assessment, and having insufficient evaluable data (defined as having < 3 days of evaluable CGM data, in which the participants had $\geq 70\%$ of the expected 288 measurements per day).

TITR at Week 12 and secondary CGM endpoints (TIR, TBR, TAR, MAGE, SDBG) were compared between treatment groups using independent-samples t-tests or Wilcoxon rank sum tests as appropriate. Point estimates and 95% CIs were calculated for each group and for between-group differences; for non-parametric analyses, Hodges-Lehman estimators with distribution-free 95% CI were used. Because all CGM endpoints were exploratory, no adjustment for multiplicity was applied, and all p-values generated were nominal. All analyses were performed using SAS[®] version 9.4.

3 RESULTS

3.1 Patient Disposition and Baseline Characteristics

Between 15 March 2024 and 30 June 2025, 781 participants were enrolled in the EFFICIENT trial. In total, 438 participants also consented to this exploratory sub-study and were screened, of whom 79 did not meet eligibility criteria. The remaining 359 were randomized to receive either the FDC (n = 178) or co-administration (n = 181), and 358 received study treatment (DAPA/MET FDC: 178; DAPA + MET: 180). The

CGM analysis set comprised 305 participants who received at least one dose before sensor placement and contributed evaluable Week 12 CGM traces (DAPA/MET FDC: 154; DAPA + MET: 151) (Fig. 1).

Baseline demographics and clinical characteristics for the CGM analysis set are summarized in Table 1. The mean (standard deviation [SD]) age was 49.9 (12.0) years in the FDC group and 51.7 (12.2) years in the co-administration group, and 66.9% of participants in both groups were male. The mean (SD) BMI was 26.9 (3.8) kg/m² in the FDC group and 27.5 (3.7) kg/m² in the co-administration group, with 18.2% and 11.3% of participants having BMI < 24 kg/m², 42.2% and 44.4% between 24–<28 kg/m², and 39.6% and 44.4% ≥28 kg/m², respectively. Baseline glycemic indices were similar between groups: mean (SD) HbA1c was 8.7% (0.7%) and 8.6% (0.6%) (HbA1c < 9% in 61.0% and 70.9%), mean (SD) fasting plasma glucose was 9.1 (1.9) and 8.8 (1.5) mmol/L, and mean (SD) 2-h plasma glucose was 17.6 (3.1) and 17.6 (3.4) mmol/L. Kidney function was preserved, with eGFR ≥ 90 mL/min/1.73 m² in 86.4% and 84.8% of participants. The most common comorbidities were dyslipidemia (65.6% vs 72.8%) and hypertension (35.1% vs 44.4%). Overall, baseline characteristics were well balanced between treatment groups.

Table 1
Patient demographics and baseline characteristics

Characteristics	DAPA/MET FDC N = 154	DAPA + MET N = 151
Age [†] , mean (SD), year	49.9 (12.0)	51.7 (12.2)
Sex, male, n (%)	103 (66.9)	101 (66.9)
Height, mean (SD), cm	167.5 (8.4)	166.5 (8.9)
Weight, mean (SD), kg	75.7 (14.5)	76.7 (14.5)
BMI [‡] , mean (SD), kg/m ²	26.9 (3.8)	27.5 (3.7)
< 24, n (%)	28 (18.2)	17 (11.3)
≥ 24 and < 28, n (%)	65 (42.2)	67 (44.4)
≥ 28, n (%)	61 (39.6)	67 (44.4)
Waist circumference, mean (SD), cm	95.2 (11.0)	97.3 (11.6)
HbA1c, mean (SD), %	8.7 (0.7)	8.6 (0.6)
< 9, n (%)	94 (61.0)	107 (70.9)
≥ 9, n (%)	60 (39.0)	44 (29.1)
Fasting insulin, mean (SD), uU/ml	14.6 (11.2)	16.3 (11.3)
2hr-insulin, mean (SD), uU/ml	52.0 (44.4)	61.8 (48.4)
Fasting c-peptide, mean (SD), ng/ml	3.0 (1.3)	3.3 (1.3)
2hr-c-peptide, mean (SD), ng/ml	7.7 (3.9)	8.6 (3.6)
Fasting plasma glucose, mean (SD), mmol/L	9.1 (1.9)	8.8 (1.5)
2hr-plasma glucose, mean (SD), mmol/L	17.6 (3.1)	17.6 (3.4)
eGFR, mean (SD), ml/min/1.73m ²	104.5 (14.3)	102.4 (15.4)
< 60, n (%)	3 (1.9)	1 (0.7)
≥ 60 and < 90, n (%)	18 (11.7)	22 (14.6)
[†] Age was calculated as: (date of informed consent - date of birth + 1) / 365.25; [‡] BMI was calculated as: Weight (kg) / (Height (cm) / 100) ² ; [§] Medical history was coded with MedDRA version 27.1.		
BMI, body mass index; CGM, continuous glucose monitoring; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; FDC, fixed-dose combination; HbA1c: hemoglobin A1c; MedDRA, Medical Dictionary for Regulatory Activities; MET, metformin; SD, standard deviation.		

