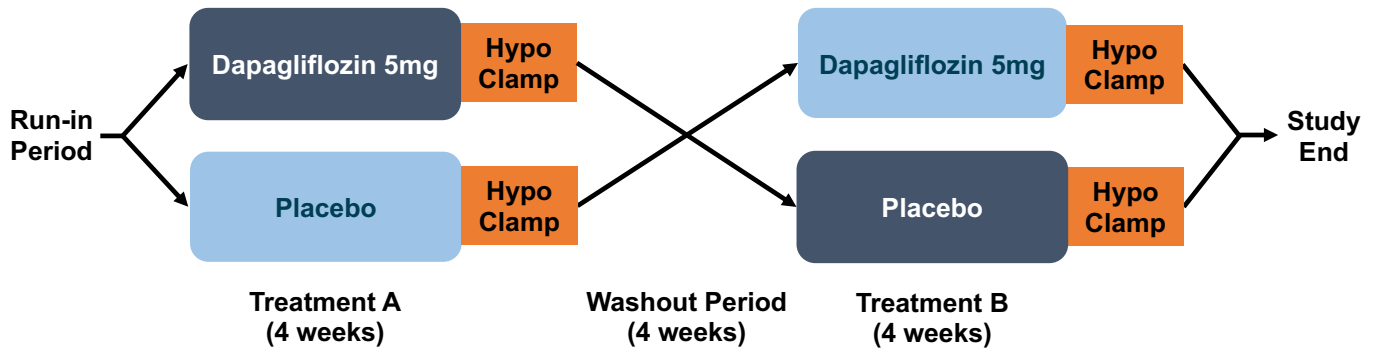


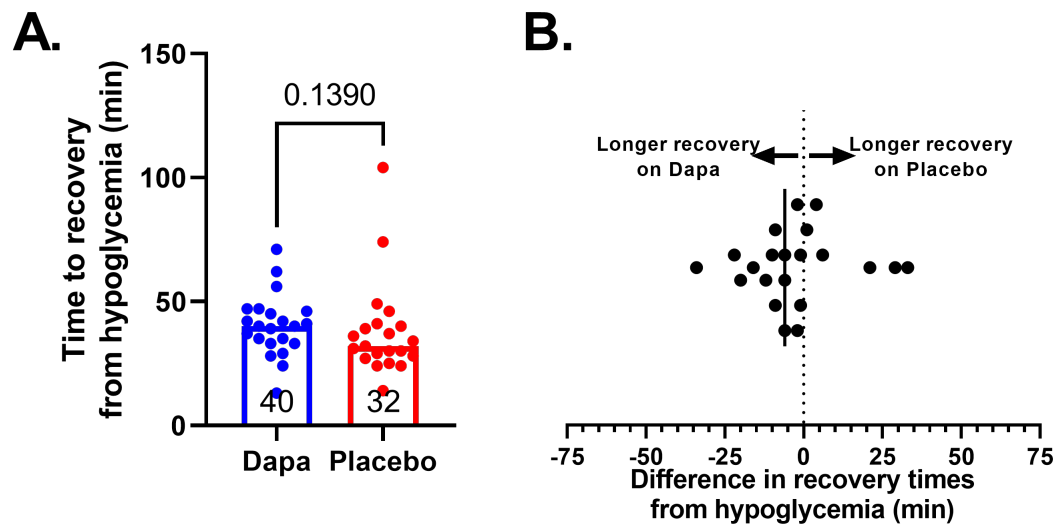
## Online-Only Supplemental Material

### SGLT2 Inhibition Increases Fasting Glucagon but Does Not Restore the Counterregulatory Hormone Response to Hypoglycemia in Participants with Type 1 Diabetes

