Congress Updates - October 04, 2023

Hypoglycaemia remains a key barrier to achieve glycaemic control in patients with diabetes and it induces a sustained inflammatory response in this patient population irrespective of the type of diabetes

People with type 1 diabetes (T1D) and type 2 diabetes (T2D) on insulin often suffer from hypoglycaemia, and if severe it is associated with increased risks of cardiovascular (CV) mortality and morbidity.[1-3] The project including 8 different sub-studies aimed to bridge the gaps in our understanding of hypoglycaemia to ultimately reduce the burden and consequences of hypoglycaemia through a comprehensive, multi-level, multi-disciplinary approach in patients with diabetes. The second sub-study conducted in humans involved 96 participants with diabetes (T1D, T2D) and without diabetes (control group). It was observed that hypoglycaemia caused an increase in monocyte count, cytokine production, inflammatory proteins and shift towards a non-classic monocyte phenotype.[4,5] This inflammatory response sustained over a week and was equally observed in volunteers irrespective of the type of diabetes.

Presented by de Galan BE (Netherlands). Introduction to the project and hypoglycaemia in CVD

Sensor-detected hypoglycaemia (SDH) does not necessarily align with the person-reported hypoglycaemia (PRH)

The Hypo-METRICS study was a multinational multicenter observational study within the Hypo-RESOLVE consortium including adults on insulin with at least 1 episode of symptomatic hypoglycemia in last 3 months (277 patients with T1D and 325 patients with T2D). Participants used a blinded continuous glucose monitoring (CGM) while maintaining their regular glucose monitoring routine. Instances of PRH were documented in real-time using the Hypo-METRICS smartphone application. The Fitbit Charge 4 recorded sleep patterns, enabling the evaluation of hypoglycemia's impact on sleep quality. Most episodes (65%) of SDH lacked noticeable symptoms, and among those with symptoms, many (43%) occurred at glucose >3.9 mmol/L (>70 mg/dL). Asymptomatic episodes do not cause noticeable declines in overall well-being.

Presented by Choudhary P (UK). Understanding the impact of symptomatic and asymptomatic hypoglycaemia: The Hypo-METRICS study

International Hypoglycaemia Study Group (IHSG) re-classified hypoglycaemia as hypoglycaemia alert [Plasma glucose (PG): <3.9 mmol/L (70 mg/dL)], serious/clinically important hypoglycaemia [PG: <3.0 mmol/L (54 mg/dL)] and severe hypoglycaemia (severe cognitive impairment requiring external assistance for recovery)

IHSG re-classified hypoglycaemia as hypoglycaemia alert [PG: <3.9 mmol/L (70 mg/dL)], serious/clinically important hypoglycaemia [PG: <3.0 mmol/L (54 mg/dL)] and severe hypoglycaemia (severe cognitive impairment requiring external assistance for recovery).[6] Many symptomatic episodes of hypoglycaemia occur at glucose >3.9 mmol/L (>70 mg/dL) (irrespective of glycated hemoglobin [HbA1c]). An increased risk of adverse events (including mortality and CV events) is observed when blood glucose lowers from 4 mmol/L (72 mg/dL) to 2 mmol/L (36 mg/dL) in patients with T1D and T2D. A few key variables along with hypoglycaemia rates over six weeks predict future hypoglycaemic risk.

Presented by Heller SR (UK). The classification of hypoglycaemia: then and now

The use of artificial intelligence-decision support system (AI-DSS) has potential to improve clinical outcomes with expert level care and reducing burden on healthcare providers

The use of artificial intelligence (AI) in real-world settings can improve clinical decisions and patient care; however, AI utilization and implementation should be easy along with being patient compliant.[7] The use of AI-based technologies has been stratified into advanced hybrid close-loop (AHCL) algorithms and the AI-DSS (a decision support system). The use of AHCL for glucose monitoring has been reported in 94.1% of patients (N = 4120), with mean serum glucose of 144.4 mg/dL, and times in range (TIR) of 76.2%.[8] Another addition to the AI-based technology is the use of algorithm to predict diabetic retinopathy in patients with T1D. The ADVICE4U study, evaluated AI-DSS (n = 60) with a physician arm (n = 62), demonstrated identical (%) time spent within target glucose range (70–180 mg/dL) for both groups.[9] The use of AI-DSS can reduce the healthcare provider burden, standardize workflow, and enhance healthcare resource utilization with better data communication between providers and patients.

