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ADA 82ND SCIENTIFIC SESSIONS New Orleans, 2022

Presents

AMERICAN DIABETES ASSOCIATION

82nd SCIENTIFIC SESSIONS

DAILY COVERAGE

TOP 7 SESSIONS: DAY-1

TOPIC OF CONTENT

SESSION-1 :
Top 5 Nutrition Controversies

Vitamin D Supplementation Improves Anxiety and Depression Status in Elderly People with Prediabetes: An Open-Label 12-Month Randomized Controlled Study

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Dr. Theocharis Koufakis,MD et al., from Ioannina, Greece, Thessaloniki, Greece.

The combination of prediabetes and depressive or anxiety symptoms is known to increase the risk of progression to diabetes. We aimed to assess the effects of vitamin D supplementation on anxiety and depression status among elderly people with prediabetes.

Participants were randomly assigned to a weekly dose of vitamin D3 of 25,000 IU (n=45) or nothing (n = 45), in addition to lifestyle measures. The State Trait Anxiety Inventory and the Patient Health Questionnaire-9 (PHQ-9) tools were used to evaluate anxiety and depression levels, respectively, at baseline, 6 and 12 months.

Participants in the intervention and control group presented comparable baseline characteristics in terms of age (73.10 ± 7.16 vs. 74.03 ± 7.64 years, respectively), fasting glucose (103.4 ± 12.05 vs. 102.29 ± 12.82 mg/dl, respectively) and HbA1c values (5.87 ± 0.21 vs. 5.87 ± 0.22 %, respectively). In the supplemented group, 25-hydroxyvitamin D concentrations increased significantly at 6 (26.56 ± 8.64 ng/ml) and 12 months (28.71 ± 9.03 ng/ml) compared to baseline (19.98 ± 6.73 ng/ml, $p<0.001$ for both comparisons). The mean trait anxiety scores were lower in supplemented individuals than the control group at 6 (38.02 ± 9.03 vs. 43.91 ± 7.18, respectively, $p=0.003$) and 12 months (32.35 ± 7.77 vs. 44.97 ± 7.78, respectively, $p<0.001$). The same pattern was evident for state anxiety scores at 6 (37.11 ± 7.88 vs. 43.20 ± 9.33, $p=0.003$) and 12 months (32.59 ± 6.45 vs. 44.60 ± 9.53, $p<0.001$). Supplemented participants demonstrated lower mean PHQ-9 scores compared with controls at 6 (15.69 ± 6.15 vs. 19.77 ± 8.96, respectively, $p=0.021$) and 12 months (13.52 ± 5.01 vs. 20.20 ± 8.67, respectively, $p<0.001$).

In a high-risk population, a weekly vitamin D supplementation scheme was effective in reducing anxiety and depression levels. Further studies are needed to elucidate the relevant mechanisms.

Telemedicine Intervention Is Effective in Changing Psychological and Behavioral Correlates of Weight Loss in the REAL HEALTH-Diabetes Trial

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Janaki Vakharia, Linda M. Delahanty, Tanayott Thaweethai, Chu Yu, Deborah J. Wexler from Boston, MA.

Prior studies have shown that telemedicine (telemed) weight loss interventions are non-

Table 1. Changes in psychological and behavioral factors and weight outcomes in the REAL HEALTH-Diabetes lifestyle intervention groups at 6 months

	Change from baseline to 6 months N (%) or mean (SD)			P-value LI-IP vs LI-Tele*
	LI-Combined	LI-IP	LI-Tele	
N	141	69	72	
Weight loss				
Mean/SD weight loss (%)	-5.10 (5.34)	-5.60 (4.87)	-4.61 (5.76)	0.273
Patients achieving 5% weight loss (n/%)	66 (46.8)	34 (49.3)	32 (44.4)	0.685
Hemoglobin A1c (%)	-0.52 (1.02)	-0.58 (0.83)	-0.47 (1.18)	0.527
Psychological Factors				
Problem Areas in Diabetes (PAID)†	-13.26 (19.79)	-12.41 (20.28)	-14.10 (19.42)	0.622
PHQ-8‡	-0.85 (3.19)	-0.97 (3.34)	-0.73 (3.06)	0.664
Treatment self-regulation questionnaire (TSRQ)§	0.39 (1.27)	0.53 (1.20)	0.25 (1.33)	0.217
Diet self-efficacy	0.19 (0.65)	0.28 (0.67)	0.11 (0.63)	0.121
Behavioral Factors				
Dietary Restraint subscale of Dutch Eating Behavior Questionnaire	0.61 (0.67)	0.62 (0.61)	0.59 (0.73)	0.785
Fat related diet questionnaire	-0.34 (0.49)	-0.35 (0.50)	-0.34 (0.48)	0.890

