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POSTPRANDIAL DYNAMICS OF PLASMA GLUCOSE, INSULIN, AND GLUCAGON IN PATIENTS WITH TYPE 2 DIABETES TREATED WITH SAXAGLIPTIN PLUS DAPAGLIFLOZIN ADD-ON TO METFORMIN THERAPY

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Running title: Saxagliptin plus dapagliflozin

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Abstract

Objective: To analyze changes in plasma glucose, insulin, and glucagon in relation to glycemic response during treatment with dual add-on of saxagliptin (SAXA) plus dapagliflozin (DAPA) to metformin XR (MET) compared with SAXA add-on or DAPA add-on alone to MET in patients with type 2 diabetes mellitus (T2DM) poorly controlled with MET.

Methods: Double-blind trial in adults with glycated hemoglobin (HbA1c) ≥8.0–≤12.0% randomized to SAXA 5 mg/d plus DAPA 10 mg/d (n=179), or SAXA 5 mg/d and placebo (n=176), or DAPA 10 mg/d and placebo (n=179) added to background MET ≥1500 mg/d. Mean change from baseline in the area under the curve from 0 to 180 minutes ($AUC_{0–180\ min}$) was calculated for glucose, insulin, and glucagon obtained during a liquid meal tolerance test (MTT).

Result: Glucose $AUC_{0–180\ min}$ was reduced more from baseline with SAXA+DAPA+MET (–12940 mg/dL) compared with SAXA+MET (–6309 mg/dL) and DAPA+MET (–11247 mg/dL). Insulin $AUC_{0–180\ min}$ significantly decreased with SAXA+DAPA+MET (–1120 µU/mL) and DAPA+MET (–1019 µU/mL) and increased with SAXA+MET (661 µU/mL). Glucagon $AUC_{0–180\ min}$ increased only with DAPA+MET (2346 pg/mL). Change in glucose (P<0.0001) and insulin (P=0.0003) $AUC_{0–180\ min}$ correlated with change in HbA1c whereas change in glucagon $AUC_{0–180\ min}$ did not (P=0.27).

Conclusion: When added to background MET, the combination of SAXA+DAPA provided additional reduction in glucose $AUC_{0–180\ min}$ and HbA1c without the increase in

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insulin seen with SAXA and without the increase in glucagon seen with DAPA. Change in insulin and glucose but not glucagon $AUC_{0–180\ min}$ correlated with change in HbA1c.

Key words: dapagliflozin, glucagon, glucose, insulin, saxagliptin, type 2 diabetes mellitus

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Introduction

We recently reported the results of a randomized, phase 3 clinical trial in which the concurrent addition of saxagliptin and dapagliflozin to metformin in patients with type 2 diabetes mellitus (T2DM) poorly controlled with metformin resulted in greater reductions in HbA1c than addition of each component alone without any increase in hypoglycemia or body weight.(1) Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that increases postprandial glucagon-like peptide-1 (GLP-1) concentrations which result in an increase in glucose-dependent insulin secretion and a reduction in glucagon secretion.(2) Dapagliflozin is an sodium-glucose cotransporter 2 (SGLT2) inhibitor that reduces plasma glucose concentrations independently of insulin secretion or action by increasing the renal excretion of glucose.(3) In patients with T2DM, saxagliptin and dapagliflozin improve glycemic control and are well tolerated when used as monotherapy (4-6) or as add-on therapy to other antidiabetic medications.(7-15)

A previous study investigating the effect of SGLT2 inhibition on counterregulatory hormones in patients with T2DM reported an increase in fasting glucagon. (16) Two recent exploratory studies demonstrated that sodium-glucose cotransporter 2 (SGLT2) inhibitors (dapagliflozin and empagliflozin) improve insulin sensitivity and β-cell function in individuals with T2DM.(17, 18) Although the SGLT2 inhibitors increased renal glucose excretion and decreased fasting plasma glucose, there was a paradoxical increase in endogenous hepatic glucose production. The authors speculated that the increase in glucose production was possibly the result of an increase in plasma glucagon that was observed in both studies.(17, 18) Because glucagon-like peptide-1 receptor agonists

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(GLP-1RA) and dipeptidyl peptidase-4 (DPP-4) inhibitors reduce plasma glucagon concentrations, (2) it was suggested that combination of a GLP-1RA or DPP-4 inhibitor with an SGLT2 inhibitor may suppress the increase in glucagon secretion induced by the SGLT2 inhibitor and enhance glycemic control.(18)

The objective of this analysis was to assess the changes in plasma glucose, insulin, and glucagon during a meal tolerance test (MTT) at baseline and after 24 weeks of treatment with dual add-on of saxagliptin plus dapagliflozin to metformin compared with saxagliptin add-on alone or dapagliflozin add-on alone to metformin in patients with poorly controlled T2DM receiving metformin monotherapy. The impact of these changes in glucoregulatory hormones on the glycemic response was also explored.

Methods

A detailed description of the study design and patient eligibility for this 24-week, randomized, double-blind, active-controlled, parallel-group phase 3 study (ClinicalTrials.gov identifier NCT01606007) has been previously published.(1) In brief, patients (≥18 years) with T2DM and glycated hemoglobin (HbA1c) ≥8.0% and ≤12.0% at screening, were eligible. Patients had to be on stable metformin therapy (≥1500 mg/d) for ≥8 weeks prior to screening and have C-peptide concentrations ≥1.0 ng/mL and body mass index ≤45.0 kg/m^2 at screening. Major exclusion criteria included pregnancy, uncontrolled hypertension (systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥100 mmHg) at randomization, fasting plasma glucose ≥270 mg/dL during the 4-week lead-in period, cardiovascular disease within 3 months of screening, congestive heart failure (NYHA class IV), estimated glomerular filtration rate

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<60 mL/min/1.73 m^2 or serum creatinine ≥1.5 mg/dL in men or ≥1.4 mg/dL in women, and significant hepatic disease. Patients were also excluded if they received any antidiabetic medication, other than metformin, for more than 14 days during the 12 weeks prior to screening.

