Randomized open-label trial of semaglutide and dapagliflozin in patients with type 2 diabetes of different pathophysiology

Chinmay Dwibedi[1,2,7], Ola Ekström[3,7], Jasmine Brandt[4,5,7], Martin Adiels[2], Stefan Franzén[2,6], Birgitta Abrahamsson[1], Anders H. Rosengren[1]

Introduction

- Treatment responses to glucose-lowering drugs vary widely, motivating more personalized therapy.
- Diabetes “clusters” such as SIDD (severe insulin-deficient) and SIRD (severe insulin-resistant) have been proposed, but their value for predicting drug response is uncertain.
- This trial tested whether subgrouping vs. continuous clinical measures better predicts response to semaglutide (GLP-1RA) or dapagliflozin (SGLT2i)

Methods

- Open-label, randomized, 6-month add-on study: semaglutide vs. dapagliflozin on background metformin in type 2 diabetes with SIDD or SIRD features (n=239).
- **Primary endpoint:** change in HbA1c; secondary endpoints included fasting/postprandial glucose, insulin secretion/sensitivity, BMI, CGM metrics.
- Full analysis set included 220 participants with ≥1 post-randomization HbA1c value

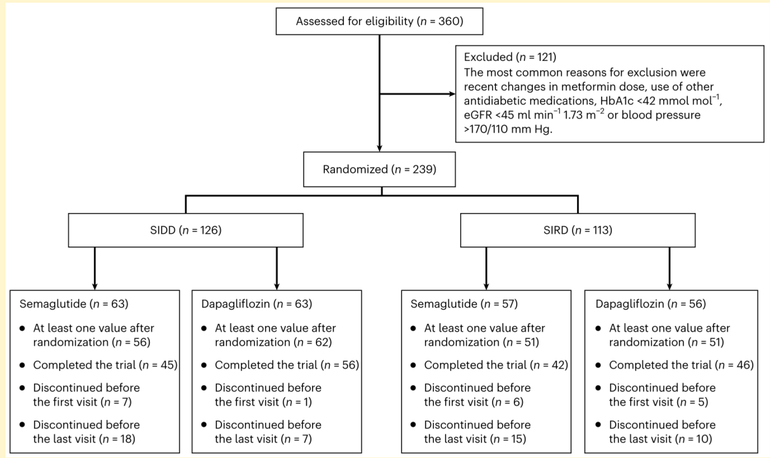

Fig. 1. Study profile shown as a CONSORT diagram.

Results

- **Glycemic efficacy:** Semaglutide lowered HbA1c more than dapagliflozin (mean difference 8.2 mmol/mol; 95% CI −10.0 to −6.3).
- **Subgroups:** Effects were numerically larger in SIDD than SIRD, but the treatment-by-subgroup interaction was not significant.
- **Secondary outcomes:** Semaglutide improved fasting/postprandial glycemia and BMI more; dapagliflozin improved HOMA2-IR more.
- **Predictors:** Continuous measures (baseline HbA1c, insulin secretion, fasting glucose, time-in-range, etc.) predicted response better than SIDD/SIRD labels.
- **Safety:** No AE differences between SIDD and SIRD; semaglutide commonly caused GI effects (some dose reductions), while urinary symptoms were more frequent with dapagliflozin.

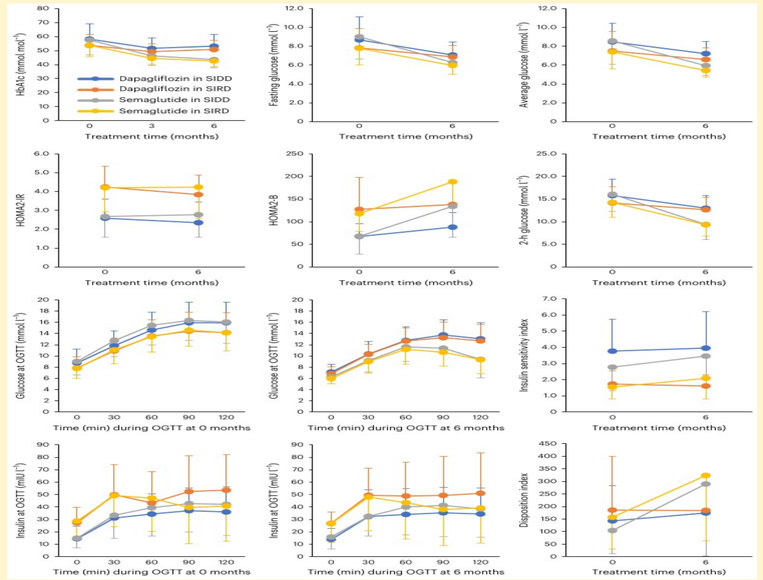

Fig. 2. Changes over time in fasting and postprandial measures.

Discussion

- Cluster-based stratification (SIDD/SIRD) did not modify treatment effect; using continuous baseline traits is more informative for tailoring add-on therapy.
- Patients with higher HbA1c/fasting & postprandial glucose and lower insulin secretion tend to derive larger glycemic benefit from semaglutide
- Patients with higher HbA1c/BMI/blood pressure (and, relatively, higher insulin secretion/high time-in-range) show stronger relative or composite improvements with dapagliflozin.

[1]Department of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden. [2]Institute of Medicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden. [3]Department of Clinical Sciences, Diabetes and Endocrinology, Lund University, Malmö, Sweden. [4]Department of Clinical Chemistry and Pharmacology, Skåne University Hospital, Lund, Sweden. [5]Clinical Studies Sweden, Forum South, Skåne University Hospital, Lund, Sweden. [6]AstraZeneca, Gothenburg, Sweden. [7]These authors contributed equally: Chinmay Dwibedi, Ola Ekström, Jasmine Brandt. e-mail: anders.rosengren@gu.se