* Comparison analysis method used for continuous variables was a two-group ANOVA and for the proportion of patients achieving 5% weight loss was the Chi-squared test
† PAID is a measure of diabetes-related distress
‡ PHQ-8 is a measure of depression
§ TSRQ is a measure of autonomous motivation for regulation of diet

inferior to in-person in achieving weight loss. The REAL-HEALTH Diabetes RCT studied the effectiveness of a group lifestyle intervention (LI) for weight loss in adults with T2D and overweight/obesity. Intervention was delivered either in-person (LI-IP) or via telephone (LI-Tele).

"We found clinically significant weight loss with no difference between arms. We sought to determine whether there was a difference between the LI-IP and LI-Tele arms in change of psychological and behavioral correlates of weight loss from baseline to 6 months. We compared the change scores for psychological (diabetes-related distress, depression, diet self-efficacy and autonomous motivation for regulation of diet) and behavioral (dietary restraint, fat related diet behavior) measures between the LI-IP (n=69) and LI-Tele (n=72) groups."

There was no significant difference between the groups in mean age (62 years), percent male (44.7%), race (79.4% white), baseline HbA1c (7.7%) and baseline BMI (34.7 kg/m^2). At 6 months, scores for all the measures improved from baseline in both arms with no significant difference between LI-IP and LI-Tele (Table 1), demonstrating that telemed LI was as effective as the in-person intervention at improving psychological and behavioral correlates of weight loss.

The Association of Prediabetes, Awareness and Risk Perception, and Lifestyle Behaviors Among U.S. Young Adults: NHANES 2005–2018

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Alice Yan, Jason J. Wang, Zumin Shi, from Milwaukee, WI, & West Friendship, MD, Doha, Qatar.

Individuals with prediabetes (preDM) are at increased risk of developing type 2 diabetes

(T2DM) and cardiovascular disease. We know little about the risk perception and lifestyle behaviors of young adults with preDM.

This nationally representative cross-sectional analysis of 2005-2018 National Health and Nutrition Examination Survey data was conducted on nonpregnant young adults (aged 19 - 34). PreDM and Diabetes (DM)were based on fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) definitions recommended by the American Diabetes Association. We used fasting sample weight to generate nationally representative estimates. Measures also include sociodemographic, lifestyle behaviors (diet, physical activity, and sleep), awareness, and perceived risk for diabetes or preDM. Analyses were accounted for the complex sample design and performed using Stata 17.

Overall, among 4272 young adults, the weighted prevalence of PreDM and DM were 26% and 2.6%, respectively. There was a significant difference ($p<0.001$) in the awareness of their disease condition between individuals with preDM (3.7%) and those with DM (13.2%). The multivariable logistic regression model found that women were less likely to have preDM than men. Obese subjects were more likely (OR=3.19, 95%CI 2.39 - 4.27) to have preDM. College education, higher income, and physical activity (600 -1200 MET minutes/week) were protective factors against preDM. Long sleep duration (>=9 hours per day) is associated with a 56% increased risk for prediabetes (95%CI 1.02 - 2.39).

The high prevalence of preDM in young adults reinforces the critical need for effective public health strategies that promote lifestyle behaviors, including physical activity, and improve sleep quality.

SESSION-2 :
Prevention or Delay of Type 2 Diabetes and Associated Comorbidities

A Weight Management Program Tailored for Adults with Type 2 Diabetes: Effects on Glycemic Control

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. John W. Apolzan, Jessica G. Larose, et al., from Baton Rouge, LA.

Clinical weight loss interventions improve glycemic control in adults with type 2 diabetes (T2D), but are costly and have limited accessibility. The objective of this trial was to test the efficacy of a diabetes-tailored widely available weight management program (WW, formerly Weight Watchers) on glycemic control in adults with T2D.

This was a prospective 24-week single arm, three-site clinical trial. Participants (n= 136) had T2D, a baseline HbA1c between 7-11%, and a BMI between 27-50 kg/m^2. All participants received the 24-wk intervention, which consisted of the WW digital + workshop program tailored for people with T2D, and included weekly virtual workshops and use of the WW App. Assessments occurred at baseline, wk 12 (83.8% retention), and wk 24 (83.1%). Primary outcome was change in HbA1c at 24 weeks. Secondary endpoints were changes in body weight and the Diabetes Distress Scale (DDS). Generalized linear effects models were used for statistical analysis (MAR) and used an intent-to-treat analysis.