At the beginning of a 4-week lead-in period, all patients were switched to the nearest metformin XR dose (1500–2000 mg/d) for the lead-in period and for the duration of the 24-week, double-blind treatment period. Patients were then randomized to receive saxagliptin 5 mg/d and dapagliflozin 10 mg/d plus metformin (SAXA+DAPA+MET), saxagliptin 5 mg/d and placebo plus metformin (SAXA+MET), or dapagliflozin 10 mg/d and placebo plus metformin (DAPA+MET) for 24 weeks. Patients were prohibited from receiving other antidiabetic medications (except for open-label rescue medications) during the screening and treatment periods.

Postprandial glucose (PPG) was assessed at baseline and week 24 following the administration of a liquid MTT (360–375 kcal; protein, 14–28.2 g; fat, 10.5–14 g; carbohydrates 42–45 g; sugars as a component of carbohydrates, 16.8–22 g, investigational-site dependent). The MTT was conducted before drug administration at baseline and 1 hour after drug administration at 24 weeks. Blood samples were drawn for the determination of glucose, insulin, and glucagon at time 0, 30, 60, 120, and 180 minutes. Mean change from baseline in the area under the curve from 0 to 180 minutes ($AUC_{0–180\ min}$) was calculated for glucose, insulin, and glucagon obtained during the MTT. Plasma insulin was measured by immunoassay (ADVIA Centaur XP

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Immunoassay System, Siemens Healthcare, Malvern, PA). Plasma glucagon was measured by radioimmunoassay (LINCO Research, St. Charles, MO).

Statistical analysis

Demographics and baseline characteristics for the randomized patients with valid MTT results at baseline and week 24 prior to rescue were summarized by treatment group. The baseline and week 24 plasma glucose, insulin, and glucagon concentrations during the MTT in patients with baseline HbA1c were summarized and plotted by time, treatment group, and baseline HbA1c. $AUC_{0-180\ min}$ was calculated based on the Trapezoidal rule from model-based estimates of the mean at each time point, including observations prior to rescue. Analysis of the mean change from baseline at 24 weeks in $AUC_{0-180\ min}$ for glucose, insulin, and glucagon obtained during the MTT, was performed using a longitudinal repeated-measures analysis with terms for baseline value, treatment group, time, the interaction of treatment group and time, and the interaction of baseline value and time. Point estimates and 95% CI were calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups. To assess the correlation of changes in HbA1c versus changes in $AUC_{0-180\ min}$ for glucose, insulin, and glucagon at 24 weeks, changes in HbA1c versus changes in fasting glucagon concentrations, and baseline fasting glucagon concentrations or glucagon $AUC_{0-180\ min}$ with baseline HbA1C post-hoc regression analyses were performed. The regression model included fixed effects of treatment and changes in $AUC_{0-180\ min}$ for glucose, insulin, and glucagon at 24 weeks,

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fasting glucagon concentrations, baseline fasting glucagon concentrations, or glucagon $AUC_{0–180\ min}$. No multiplicity control was applied.

RESULTS

A total of 466 of 534 (87%) randomized patients provided MTT data. Equal numbers of men and women participated in the MTT, and were predominantly white, with a mean age of 55 years. Mean duration of type 2 diabetes was approximately 7.5 years and mean baseline HbA1c was 8.92% **(Table 1)**. Patient demographics and baseline characteristics were balanced across treatment groups.

As previously reported,(1) the primary end point, adjusted mean (±SE) change from baseline in HbA1c at 24 weeks, was reduced to a significantly greater extent with SAXA+DAPA+MET (–1.47±0.08%) than with SAXA+MET (–0.88±0.08%, $P<0.0001$) or DAPA+MET (–1.20±0.08%, $P=0.017$).

At baseline, the time course (0–180 min) of PPG, insulin, and glucagon concentrations were similar among the 3 treatment groups during the MTT **(Figure 1A–C)**. After 24 weeks of treatment, PPG was reduced for all time points across all 3 treatment groups versus baseline values. During the MTT, PPG was reduced more after treatment with SAXA+DAPA+MET than with SAXA+MET and to a similar degree compared with DAPA+MET **(Figure 1D)**. Insulin decreased to a similar extent in the SAXA+DAPA+MET and DAPA+MET groups whereas it increased in the SAXA+MET group **(Figure 1E)**. Glucagon increased in the DAPA+MET group but decreased in the SAXA-containing treatment groups **(Figure 1F)**.

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All 3 treatment groups had reductions in post-MTT (0–180 min) glucose $AUC_{0–180\ min}$ after 24 weeks of treatment **(Figure 2A)**. Adjusted mean change (95% CI) from baseline in glucose $AUC_{0–180\ min}$ was reduced more with SAXA+DAPA+MET (–12,940 mg/dL [–14,095, –11,785]) compared with SAXA+MET (–6309 mg/dL [–7490, –5127]) and DAPA+MET (–11,247 mg/dL [–12,444, –10,050]). The reduction in glucose $AUC_{0–180\ min}$ for the SAXA+DAPA+MET treatment group was observed in the presence of a significantly decreased adjusted mean change from baseline in insulin $AUC_{0–180\ min}$ (–1120 µU/mL [–1634, –607]) **(Figure 2B)** and no change in glucagon $AUC_{0–180\ min}$ (–289 pg/mL [–1191, 613]) **(Figure 2C)**. Treatment with SAXA+MET was associated with a significant mean adjusted increase from baseline in insulin $AUC_{0–180\ min}$ (661 µU/mL [131, 1191]) and no change in glucagon $AUC_{0–180\ min}$ (–415 pg/mL [–1355, 525]). The reduction in glucose $AUC_{0–180\ min}$ after DAPA+MET treatment was observed in the presence of a significant adjusted mean reduction from baseline in insulin $AUC_{0–180\ min}$ (–1019 [–1550, –487]) and a significant adjusted mean increase in glucagon $AUC_{0–180\ min}$ (2346 pg/mL [1417, 3276]).