Characteristics	DAPA/MET FDC N = 154	DAPA + MET N = 151
≥ 90, n (%)	133 (86.4)	128 (84.8)
Medical history [§] , n (%)		
Dyslipidemia	101 (65.6)	110 (72.8)
Albuminuria	19 (12.3)	16 (10.6)
Heart failure	1 (0.6)	1 (0.7)
Chronic kidney disease	13 (8.4)	13 (8.6)
Hypertension	54 (35.1)	67 (44.4)
[†] Age was calculated as: (date of informed consent - date of birth + 1) / 365.25; [‡] BMI was calculated as: Weight (kg) / (Height (cm) / 100) ² ; [§] Medical history was coded with MedDRA version 27.1.		
BMI, body mass index; CGM, continuous glucose monitoring; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; FDC, fixed-dose combination; HbA1c: hemoglobin A1c; MedDRA, Medical Dictionary for Regulatory Activities; MET, metformin; SD, standard deviation.		

3.2 Primary Exploratory Endpoint: TITR

Five patients in the FDC group and six in co-administration group had insufficient evaluable data and were excluded from the analysis of CGM metrics, and the final analysis set included 149 patients in the FDC group and 144 in the co-administration group.

At Week 12, median TITR was 71.5% (Q1, Q3: 56.3, 85.5) in the FDC group and 75.0% (64.6, 86.0) in the co-administration group, with a between-group difference of – 3.07 percentage points (95% CI: –7.16 to 0.81; nominal p = 0.13). Both groups exceeded the 50% target recommended by current clinical guidance (Fig. 2).

3.3 TIR, TBR, and TAR

TIR, TBR, and TAR were similar between groups. Median TIR was 90.7% (Q1, Q3: 83.3, 97.6) with FDC and 93.4% (88.2, 97.4) with co-administration; the between-group difference in medians was – 1.74 percentage points (95% CI: –3.75 to 0.00; nominal p = 0.04) (Fig. 3A). Median TBR was 0.0% (0.0, 0.2) with FDC and 0.0% (0.0, 0.3) with co-administration; with no statistically significant difference (nominal p = 0.38). Median TAR was 7.5% (1.2, 16.1) with FDC and 6.3% (1.9, 11.5) with co-administration; the between-group difference was 0.90 percentage points (95% CI: –0.14 to 3.13; nominal p = 0.10) (Fig. 3B).

3.4 MAGE and SDBG

Median MAGE was 2.7 mmol/L (Q1, Q3: 2.1, 3.6) with FDC and 2.7 mmol/L (2.1, 3.4) with co-administration; the between-group difference in medians was 0.04 mmol/L (95% CI: -0.18 to 0.26; nominal $p = 0.71$). Median SDBG was 1.6 mmol/L (1.2, 2.0) with FDC and 1.6 mmol/L (1.2, 1.9) with co-administration; the between-group difference in medians was 0.05 mmol/L (95% CI: -0.06 to 0.17; nominal $p = 0.34$) (Fig. 4).

4 DISCUSSION

This prespecified exploratory CGM sub-study of EFFICIENT provides the first CGM-derived evidence on the glycemic profiles of the dapagliflozin/metformin FDC. TITR was examined as the primary exploratory endpoint, with other CGM measures (TIR, TAR, TBR, MAGE, SDBG) prespecified as secondary exploratory endpoints to provide a multidimensional view of daily glycemic control. Importantly, once-daily FDC achieved glycemic profiles comparable to co-administration across prespecified CGM metrics, with all measures exceeding guideline-recommended CGM targets for adults with T2DM.[24–26] These results help fill in the evidence gap for non-insulin, SGLT2i-based oral therapy and underscore the value of CGM in complementing HbA1c by providing detailed insights into day-to-day glycemic patterns, thereby supporting early risk stratification and regimen optimization in clinical practice.

The primary exploratory endpoint TITR is emerging as a stricter CGM target than conventional TIR. Multiple cohort analyses and real-world studies have linked higher TITR with lower risks of microvascular events and mortality in T2DM, suggesting that it could help predict long-term outcomes, and supporting its use alongside HbA1c in clinical decision-making.[28, 29] For example, in a prospective cohort of adults with T2DM, TITR at baseline showed a linear inverse association with all-cause and cardiovascular mortality independent of HbA1c; each 10% lower TITR was associated with a 4% higher risk of both outcomes, providing additional prognostic information beyond conventional metrics.[29] Recent guidelines and studies likewise increasingly emphasize TITR as a meaningful marker of glycemic quality.[30, 31] In this study, median TITR at Week 12 far exceeded the guideline-recommended target of $> 50\%$ for both groups, with no significant difference between treatment groups (71.5% vs. 75.0%; nominal $p = 0.13$), consistent with prior studies of the robust glucose-lowering efficacy of SGLT2i–metformin dual therapy.[15]