Schafer C. Boeder, Justin M. Gregory, Erin R. Giovannetti, Jeremy H. Pettus

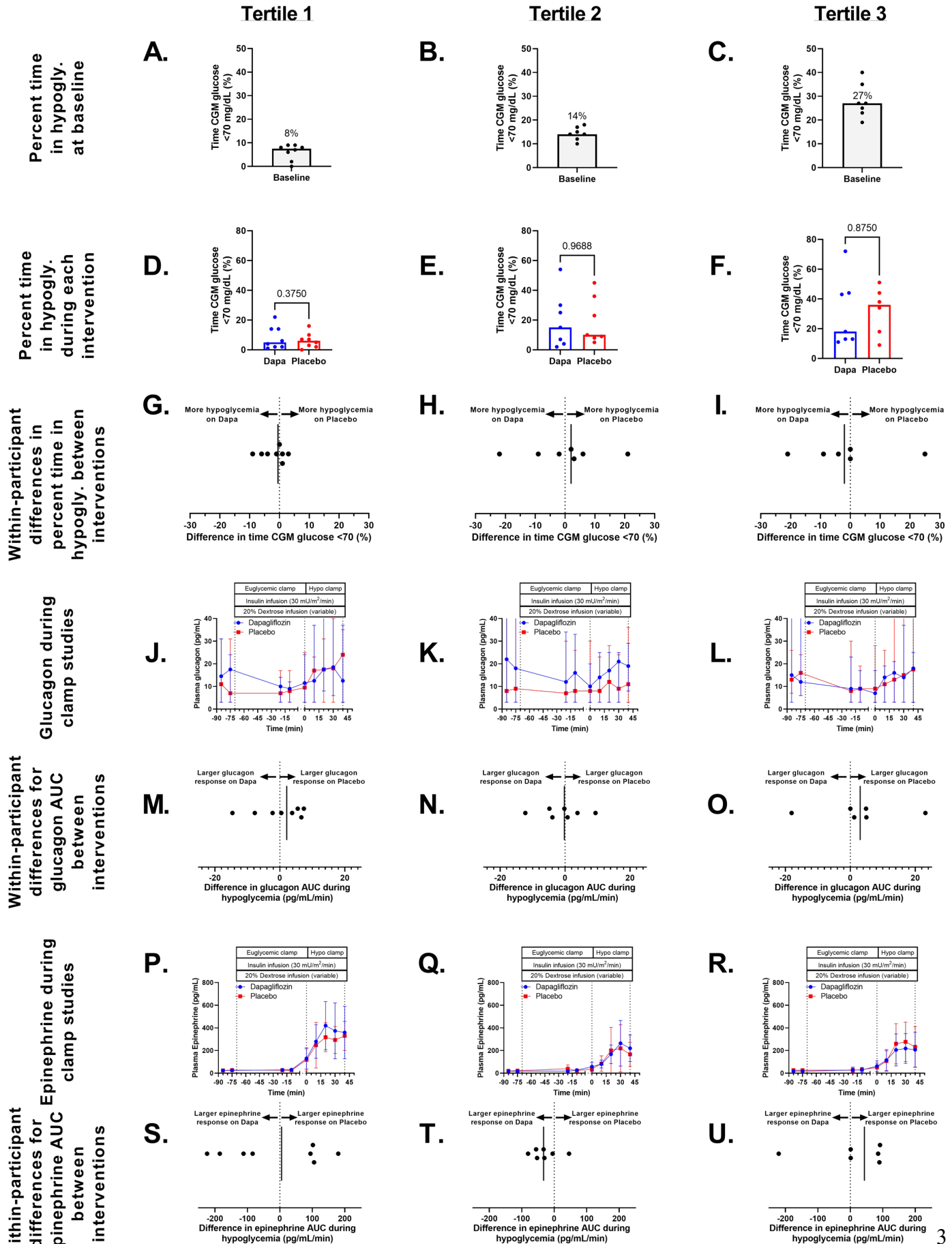


Supplemental figure 1: Crossover study design. After the run-in period, participants were randomized 1:1 in a double-blind fashion to receive either dapagliflozin 5 mg daily or placebo for 4 weeks (Treatment A). At the end of Treatment A, participants completed a staged euglycemia-hypoglycemia clamp procedure, and then entered a four-week washout period during which they received no study drug. At the end of washout, participants crossed over into Treatment B to receive either placebo (if they received dapagliflozin during Treatment A) or dapagliflozin 5 mg (if they received placebo during Treatment A). At the end of Treatment B, participants underwent a second hypoglycemic clamp procedure.