Analysis of the differences between SAXA+MET and DAPA+MET was not prespecified for this study. However, the directionally different changes in glucagon and insulin AUCs with SAXA+MET vs DAPA+MET, respectively, and the clear separation of the 95% CIs for all 3 parameters suggest that the changes observed with SAXA+MET differ from those with DAPA+MET.

As observed in the whole patient population, the time course (0–180 min) of PPG, insulin, and glucagon concentrations during the MTT at baseline and after 24 weeks of

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treatment were similar among the 3 treatment groups when patients were stratified by baseline HbA1c **(Figures 3–5)**.

Analysis of glucose, insulin, and glucagon $AUC_{0–180\ min}$ change from baseline during an MTT over a broad range of baseline HbA1c subgroups **(Figure 6)** did not change the interpretation of the primary analysis.

To explore the correlation of changes in HbA1c with changes in the $AUC_{0–180\ min}$ for glucose, insulin, and glucagon during treatment, linear regression models showed that changes in glucose $AUC_{0–180\ min}$ (P<0.0001) and insulin $AUC_{0–180\ min}$ (P=0.0003) had significant effects on changes in HbA1c. However, neither changes in glucagon $AUC_{0–180\ min}$ (P=0.27) nor changes in fasting glucagon concentrations (P=0.71) had a significant impact on changes in HbA1c. Furthermore, before treatment (baseline), neither fasting glucagon (P=0.82) nor glucagon $AUC_{0–180\ min}$ (P=0.81) correlated with HbA1c.

Discussion

This study provides confirmation of the pharmacodynamic effects of saxagliptin as an inhibitor of DPP-4 (incretin enhancer) and dapagliflozin as an inhibitor of SGLT2, as well as new insights into the pharmacodynamic effects of their combination in patients with T2DM. In agreement with the previously reported significant improvements in HbA1c (1), all 3 treatment groups had reductions in glucose $AUC_{0–180\ min}$ following an MTT after 24 weeks of treatment. The reduction in glucose $AUC_{0–180\ min}$ for the SAXA+MET

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treatment group was observed in the presence of an increased insulin $AUC_{0–180\ min}$ and a decreased glucagon $AUC_{0–180\ min}$, confirming that saxagliptin as a DPP-4 inhibitor improves glycemic control by both glucose-dependent stimulation of insulin secretion and suppression of glucagon secretion.(2) On the other hand, the reduction in glucose $AUC_{0–180\ min}$ in the DAPA+MET treatment group was observed in the presence of a reduction in insulin $AUC_{0–180\ min}$, consistent with the insulin-independent mechanism of action of dapagliflozin and other SGLT2 inhibitors.(19) The changes in glucose, insulin, and glucagon during the MTT occurred in patients with a broad range of baseline HbA1c and did not change the primary interpretation of the results.

The previously reported increase in fasting plasma glucagon in small mechanistic studies after 12 weeks (16) and postprandial plasma glucagon concentration in response to 2 (18) or 4 weeks(17) of treatment with SGLT2 inhibitors was confirmed for the first time in a large clinical study. In the DAPA+MET treatment group, but not in the SAXA+DAPA +MET group, post-MTT glucagon $AUC_{0–180\ min}$ increased after 24 weeks of treatment. The suppression of postprandial glucagon with SAXA+DAPA+MET treatment suggests that DPP-4 inhibition, when used in combination with dapagliflozin, prevented SGLT2-inhibitor–associated hyperglucagonemia. This mechanism and the associated greater reduction in glucose $AUC_{0–180\ min}$ may, in part, account for the greater improvement in HbA1c observed with SAXA+DAPA+MET compared with the other treatment groups.(1)

The regulation of glucagon secretion is complex and involves the direct and indirect action of nutrients, hormones, and neurotransmitters on the α-cells of the pancreas.(20)

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The mechanism(s) by which SGLT2 inhibitors increase glucagon secretion is not known. A recent preliminary report found the expression of the genes for SGLT1 and SGLT2 in human pancreatic tissue and in purified human α-cells. (21) Moreover, dapagliflozin or selective siRNA knockdown of SGLT2 in cultured α-cells and human islets stimulated glucagon gene expression and secretion. This observation, if confirmed, may provide one basis for SGLT2-inhibitor-induced glucagon secretion. However, glucagon regulation is complex and several organ systems may be involved.(22, 23) Thus, further studies are needed.

The profile of the changes from baseline at 24 weeks in glucose $AUC_{0–180\ min}$ was similar to the profile of HbA1c changes previously reported (eg, SAXA+DAPA+MET > DAPA+MET . SAXA+MET).(1) In a post-hoc analysis, we found that changes in both glucose $AUC_{0–180\ min}$ and insulin $AUC_{0–180\ min}$ during the MMT were associated with changes in HbA1c during the study. In contrast, neither changes in fasting glucagon nor changes in glucagon $AUC_{0–180\ min}$ had an independent effect on HbA1c changes. It is generally recognized that the consistent finding of both fasting hyperglucagonemia as well as lack of postprandial suppression of glucagon in patients with T2DM, through an effect on increased hepatic glucose production, may contribute to the pathogenesis of impaired glucose tolerance and T2DM. (22, 23) Far less is known about the contribution to glycemic control of relative variations in baseline and posttreatment differences in glucagon. In the present study, we did not find a correlation between baseline or posttreatment glucagon with baseline HbA1c or HbA1c change. This is also consistent with the extensive glucose-lowering effect of dapagliflozin observed in this study, despite a 10% increase in glucagon concentration during the MTT.