Participants were 56.8 ± 0.8 y (Mean ± SEM), 80.2% Female, 62.2% non-Hispanic white. Baseline BMI was 36.2±0.6 kg/m^2. Baseline HbA1c, weight, and total DDS score were 7.9±0.1%, 104.3±1.8 kg, and 2.2±0.1, respectively. HbA1c decreased 0.6±0.1% at wk 12 and 0.8±0.1% at wk 24 (both p <.0001). Body weight decreased 4.6±0.5% at wk 12 and 5.7±0.5% at wk 24 (both p <.0001). Total DDS score decreased 0.2±0.1 at wk 12 and 0.3±0.1 at wk 24 (both p <.0001).

The widely available WW program, modified for those with T2D, had favorable and clinically meaningful effects on glycemic control, body weight, and diabetes distress at 12 and 24 weeks.

Tirzepatide Slowed Progression of Chronic Kidney Disease in Patients with Type 2 Diabetes with Increased Cardiovascular Risk

Friday, 3rd June 2022

A pre-specified exploratory analysis from the SURPASS-4 trial showed tirzepatide, a novel once-weekly medication for the treatment of diabetes, improved kidney outcomes for adults with type 2 diabetes who have increased cardiovascular risk.

SURPASS-4 was part of the SURPASS global clinical development program for Eli Lilly and Company's tirzepatide. Findings were presented on Friday June 3rd 2022 at the 82nd Scientific Sessions of the American Diabetes Association® (ADA).

Chronic kidney disease (CKD) is a common complication of type 2 diabetes, a condition that worsens over time and can cause the kidneys to fail. With one in three adults with diabetes

Dr. H.J. L. Heerspink
PhD, PharmD,
University Medical Center Groningen, Netherlands

impacted by CKD, there is an unmet need for new therapies to reduce the development and progression of CKD in patients with diabetes.

This pre-specific exploratory analysis of SURPASS-4 evaluated the progression to pre-specified kidney endpoints between tirzepatide and titrated daily insulin glargine (iGlar). The rate of decline in kidney function and urinary albumin excretion were used as outcomes. The clinical endpoint was a decline of 40% or more from baseline, renal death, progression to end-stage renal disease analyzed with and without new onset macroalbuminuria as additional component. A total of 1,995 patients were enrolled, with a mean age of 63.6 years and blood glucose (blood sugar) level, or A1C, of 8.5%. Patients were followed up to 104 weeks.

The results show tirzepatide participants experienced fewer renal complications, compared to those that received insulin. In particular, the rates of new onset of macroalbuminuria, a signal of poor renal outcomes, were significantly lower in the tirzepatide arm (Hazard Ratio = 0.41). Additionally, in individuals with type 2 diabetes and high cardiovascular risk, tirzepatide reduced the rate of kidney function loss and the amount of urinary protein excretion, a risk marker for progression of CKD.

"With these exploratory findings of SURPASS-4, we are seeing the results of combined GIP/GLP-1 receptor agonists on the kidney function of patients with type 2 diabetes for the very first time," said H.J. L. Heerspink, PhD, PharmD, University Medical Center Groningen, Netherlands. "The findings will be of interest to physicians treating people with

diabetes who may have chronic kidney disease"

Tirzepatide is a novel, once-weekly injectable glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that integrates the actions of the GIP and GLP-1 incretins into a single molecule, representing a new class of medicines for the treatment of type 2 diabetes. In the U.S., tirzepatide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

Effect of Dapagliflozin on Renal and Hepatic Glucose Kinetics in T2DM and NGT Subjects

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Dr. Carolina Solis-Herrera et al., from San Antonio Texas.

"We previously have shown that both acute and chronic SGLT-2 inhibition increases endogenous glucose production (EGP). However, the organ - liver versus kidney - responsible for the increase in EGP has not been identified. We assessed the effect of a single dose of Dapagliflozin or Placebo on renal glucose production in 13 T2DM (age=57.5±1.8 yrs, BMI = 30±1.4 kg/m^2) and 9 NGT (age 42±2 3 yrs, BMI = 30±1.1 kg/m^2) subjects."

Renal glucose production was measured using arteriovenous balance technique across the kidney combined with [3-3H] glucose infusion and PAH infusion (for determination of renal blood flow) before and 4 hours after administration of Dapagliflozin (10 mg) and Placebo; thus, each subject served as their own control. EGP increased following DAPA in both T2DM (2.00±0.11 to 2.43±0.15, P<0.05) and

Dr. Carolina Solis-Herrera, MD
San Antonio Texas

NGT (1.72±0.11 to 2.1±0.16, p<0.05), while it decreased after placebo in T2DM (2.02±0.12 vs. 1.15±0.06) and NGT (2.10±0.2 vs. 2.05±0.1) (both p<0.01, DAPA vs. placebo).