Beyond TITR, metrics such as TIR, TBR, TAR, MAGE, and SDBG provide a multidimensional view of glycemic variability. Recent guidance supports their use for guiding personalized therapy and predicting clinical risks.[32, 33] At Week 12, median TIR was 90.7% in the FDC group and 93.4% with co-administration; median TBR was 0% in both groups, median TAR was 7.5% and 6.3%. Against guideline-recommended targets of $TIR \geq 70\%$, $TBR < 4\%$, $TAR < 25\%$, the values observed in this study far exceeded these thresholds, indicating favorable glycemic control. Quartile estimates were likewise above these thresholds, suggesting that most patients achieved adequate control. Alongside the primary exploratory endpoint TITR, meeting these thresholds suggests that SGLT2i-based oral therapy achieves robust glycemic control without increasing hypoglycemia risk. Day-to-day glycemic variability, as reflected by MAGE and SDBG, was also low. Overall, these findings are consistent with prior evidence indicating that

SGLT2i can reduce glycemic variability versus DPP-4 inhibitors and sulfonylureas.[34, 35] On a related note, since glycemic variability has been associated with microvascular complications,[10, 11, 36] the glycemic stability observed in this study suggests that SGLT2i may confer microvascular protection in addition to its established benefits on major cardiorenal outcomes. Further studies are warranted to assess the durability of these effects and their potential impacts on long-term microvascular complications.

From a care perspective, multidimensional CGM metrics offer a more comprehensive view of day-to-day glycemic control, which are of great clinical significance. For instance, patients exhibiting greater variability, despite meeting average glycemic targets, can be identified early, and targeted CGM deployment in this subgroup is more likely to inform treatment adjustments and improve outcomes. However, despite its potential, the evidence base for CGM for non-insulin, oral-glucose-lowering agents remains limited. Most randomized studies are conducted in insulin-treated cohorts, and TITR is rarely prespecified, with its interpretation alongside other metrics not well defined in oral regimens.[37–39] This study helps address that gap by providing the first randomized CGM-based characterization of an SGLT2i–metformin FDC, demonstrating the feasibility and clinical utility of TITR-anchored CGM profiling. Our findings support the use of targeted CGM in patients with suspected variability or following therapy changes and motivate future serial-CGM studies to determine optimal monitoring frequency and actionable thresholds.

Although TIR showed a marginally significant difference between groups (90.7% versus 93.4% [nominal $p = 0.04$]), the nominal p limits interpretation. Moreover, this difference is unlikely to be clinically meaningful since the absolute difference was small and both groups exceeded recommended targets. Meanwhile, all other CGM metrics showed no statistically significant differences between groups. The lack of clinically meaningful differences across all CGM endpoints indicates comparable therapeutic efficacy between FDC and co-administration, supporting their clinical interchangeability. In practice, choosing the once-daily FDC would not compromise glycemic outcomes in patients who prioritize treatment simplicity or wish to reduce pill burden. Mechanistically, SGLT2i lower plasma glucose independently of insulin, while metformin improves both hepatic and peripheral insulin sensitivity.[40] When used together, these two agents attenuate postprandial glucose excursions with minimal risk of hypoglycemia.[41] Beyond the dual therapy's established clinical benefits, delivering it as a once-daily FDC may further enhance its benefits through regimen simplification. As noted, evidence from various chronic diseases indicates that FDC can improve treatment adherence,[19, 42] which is critical for long-term effective glycemic control and patient outcomes.

The primary limitation of this study is that all CGM endpoints were exploratory and were not adjusted for multiple comparisons. As such, statistical inferences should be interpreted cautiously and considered hypothesis-generating. Secondly, each participant underwent CGM monitoring only once, yielding a single five-day glucose profile at Week 12. While this pragmatic approach minimized participant burden, it may not fully capture fluctuations in glycemic control across the study period. Finally, the 24-week duration of the parent study limited assessments of outcomes such as β -cell preservation, long-term

glycemic durability, and the incidence of diabetes-related complications. These limitations underscore the need for longer-term and more frequent monitoring to fully evaluate the clinical significance of day-to-day glucose control. Future studies could adopt longitudinal CGM designs with measurements at baseline and multiple follow-up time points. Trials with sufficient follow-up and statistical power to evaluate further clinical outcomes, such as microvascular complications, would be valuable.[33] In addition, evaluating structured CGM use (as recommended by international guidelines) in non-insulin-treated populations, particularly among individuals with high glycemic variability or recent therapy changes, may further clarify its utility in clinical decision-making and impact on long-term outcomes.[24, 32]

In summary, this prespecified exploratory CGM sub-study provided the first evidence of CGM-based metrics of SGLT2i-based FDC, and demonstrated that both the once-daily dapagliflozin/metformin FDC and free co-administration group achieved high levels of daily glycemic control that exceeded guideline targets, with minimal hypoglycemia risk. CGM metrics, including TITR, were comparable between FDC and administration, supporting the use of FDC for treatment simplification, particularly for those with high pill burden. Further studies with longer follow-up and serial CGM assessments are warranted to determine whether early achievement of high TITR and low glycemic variability translates into durable control and reduced risks of diabetes-related complications.