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This study was limited by the absence of a placebo group. In addition, the analysis of the impact of changes in glucose, insulin, and glucagon $AUC_{0–180\ min}$ on changes in HbA1c was post hoc in nature and can only be hypothesis generating.

In conclusion, we have confirmed in a large group of patients with T2DM poorly controlled with metformin that the SAXA+DAPA combination provided additional reduction in glucose $AUC_{0–180\ min}$ and HbA1c without the increase in insulin seen with saxagliptin and without the increase in glucagon seen with dapagliflozin. This study provides new insights into the pharmacodynamic effects of the combination of saxagliptin and dapagliflozin on glucoregulatory hormones in patients with T2DM.

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Some of the data from this study were presented at the American Diabetes Association 74th Scientific Sessions, June 13 -–17, 2014, San Francisco, CA and the 50th European Association for the Study of Diabetes Annual Meeting, September 15–19, 2014, Vienna, Austria.

Conflicts of Interest:

Drs. Hansen and Iqbal are full-time employees of Bristol-Myers Squibb. Drs. Ekholm, Cook, and Hirshberg are full-time employees of AstraZeneca.

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Table 1. Demographics and baseline characteristics

	Saxagliptin + dapagliflozin + metformin	Saxagliptin + metformin	Dapagliflozin + metformin	Total
n	160	154	152	466
Age, y	54 (9.9)	55 (9.5)	54 (9.6)	54 (9.7)
Women,	86 (54)	71 (46)	79 (52)	236 (51)
Race				
White	106 (66)	104 (68)	108 (71)	318 (68)
African American	17 (11)	18 (12)	15 (10)	50 (11)
Asian	12 (8)	10 (7)	10 (7)	32 (7)
Other	25 (16)	22 (14)	19 (13)	66 (14)
Weight, kg	86 (17.9)	88 (18.9)	86 (18.6)	87 (18.4)
BMI, kg/m^2	32 (4.8)	32 (5.2)	31 (5.4)	32 (5.1)
Duration of diabetes, y	7.2 (5.0)	8.0 (5.3)	7.4 (5.3)	7.5 (5.2)
HbA1c, %	8.97 (1.19)	8.96 (1.07)	8.84 (1.13)	8.92 (1.13)
FPG, mg/dL	181 (46.3)	191 (46.6)	184 (46.6)	185 (46.6)
120 min-PPG, mg/dL	243 (55.7)	256 (64.3)	246 (56.7)	248 (59.1)
Fasting C-peptide, ng/mL	2.2 (0.93)	2.1 (0.89)	2.2 (1.05)	2.2 (0.96)
eGFR, mL/min/1.73m^2	96.0 (17.8)	92.5 (19.3)	92.9 (19.5)	93.8 (18.9)

Data are mean (SD) or n (%). BMI=body mass index; eGFR=estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease (MDRD) formula;

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FPG=fasting plasma glucose; HbA1c=glycated hemoglobin; PPG=postprandial plasma glucose.

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Figure Legends

Figure 1. **Baseline and week 24 means (SE) for plasma (A, D) glucose, (B, E) insulin, and (C, F) glucagon concentrations during an MTT.** DAPA=dapagliflozin; MET=metformin; MTT=meal tolerance test; SAXA=saxagliptin.

Figure 2. Adjusted mean change from baseline in AUC 0 to 180 minutes for (A) glucose, (B) insulin, and (C) glucagon at 24 weeks during an MTT.
DAPA=dapagliflozin; MET=metformin; MTT=meal tolerance test; SAXA=saxagliptin.

Figure 3. Baseline and week 24 means (SE) for plasma (A, D) glucose, (B, E) insulin, and (C, F) glucagon concentrations during an MTT in patients with baseline HbA1c <8%. DAPA=dapagliflozin; HbA1c=glycated hemoglobin; MET=metformin; MTT=meal tolerance test; SAXA=saxagliptin.

Figure 4. **Baseline and week 24 means (SE) for plasma (A, D) glucose, (B, E) insulin, and (C, F) glucagon concentrations during an MTT in patients with baseline HbA1c ≥8% and <9%.** DAPA=dapagliflozin; HbA1c=glycated hemoglobin; MET=metformin; MTT=meal tolerance test; SAXA=saxagliptin.

Figure 5. Baseline and week 24 means (SE) for plasma (A, D) glucose, (B, E) insulin, and (C, F) glucagon concentrations during an MTT in patients with baseline HbA1c ≥9%. DAPA=dapagliflozin; HbA1c=glycated hemoglobin; MET=metformin; MTT=meal tolerance test; SAXA=saxagliptin.

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Figure 6. **Adjusted mean change from baseline in AUC 0 to 180 minutes for (A) glucose, (B) insulin, and (C) glucagon at 24 weeks during an MTT in patients with baseline HbA1C of <8%, ≥8% and <9%, and ≥9%.** DAPA=dapagliflozin; HbA1c=glycated hemoglobin; MET=metformin; MTT=meal tolerance test; SAXA=saxagliptin.

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Figure 1.