Presented by Phillip M (Israel). AI for diabetes management and state-of-the art today

The use of AI has been beneficial in improving clinical outcomes. European Diabetes Forum (EUDF) has rolled out a roadmap to create an AI-based clinical decision support system (CDSS) for patients with diabetes

A genome-wide association study in 476,326 individuals, using AI, identified genetic variations in the glucagon-like peptide-1 receptor (GLP-1 R) linked to organ diseases and glucose hemostasis.[10] A cohort study, using machine learning (ML), predicted diabetes in 60,000 individuals with normal fasting glucose, identifying serum glucose as a crucial factor.[11] However, there are major challenges faced, such as low usage of apps in individuals with diabetes (<20%)[12] and a mean drop-out from app-based studies (43%) in patients with diabetes and metabolic disease.[13] The use of AI-driven CDSS is currently under investigation by the EUDF. The recent data report that AI can be classified into neural networks and ML, with application currently undergoing a 5-point Likert scale survey to understand more about the use of AI-based CDSS in diabetes. The use of CDSS can provide better clinical outcomes; however, barriers such as standardization, AI algorithms, and involvement of stakeholders are a few challenges to overcome.

Presented by Battelino T (Slovenia). Implementing AI: roadmap and guidelines

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Congress Updates - October 05, 2023

GPDetect study has proven that CGM is a useful tool for identifying glycemic excursions in patients with T2D receiving basal insulin (BI)

CGM in patients with T2D treated with BI is limited. The GPDetect study, a prospective, multicentre, observational study including patients with T2D (N = 140) treated with Glargine-100 U/mL (Gla-100) for ≥6 months evaluated the CGM metrics of Gla-100 in real world primary care setting. The primary endpoint was percentage of patients achieving a time below range (TBR; <70 mg/dL) ≤4%. The overall coefficient of variation was low (28.6%); TBR standard deviation (SD) 54-69 and <54 mg/dL was within target — 2.1% (4.4) and 0.3% (0.1), respectively; TIR 70-180 mg/dL was 68.9%. The overall incidence of hypoglycaemia (<70 mg/dL) was 60% and hyperglycaemia (>180 mg/dL) was 100%. Even though T2D was generally well controlled, the incidence and duration of hypoglycaemia and hyperglycaemia remained high, with persistent hyperglycaemia during day, due to the lack of 24-hour coverage of first-generation BI (administered mainly at night).

Presented by Bellido V (Spain). Detection of glycaemic excursions in people with type 2 diabetes treated with gla-100 in primary care through continuous glucose monitoring: the GPDetect study

The American Diabetes Association/European Association for the Study of Diabetes target of HbA1c <7.0% was met by 67% of participants using hybrid closed-loop (HCL) insulin therapy

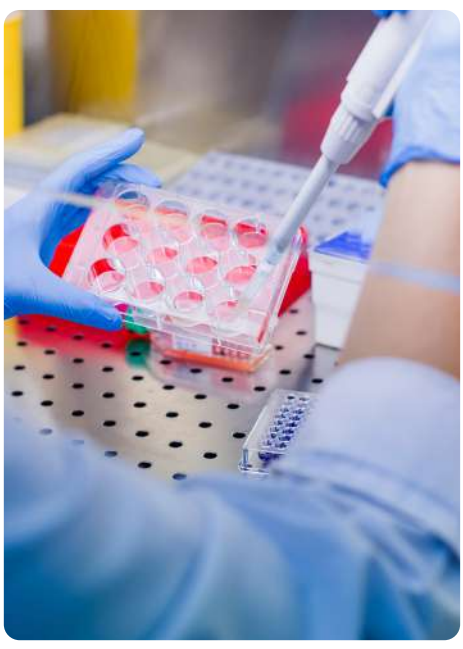
The T1D exchange online registry aims to gather data on T1D management and connect individuals with related research opportunities. After confirming T1D diagnosis, patients provide online consent and complete an enrollment questionnaire. The cohort includes 12,642 (age 1 to 92 years) participants, all who completed at least one questionnaire since January 2022. Self-reported data on characteristics, diabetes technology use, and HbA1c were tabulated. Associations between device use group, race ethnicity, insurance status and HbA1c were assessed. In a high technology use cohort, where 86% utilized CGM, around 50% were employing automated insulin delivery (AID). Participants without private insurance or relying on public insurance were less likely to use AID. Despite adjusting for insurance, participants of black race were still less likely to use AID than white race. Participants employing HCL/AID had a lower mean HbA1c compared to those using different devices.