Abbreviations

ADA: American Diabetes Association

BMI: Body mass index

CI: Confidence interval

CGM: Continuous glucose monitoring

DAPA: Dapagliflozin

eGFR: Estimated glomerular filtration rate

FDC: Fixed-dose combination

HbA1c: Hemoglobin A1c

MAGE: Mean amplitude of glycemic excursion

MET: Metformin

NYHA: New York Heart Association

Q1, Q3: First quartile, third quartile

SD: Standard deviation

SDBG: Standard deviation of blood glucose

SGLT2i: Sodium-glucose cotransporter-2 inhibitor

T2DM: Type 2 diabetes mellitus

TAR: Time above range

TBR: Time below range

TITR: Time in tight range

TIR: Time in range

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Review Board/Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (Approval No. 2023-Ke-772-3) and all other participating sites. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

Data underlying the findings described in this article may be obtained from the corresponding author upon reasonable request, in accordance with AstraZeneca's data sharing policy.

Competing interest

Li Li is an employee of AstraZeneca China. All other authors declare no potential conflict of interest relevant to this article.

Funding

This work was supported by AstraZeneca China.

Author contributions

GW, JL, and LL conceptualized and designed the methodology of the study. All authors were involved in investigation and formal analysis. JL, YW, and GW prepared the original draft of the manuscript. All authors revised, edited, and approved the manuscript for submission.

Acknowledgements

The authors thank all patients and study staff involved in this study. Medical writing and editorial assistance were provided by Gaole Lin and Ruilin Chen (Costello Medical, funded by AstraZeneca China) in compliance with international guidelines for Good Publication Practice (GPP 2022).

References

1. Zhou YC, Liu JM, Zhao ZP, Zhou MG, Ng M. The national and provincial prevalence and non-fatal burdens of diabetes in China from 2005 to 2023 with projections of prevalence to 2050. *Mil Med Res*. 2025;12(1):28.
2. Cai XL, Shen J, Ye BQ, Li Q, Clark DAS, Ji LN. Characteristics, treatment patterns, and glycemic control of older type 2 diabetes mellitus patients in China. *Chin Med J (Engl)*. 2021;134(23):2893–5.
3. Xing XY, Wang XY, Fang X, Xu JQ, Chen YJ, Xu W, et al. Glycemic control and its influencing factors in type 2 diabetes patients in Anhui, China. *Front Public Health*. 2022;10:980966.
4. Drechsler C, Krane V, Ritz E, März W, Wanner C. Glycemic control and cardiovascular events in diabetic hemodialysis patients. *Circulation*. 2009;120(24):2421–8.
5. Wang Q, Gan Z, Gao Q, Wang M, Zhan B. The associations of risk of cardiovascular disease with development stages of diabetes in Chinese population: findings from a retrospective cohort study in QuZhou city. *BMC Endocr Disord*. 2024;24(1):18.
6. Wang X, Chen L, Shi K, Lv J, Sun D, Pei P et al. Diabetes and chronic kidney disease in Chinese adults: a population-based cohort study. *BMJ Open Diabetes Res Care*. 2024; 12(1).
7. Cardiovascular disease and. risk management: standards of care in diabetes-2025. *Diabetes Care*. 2025;48(1 Suppl 1):S207–38.
8. Chinese Diabetes Society. Guideline for the prevention and treatment of diabetes mellitus in China (2024 edition). *Chin J Diabetes Mellitus*. 2025;17(1):16–139.
9. Blonde L, Dipp S, Cadena D. Combination Glucose-Lowering Therapy Plans in T2DM: Case-Based Considerations. *Adv Ther*. 2018;35(7):939–65.
10. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995–2008.
11. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347–57.
12. Anson M, Zhao SS, Essa H, Austin P, Ibarburu GH, Lip GYH, et al. Metformin and SGLT2i as first-line combination therapy in type 2 diabetes: A real-world study With a focus on ethnicity. *Clin Ther*. 2023;45(12):1259–65.