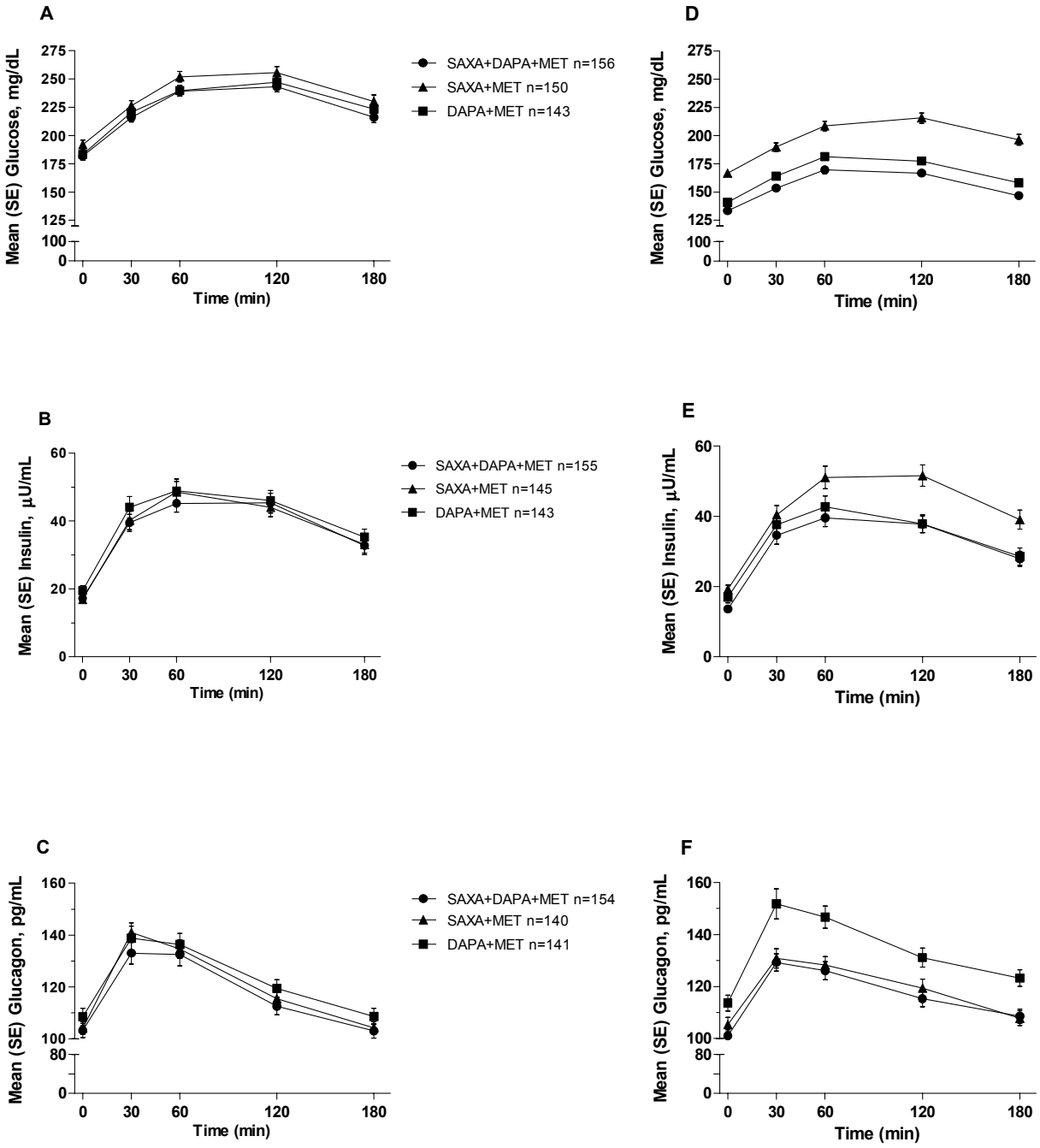

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Figure 2.