Presented by Miller KM (USA). T1D exchange online registry: Characteristics of diabetes management among over 12,000 individuals with Type 1 Diabetes

The Early Surveillance for Autoimmune Diabetes (ELSA-1) study provides the first qualitative evidence demonstrating that, with adequate information and support, parents support T1D screening and stakeholders acknowledge the relevance of screening research

The ELSA-1 is the largest T1D screening study in the United Kingdom, involving 20,000 children aged 3–13 years. The study measured islet autoantibodies to facilitate awareness of early symptoms of T1D and explored the perspectives of parents and stakeholders. The study included 60 semi-structured interviews with 38 parents and 27 stakeholders. Stakeholders proposed and highlighted the benefits of screening for diabetic ketoacidosis and emphasized the need for guidelines for the management of at-risk patients in primary and secondary care, along with psychological support for these families to prepare for a future with a child at risk. Parents suggested having a clear communication about the risk information, less invasive techniques, and structured support from stakeholders.

Presented by Randell M.J (UK). Parent and provider's views towards paediatric screening for type 1 diabetes [ELSA 1 Study]



Glutamic acid decarboxylase antibody positive (GADA+) individuals are more prone to development of diabetes due to lower insulin secretion and higher T2D polygenic risk scores (PRS)

GADA positivity is common in autoimmune diabetes and increases the risk of future diabetes. Data from two studies, Botnia Prospective (n = 5959) and Prevalence, Prediction and Prevention (PPP)-Botnia (n = 5208) were collected for 95 GADA+ patients (case) and 263 GADA − patients (control). Assessment of corrected insulin response (CIR), disposition index (DI), and PRS for T1D and T2D was conducted. Insulin secretion was significantly lower in T1D PRS compared to control group (DI: B = -0.66 [standard error (SE), 0.23], p = 0.005, CIR: B = -0.61 [SE, 0.23], *p = 0.009*). A total of 10.5% of cases developed diabetes versus 2.1% of the control (*p < 0.05*). At basal visit, GADA+ patients who developed diabetes reported higher T2D PRS (0.47 (interquartile range [IQR], 1.19/-0.18 [IQR, 1.61]), lower DI (5828 [IQR, 10073]/18210 [IQR, 29421]) compared to GADA+ patients who did not develop diabetes. GADA+ and GADA− patients did not differ significantly; however, T1D PRS was higher in GADA+ patients vs GADA− patients. Higher T2D PRS with higher body mass index (BMI) and lower insulin secretion were reported, but not in T1D PRS, which was associated with the development of diabetes in GADA+ individuals.

Presented by Hakaste L (Finland). Association of GADA-positivity with beta cell function in individuals without diabetes in Botnia Prospective and PPP-Botnia studies

T1D-genetic risk score (GRS) can help differentiate patients with T1D with other forms of diabetes, including monogenic diabetes, for which a gene-tailored treatment is available

Diagnosing etiological sub-types of diabetes is challenging especially in children, neonates, and young adults. The T1D-GRS reflects the odds ratios of multiple single nucleotide polymorphisms (SNPs) associated with T1D. A study was conducted at the Slovak Children's Diabetes Center including 916 children with newly diagnosed hyperglycemia, 25 healthy adult controls and 183 genetically confirmed monogenic diabetes patients to evaluate the use of GRS in the diagnosis of monogenic diabetes. The results for 30 SNPs showed that the GRS was higher for T1D in all three groups: healthy controls, monogenic diabetes controls, and newly diagnosed children with hyperglycemia. ROC analysis and cut-off showed that the test had good discrimination with an area under the curve of 0.886 and both sensitivity and specificity at around 82%. Overall, these findings suggest that T1D-GRS can help in differentiating patients with T1D from those with other forms of diabetes, including monogenic diabetes.