13. Wong CKH, Lau KTK, Tang EHM, Lee CH, Lee CYY, Woo YC, et al. Cardiovascular benefits of SGLT2 inhibitors in type 2 diabetes, interaction with metformin and role of erythrocytosis: a self-controlled case series study. *Cardiovasc Diabetol*. 2022;21(1):92.
14. Scheen AJ. SGLT2 inhibitors as add-on therapy to metformin for people with type 2 diabetes: a review of placebo-controlled trials in Asian versus non-Asian patients. *Diabetes Metab Syndr Obes*. 2020;13:2765–79.
15. Xu L, Wu Y, Li J, Ding Y, Chow J, Li L, et al. Efficacy and safety of 11 sodium-glucose cotransporter-2 inhibitors at different dosages in type 2 diabetes mellitus patients inadequately controlled with metformin: a Bayesian network meta-analysis. *BMJ Open*. 2025;15(2):e088687.
16. Guo L, Wang J, Li L, Yuan L, Chen S, Wang H, et al. Real-world safety of dapagliflozin plus metformin in patients of type 2 diabetes mellitus in China: Post-hoc analysis of the DONATE study. *Diabetes Res Clin Pract*. 2025;219:111959.
17. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycemia in type 2 diabetes, 2022. a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2022;45(11):2753–86.
18. Pharmacologic approaches to. glycemic treatment: standards of care in diabetes-2025. *Diabetes Care*. 2025;48(1 Suppl 1):S181–206.
19. Wei Q, Zhou J, Li H, Wang L, Wu Y, Ma A, et al. Medication adherence with fixed-dose versus free-equivalent combination therapies: Systematic review and meta-analysis. *Front Pharmacol*. 2023;14:1156081.
20. Bergenstal RM, Hachmann-Nielsen E, Kvist K, Peters AL, Tarp JM, Buse JB. Increased derived time in range is associated with reduced risk of major adverse cardiovascular events, severe hypoglycemia, and microvascular events in type 2 diabetes: a post hoc analysis of DEVOTE. *Diabetes Technol Ther*. 2023;25(6):378–83.
21. Alfieri V, Myasoedova VA, Vinci MC, Rondinelli M, Songia P, Massaiu I et al. The role of glycemic variability in cardiovascular disorders. *Int J Mol Sci*. 2021; 22(16).
22. Dunn TC, Ajjan RA, Bergenstal RM, Xu Y. Is it time to move beyond TIR to TITR? Real-world data from over 20,000 users of continuous glucose monitoring in patients with type 1 and type 2 diabetes. *Diabetes Technol Ther*. 2024;26(3):203–10.
23. Lachin JM, Bebu I, Gao X, Nathan DM, Zinman B. Association of estimated time-in-range capillary glucose levels versus HbA1c with progression of microvascular complications in the diabetes control and complications trial. *Diabetes Care*. 2022;45(10):2445–8.
24. Diabetes technology. standards of care in diabetes-2025. *Diabetes Care*. 2025;48(1 Suppl 1):S146–66.
25. Glycemic goals and. hypoglycemia: standards of care in diabetes-2025. *Diabetes Care*. 2025;48(1 Suppl 1):S128–45.

26. Bao Y, Zhu D. Clinical application guidelines for blood glucose monitoring in China (2022 edition). *Diabetes Metab Res Rev.* 2022;38(8):e3581.
27. Simonson DC, Testa MA, Ekholm E, Su M, Vilsbøll T, Jabbour SA, et al. Continuous glucose monitoring profiles and health outcomes after dapagliflozin plus saxagliptin vs insulin glargine. *J Clin Endocrinol Metab.* 2024;109(12):e2261–72.
28. Wang Y, Lu J, Yu J, Ni J, Wang M, Lu W, et al. Association between time in tight range and incident diabetic retinopathy in adults with type 2 diabetes. *Diabetes Obes Metab.* 2025;27(3):1415–22.
29. Cai J, Liu J, Lu J, Ni J, Wang C, Chen L, et al. Impact of time in tight range on all-cause and cardiovascular mortality in type 2 diabetes: a prospective cohort study. *Diabetes Obes Metab.* 2025;27(4):2154–62.
30. Battelino T, Alexander CM, Amiel SA, Arreaza-Rubin G, Beck RW, Bergenstal RM, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. *Lancet Diabetes Endocrinol.* 2023;11(1):42–57.
31. Nishimura R, Okada Y, Kuroda A, Suzuki J, Hirota Y, Matsuhisa M et al. Consensus statement on novel glucose-related metrics obtained through advanced medical devices: English version. *Diabetol Int.* 2025.
32. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care.* 2019;42(8):1593–603.
33. Yapanis M, James S, Craig ME, O'Neal D, Ekinici EI. Complications of Diabetes and Metrics of Glycemic Management Derived From Continuous Glucose Monitoring. *J Clin Endocrinol Metab.* 2022;107(6):e2221–36.
34. Venkatachalapathy P, Mohandoss K, Munisamy M, Sellappan M. Comparative effectiveness of oral hypoglycemic agents for glycemic control and glycemic variability in patients with type 2 diabetes mellitus: using flash glucose monitoring. *Curr Diabetes Rev.* 2024;21(1):e160124225706.
35. Vianna AGD, Lacerda CS, Pechmann LM, Polesel MG, Marino EC, Scharf M, et al. Improved glycaemic variability and time in range with dapagliflozin versus gliclazide modified release among adults with type 2 diabetes, evaluated by continuous glucose monitoring: A 12-week randomized controlled trial. *Diabetes Obes Metab.* 2020;22(4):501–11.
36. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383(15):1436–46.
37. Ferreira ROM, Trevisan T, Pasqualotto E, Chavez MP, Marques BF, Lamounier RN, et al. Continuous glucose monitoring systems in noninsulin-treated people with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Technol Ther.* 2024;26(4):252–62.
38. Miller EM. Using continuous glucose monitoring in clinical practice. *Clin Diabetes.* 2020;38(5):429–38.
39. Moon SJ, Kim KS, Lee WJ, Lee MY, Vigersky R, Park CY. Efficacy of intermittent short-term use of a real-time continuous glucose monitoring system in non-insulin-treated patients with type 2 diabetes:

- A randomized controlled trial. *Diabetes Obes Metab.* 2023;25(1):110–20.
40. Vallon V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. *Annu Rev Med.* 2015;66:255–70.
41. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. *Int J Clin Pract.* 2012;66(5):446–56.
42. Derington CG, Bress AP, Herrick JS, Jacobs JA, Zheutlin AR, Berchie RO, et al. Antihypertensive medication regimens used by US adults with hypertension and the potential for fixed-dose combination products: the national health and nutrition examination surveys 2015 to 2020. *J Am Heart Assoc.* 2023;12(11):e028573.

Figures

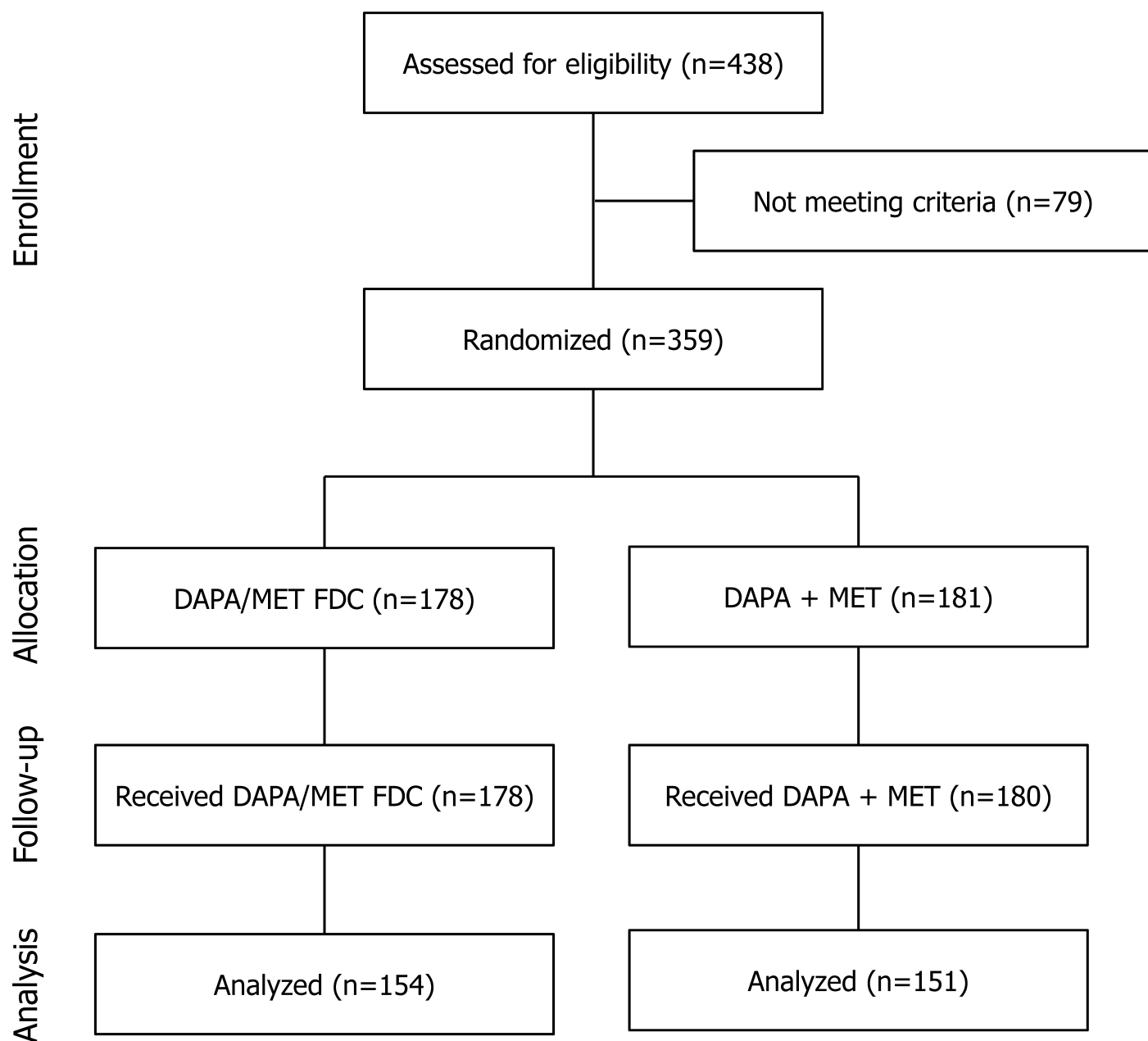


Figure 1

Patient disposition. CGM, continuous glucose monitoring; DAPA, dapagliflozin; FDC, fixed-dose combination; MET, metformin.