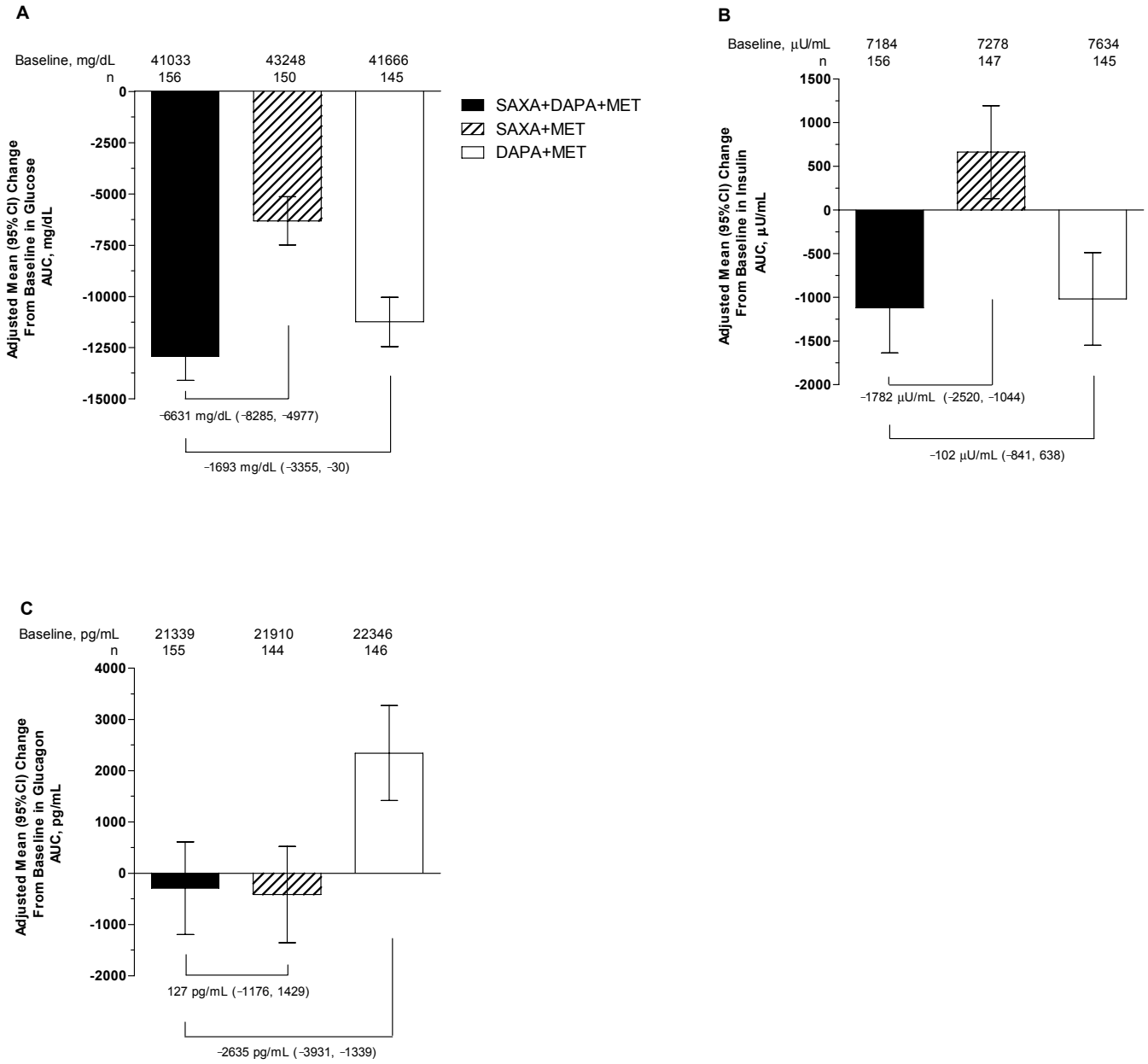

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Figure 3.

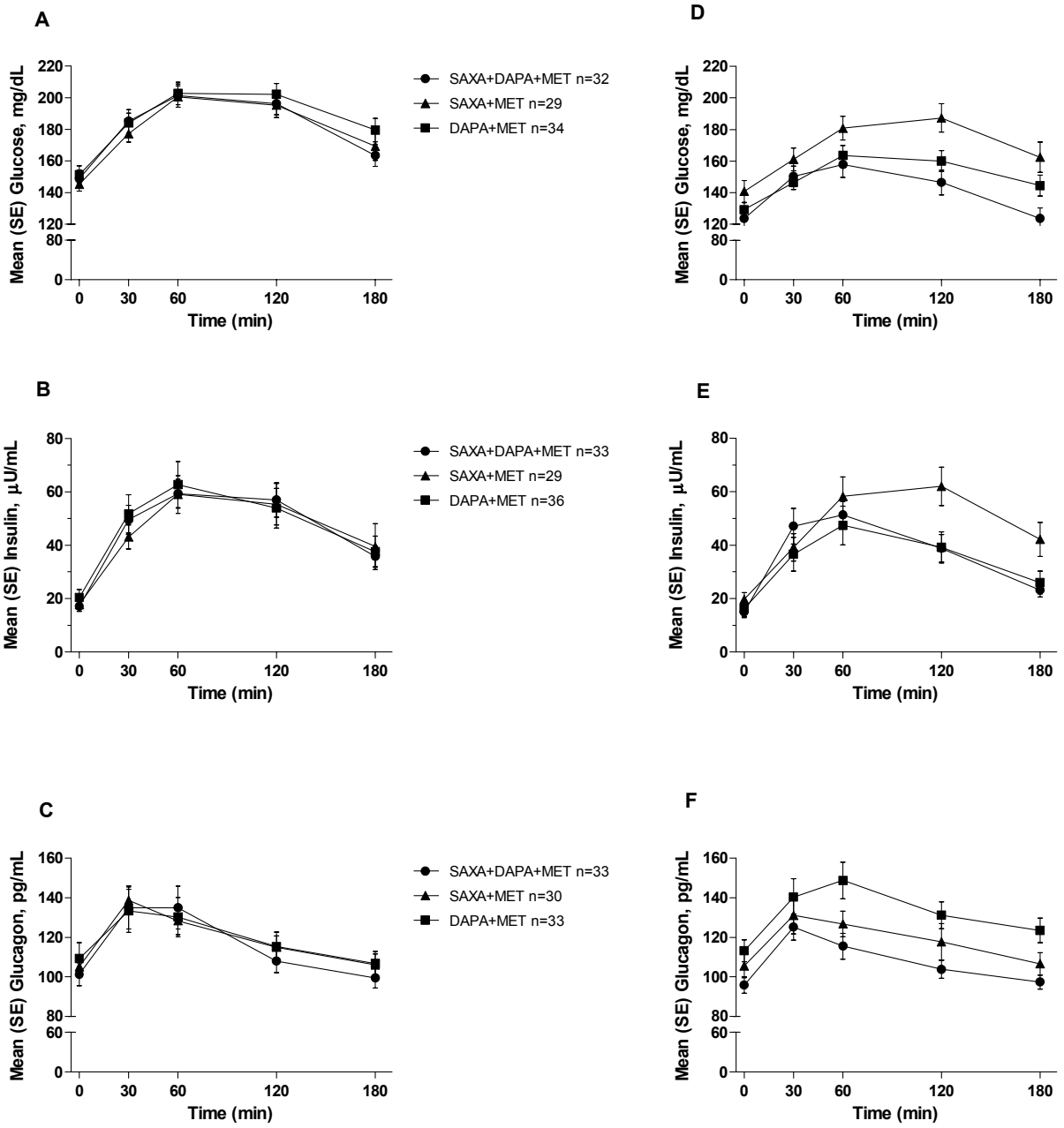

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Figure 4.