Presented by Skopkova M (Slovakia). Implementation of genetic risk score for type 1 diabetes in children with newly diagnosed diabetes

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EASD 2023 - Hits and Misses

Activating two or three G´s; one of us is lonely

Highlight	Agent Class	Methodology	Result

CT-388, a novel once-weekly dual GLP-1 and GIP receptor modulator, is safe, well-tolerated, and produces more than 8% weight loss in 4 weeks in overweight and obese adults

Presented by M.V. Chakravarthy (USA)

Highlight	Agent Class	Methodology	Result
• CT-388 up-titrated to 12 mg was well-tolerated over 4 weeks with significant weight loss supporting continued clinical investigation with higher starting and total dose(s) in overweight and obese adults	• Biased dual GLP-1/glucose-dependent insulinotropic polypeptide (GDIP) receptor modulator	• **Subject:** Overweight and obese adults; Arm 1: single ascending dose (cohorts 1–5; 0.5–7.5 mg; n = 40); Arm 2: multiple ascending dose (cohorts 6–8; 5–12 mg; n = 24) • **Study:** Phase 1 • **Comparator:** Placebo • **Primary end point:** Safety and tolerability	**Arm 2 results** • CT388 was well-tolerated; no serious, grade 3, or fatal treatment emergent adverse events (TEAEs); no discontinuations due to TEAES; nausea and vomiting were the most common gastrointestinal (GI)-related TEAEs • Pharmacokinetic profile was consistent with once-weekly dosing (mean $t_{½}$ ~150 h) • Weight loss was clinically and statistically significant ($p < 0.001$) vs placebo with a loss of 8.4% (7.7 kg) and 7 cm reduction in waist circumference with 5/8/12/12 mg up-titrated dose

Retatrutide, a triple (GIP/GLP-1/glucagon receptor agonist), provides robust HbA1c and body weight reductions to people with type 2 diabetes: a 36-week, Phase 2 study[14]

Presented by T. Coskun (USA)

Highlight	Agent Class	Methodology	Result
• Retatrutide demonstrated clinically meaningful body weight reduction and improvements in glycaemic control compared with placebo and dulaglutide 1.5 mg, and was well tolerated in patients with T2D	• Once-weekly triple receptor [Gastric inhibitory polypeptide (GIP) /GLP-1/glucagon receptor)] agonist	• **Subject:** Adult T2D, (HbA1c, ≥53 (≤7%) to ≤91mmol/mol (≤10.5%) with diet and exercise on stable dose of metformin, BMI: 25-50 kg/m^2 (N = 338) • **Study:** 36-week, randomised Phase 2 study • **Comparator:** Placebo and dulaglutide, 1.5 mg • **Primary end point:** Percentage change in HbA1c from baseline to 24 and 36 weeks	• At 36 weeks, up to 82% of participants achieved HbA1c levels of <53 mmol/mol (<7%) and ≤48 mmol/mol (≤6.5%); 31% participants achieved HbA1c levels <39 mmol/mol (<5.7%) taking retatrutide • At 36 weeks, up to 63% and 40% of the participants achieved ≥15% and ≥20% weight loss, respectively, with retatrutide • The most common TEAEs were GI, mild to moderate in severity and common in 4-mg starting dose than in 2-mg starting dose group

Once-weekly triple receptor (GIP/GLP-1/glucagon) agonist retatrutide (LY3437943): Efficacy and safety in a 48-week obesity phase 2 trial

Presented by A.M. Jastreboff (USA)

Highlight	Agent Class	Methodology	Result
• Retatrutide treatment for 48 weeks provided substantial and clinically meaningful weight loss with dose-dependent efficacy.	• GIP/GLP-1/glucagon agonist • **Dose:** Retatrutide 1 mg, 4 mg, 8 mg, and 12 mg	• **Subject:** Obese adults (BMI ≥30 or 27 kg/m^2; N = 338) with at least one of the following weight-related conditions: hypertension, dyslipidemia, or CV disease • **Study:** A Phase 2, randomized, double-blind 48-week trial • **Comparator:** Placebo • **Primary end point:** Percent change in weight from baseline at 24 weeks. • **Secondary end points:** Percent change in weight from baseline at 48 weeks, weight reduction threshold at 24- and 48-weeks.	• At 24 weeks, retatrutide group showed up to 17.9% weight reduction compared to placebo (1.6%) • At 48 weeks, patients achieved average weight reduction of 24.2% with 12-mg retatrutide; resulted in absolute weight reduction of 26 kg. • Patients receiving 12-and 8-mg retatrutide reached the weight-reduction threshold ≥5%, nearly half lost ≥25% and one quarter lost ≥30% body weight with 12 mg dose and all cardio-metabolic measures were improved.