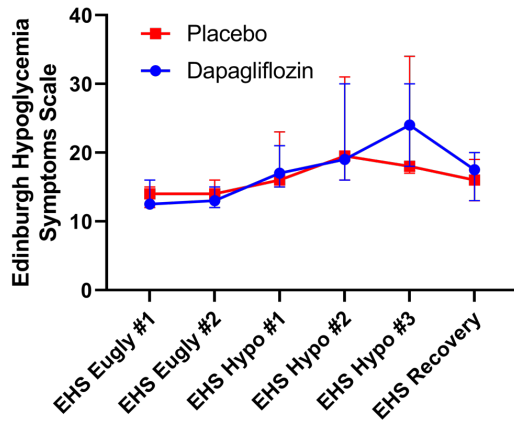
Supplemental figure 2: A) Differences in the time needed for plasma glucose concentration to rise from hypoglycemic level of the clamp to a level  $\geq 70$  mg/dL for dapagliflozin (blue circles) versus placebo (red circles). Median values are annotated within each column and are represented by the bar. Dots depict individual values for each participant. P-values determined by Wilcoxon match-pairs signed rank tests are indicated above brackets. B) Within-participant differences (placebo minus dapagliflozin) for recovery time from hypoglycemia. The black vertical line signifies the median difference for the entire study cohort.

## Tertiles for time CGM glucose <70 mg/dL prior to randomization

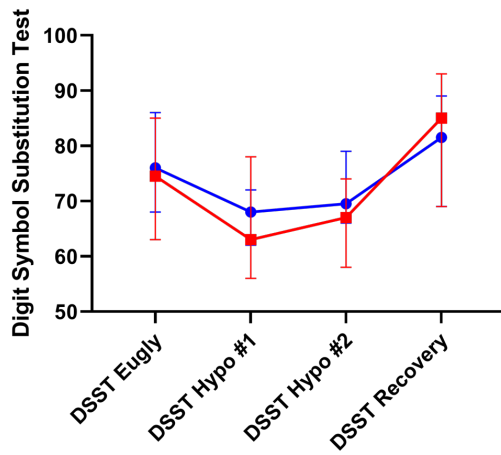


Supplemental figure 3: Subgroup analysis of counterregulatory hormone response to hypoglycemia. Subgroups are arranged in columns by tertile of CGM percent time in hypoglycemia immediately prior to enrollment (i.e., CGM glucose < 70 mg/dL). Rows are arranged by parameter of interest: Percent time in hypoglycemia immediately prior to enrollment (A-C), percent time in hypoglycemia during each intervention (D-F), within-participant differences (placebo minus dapagliflozin) for percent time in hypoglycemia (G-I), arterialized plasma glucagon concentrations during hypoglycemic clamp studies (J-L), within-participant differences for glucagon area under the curve (AUC) between interventions (M-O), arterialized plasma epinephrine concentrations during hypoglycemic clamp studies (P-R), within-participant differences for epinephrine AUC between interventions (S-U). Data are summarized as medians and 95% confidence intervals in J-L and P-R. Black vertical lines signify the median differences for the entire study cohort in G-I, M-O, and S-U.

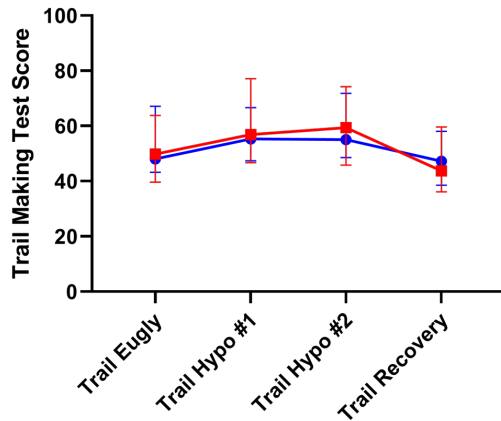
**A.**



**B.**



**C.**



Supplemental figure 4: A) Hypoglycemia symptoms as assessed by the Edinburgh Hypoglycemia Symptoms Scale and Cognitive function quantified by the Digit Symbol Substitution Test (B) and Trail Making Test Score (C) during hyperinsulinemic hypoglycemic clamp studies after four weeks of placebo (red squares) or dapagliflozin (dapa, blue circles) in the crossover study. Data are summarized as medians and 95% confidence intervals.