DOI:10.4158/EP14489.OR

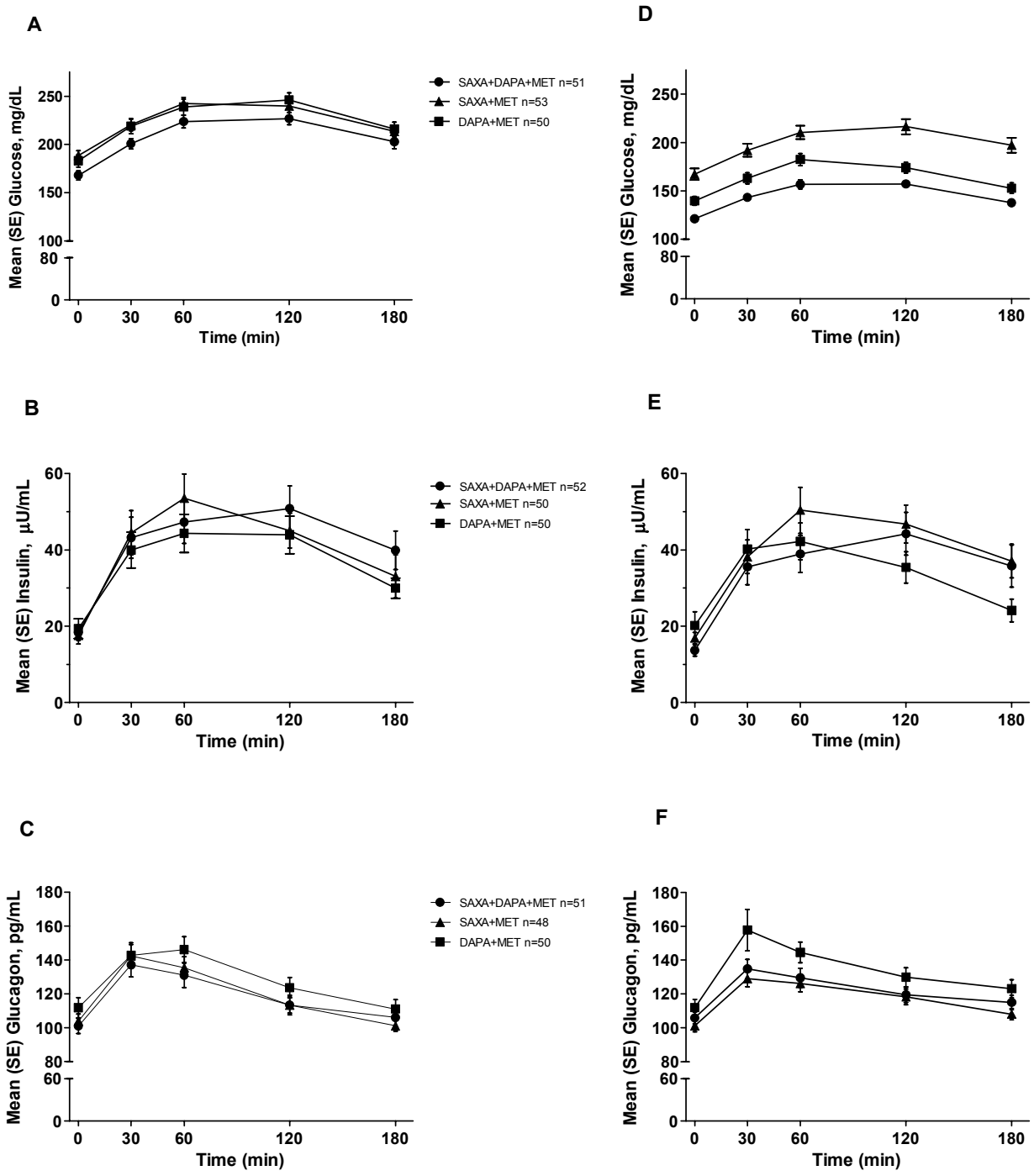

Figure 5.

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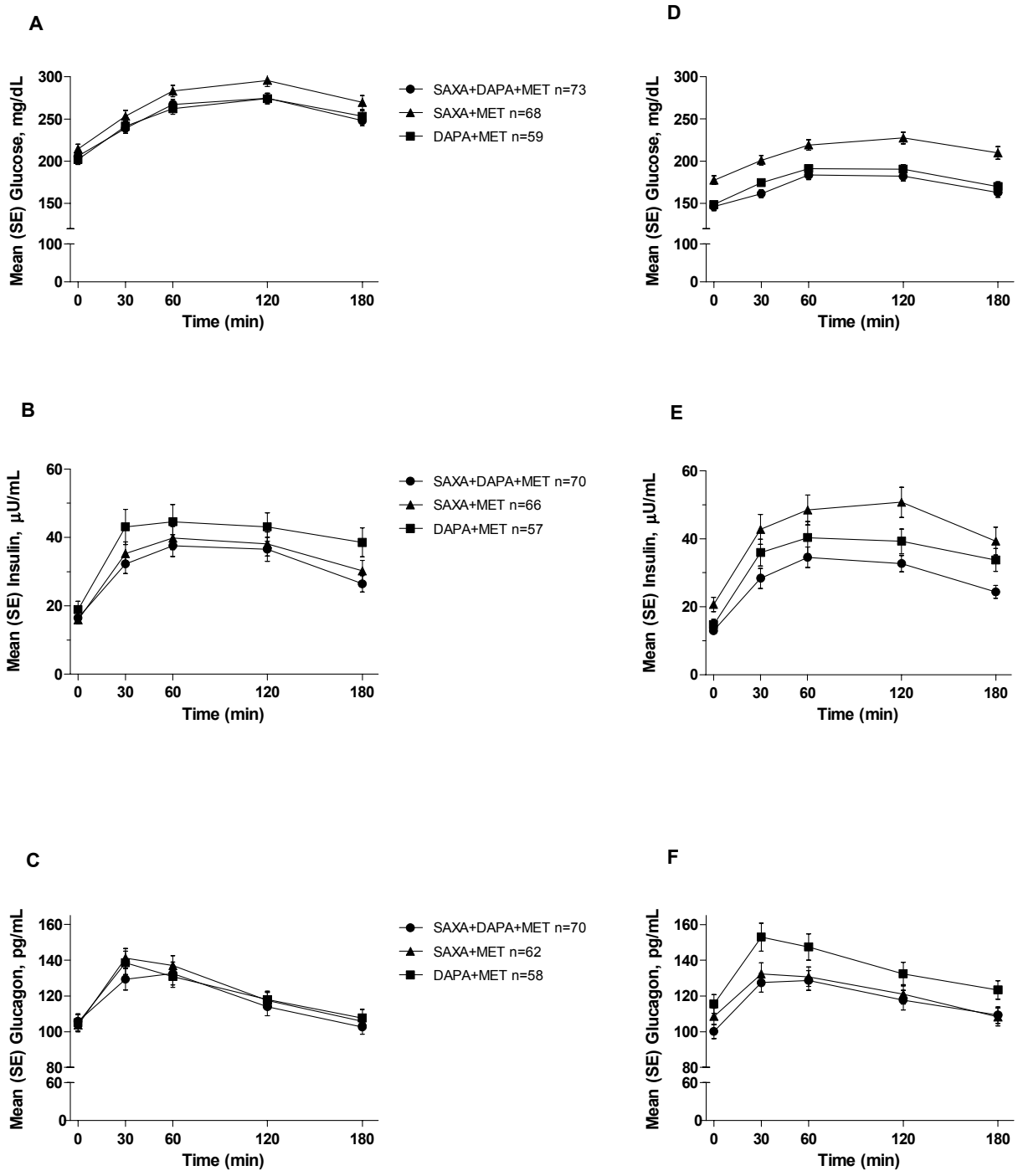