Efficacy of cotadutide dual Glucagon-Like Peptide-1 (GLP-1)-glucagon receptor (GCGR) agonist on albuminuria and glycaemic control in patients with diabetic kidney disease

Presented by D. Robertson (UK)

Highlight	Agent Class	Methodology	Result
• Cotadutide, a dual GLP1-GCGR agonist is beneficial for glycemic control in patients having chronic kidney disease (CKD) with T2D	• Dual GLP1-GCGR agonist	• **Subject:** Patients having CKD with T2D (N = 248) • **Study:** 26-week, Phase 2b • **Doses used**: Cotadutide 100 µg once daily (QD); Cotadutide 300 µg QD; Cotadutide 600 µg QD; Semaglutide 1 mg once a week; Placebo QD • **Comparator:** Placebo • **Primary end point:** Percent change in Urine Albumin-Creatinine Ratio (UACR) from baseline to week 15	• Cotadutide 100 µg and 300 µg was better tolerated versus cotadutide 600 µg and semaglutide 1 mg • Cotadutide 300 µg and 600 µg significantly reduced UACR at 15 and 26 weeks (39.9% and 49.9% at 26 weeks, respectively) • Significant body weight and glucose reduction with cotadutide

A Phase II, randomised, double-blind, placebo-controlled, dose-finding study of survodutide (BI 456906) in people living with overweight/obesity

Presented by C.W. Le Roux (UK)

Highlight	Agent Class	Methodology	Result
• Survodutide appears to be a promising new anti-obesity treatment that reduced body weight up to 18.7% with improvements in cardiometabolic outcomes after 46 weeks.	• Once-weekly GCGR/GLP-1R dual agonist administered subcutaneously (s.c.)	• **Subject:** Obese adults (BMI ≥27 kg/m^2; N = 387) • **Study:** A multicentre, 46-week, Phase 2 trial • **Primary end point:** Percent change in body weight from baseline to week 46. • **Secondary endpoints:** Absolute changes in bodyweight, waist circumference, systolic and diastolic blood pressure (BP) from baseline to week 46.	• At 46 weeks, the planned treatment of survodutide (n = 76) reduced absolute body weight up to 18.5 kg, compared to 19.5 kg in the actual treatment group (n = 54) receiving 4.8 mg doses. • At 46 weeks, the reduction in body weight had not reached a plateau; further reductions expected with longer treatment duration. • Doses ≥2.4 mg substantially reduced BP.

Phase 2, randomized, placebo-controlled trial of pemvidutide, a glp-1/glucagon dual receptor agonist, in subjects with overweight or obesity: a 24-week interim analysis

Presented by L. Aronne (USA)

Highlight	Agent Class	Methodology	Result
• Pemvidutide significantly reduced 10.7% of body weight in 24 weeks. In addition, reduced low-density lipoprotein cholesterol and triglycerides levels with pemvidutide was reported with tolerability among patients. A 48-week trial results will be announced in Q4 2023.	• Pemvidutide is a GLP-1/Glucagon dual receptor agonist. • **Dose:** 1.2 mg, 1.8 mg, and 2.4 mg weekly	• **Subject:** Adult, T2D patients overweight or with obesity, (N = 160) randomized (1:1:1:1) to 1.2, 1.8 and 2.4 mg weekly with pemvidutide and placebo • **Primary end point:** Weight loss through Week 24 and 48 Safety, BP, and serum lipids levels was also assessed	• The mean weight loss for Week 24 was 7.3%, 9.4% and 10.7% with 1.2 mg, 1.8 mg and 2.4 mg of pemvidutide, respectively vs 1% with placebo ($p < 0.001$ vs placebo) • Nausea, vomiting, and diarrhea were reported in few patients, serious adverse events in 2.5% of patients (1.2 and 1.8 mg), and 4.9% of patients (2.4 mg) • All doses reported reductions in serum lipid levels compared to placebo ($p < 0.001$). Significant reductions were reported in BP without changes in heart rate.

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