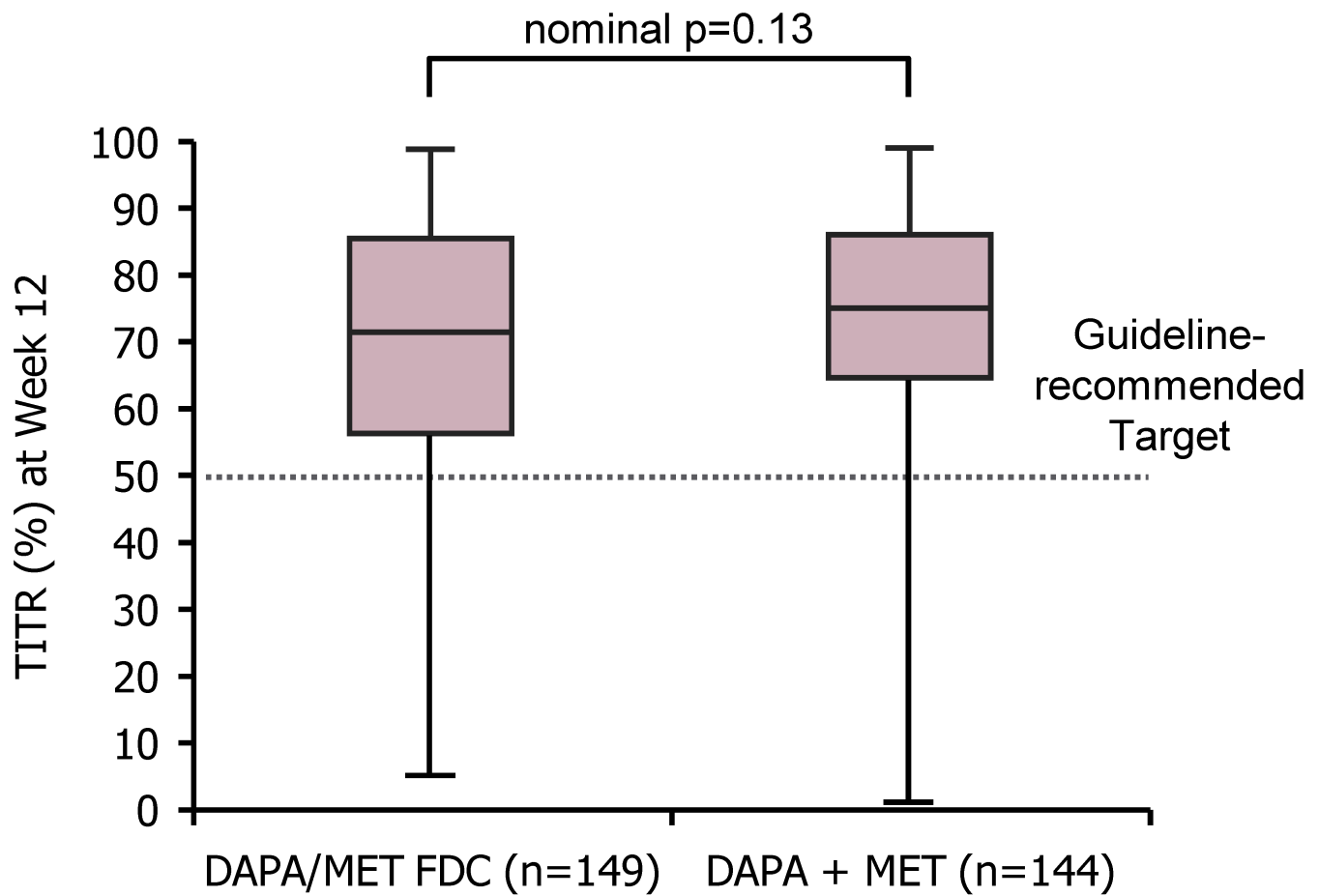


Figure 2

TITR at week 12. DAPA, dapagliflozin; FDC, fixed-dose combination; MET, metformin; TITR, time in tight target range.