Figure 6.

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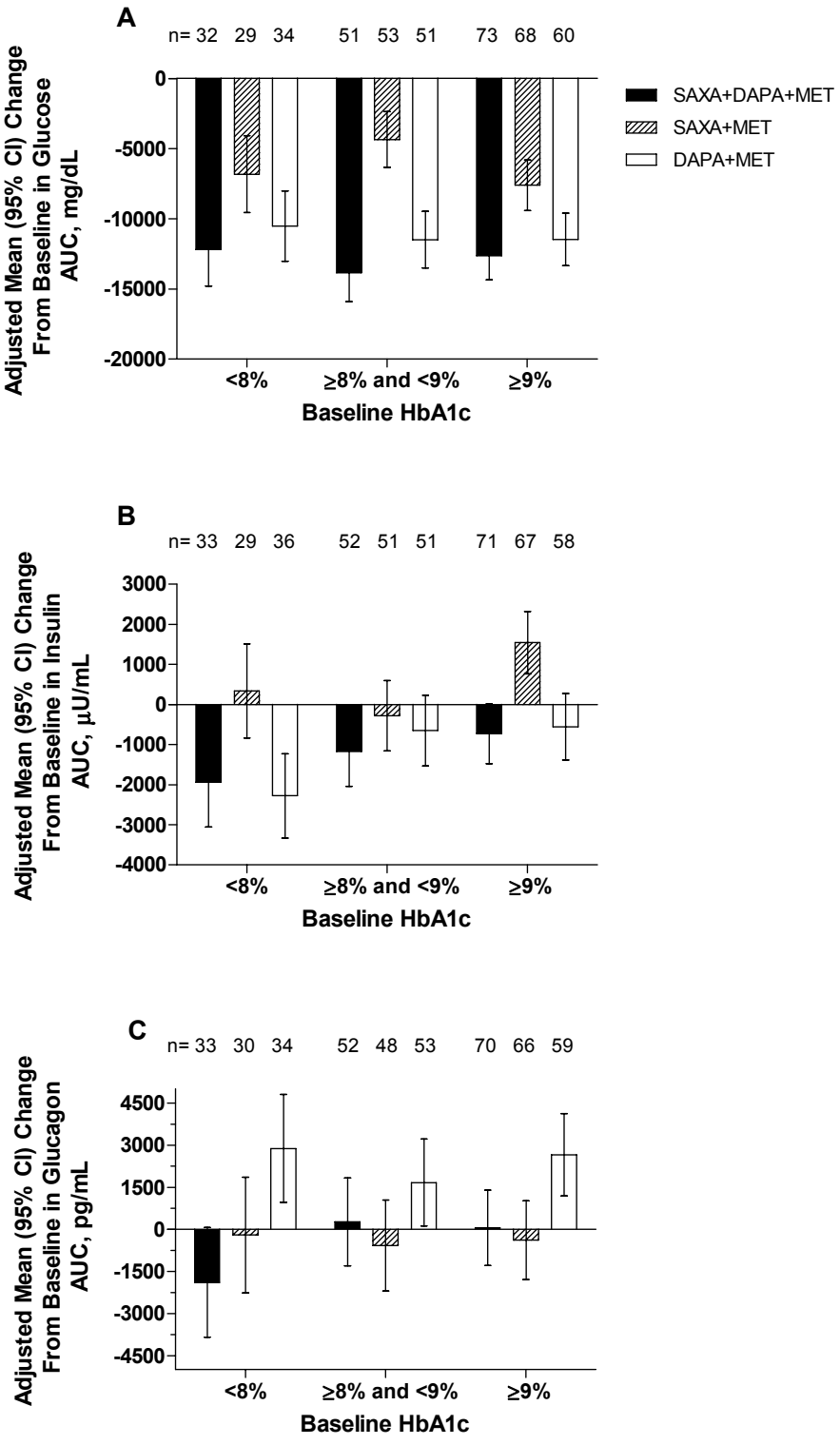

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