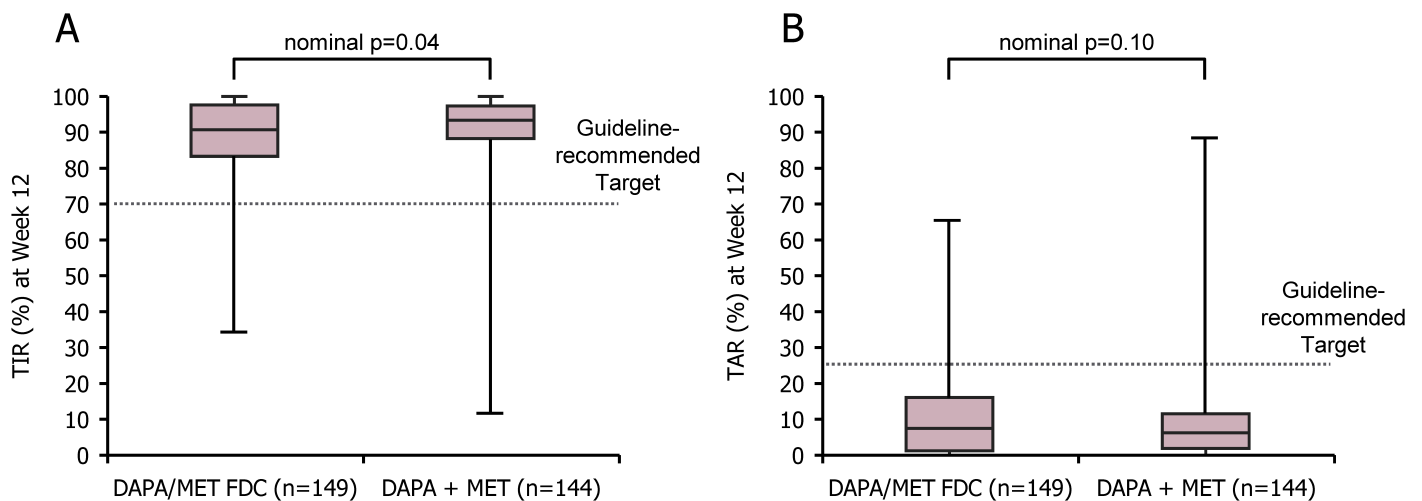


Figure 3

(A) TIR and **(B)** TAR at week 12. DAPA, dapagliflozin; FDC, fixed-dose combination; MET, metformin; TAR, time above range; TIR, time in range.

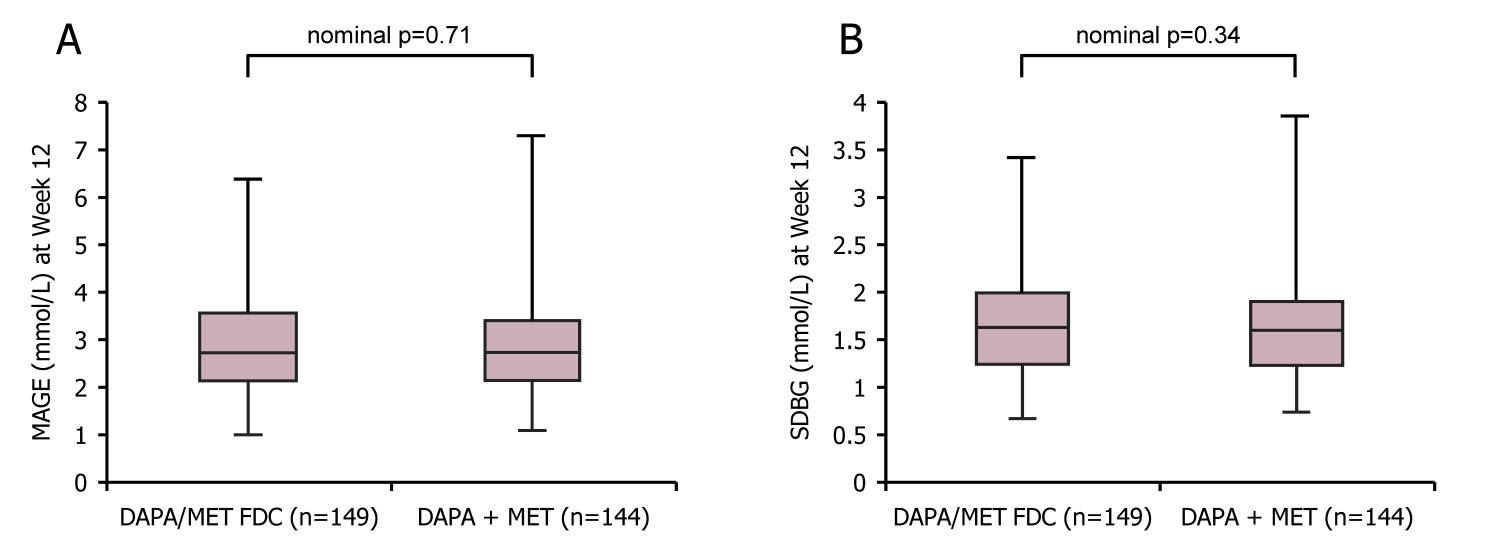


Figure 4

(A) MAGE and **(B)** SDBG at week 12. DAPA, dapagliflozin; FDC, fixed-dose combination; MAGE, mean amplitude of glycemic excursion; MET, metformin; SDBG, standard deviation of blood glucose.