The fractional renal extraction of glucose (0.02± 0.004 vs. 2.99 ± 1.0, p=0.001 in T2DM, and 0.02± 0.004 vs. 1.62± 1.4 in NGT, p=NS) and renal glucose uptake (0.067 ± 0.02 vs. 0.347 ± 0.06 in T2DM and 0.08 ± 0.02 vs. 0.27 ± 0.08 mg/kg.min in NGT) were higher following DAPA vs. placebo (p<0.05) and were entirely explained by the increase in glucosuria. There was a small, non-significant increase (0.065 & 0.032 mg/kg.min, respectively) in renal glucose production (RGP) following dapagliflozin in T2DM and NGT compared to the 0.45 mg/kg.min increase in total body EGP.

A single dose of Dapagliflozin significantly increases EGP which primarily is explained by an increase in hepatic glucose production.

Identifying Blood Biomarkers for Type 2 Diabetes Subtyping: A Report from the ORIGIN Trial

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Marie Pigeyre, Hertzel C. Gerstein, Leif Groop, Sibylle Hess, Guillaume Pare, from Hamilton, ON, Canada, Helsinki, Finland, Frankfurt, Germany.

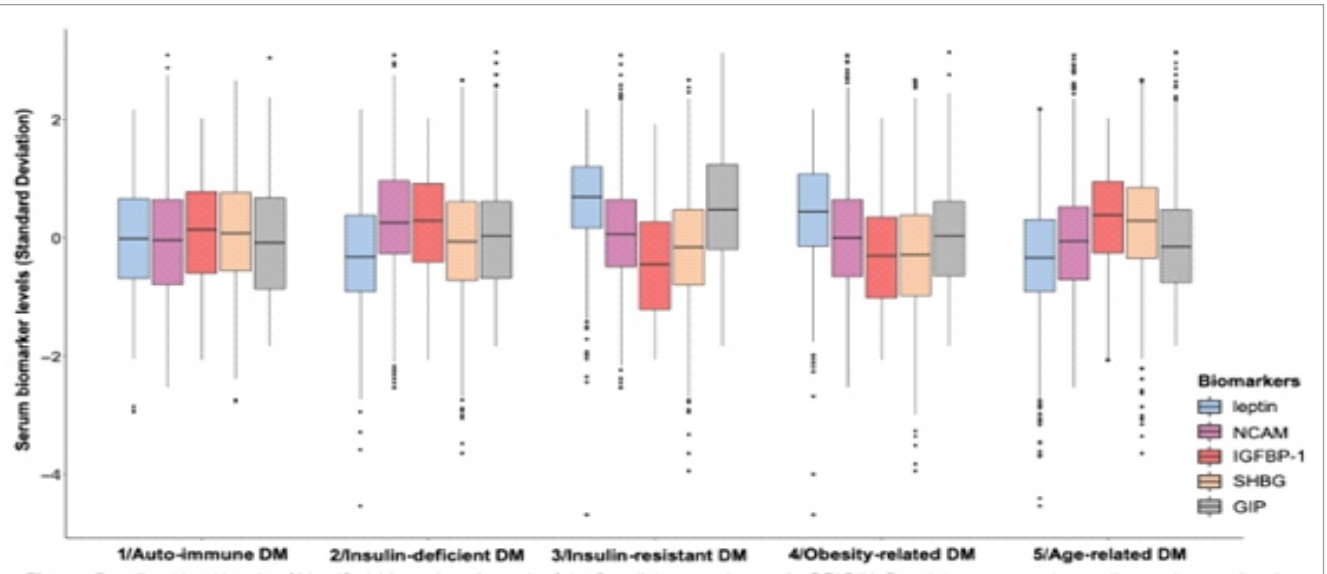


Figure: Baseline blood levels of identified biomarkers in each of the five diabetes subtypes in ORIGIN. Boxplots represent the median and second and third quartiles; error bars represent the 95% confidence interval.

Diabetes (DM) can be classified into 5 subtypes characterized by distinct progression in dysglycaemia and complications. Using 5 clinical variables, we categorized 7017 participants from the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial into 1/auto-immune DM (n=241), 2/insulin-deficient DM (n=1594), 3/insulin-resistant DM (n=914), 4/obesity-related DM (n=1595), 5/age-related DM (n=2673).

Yet, whether blood biomarkers are associated with these subtypes is unknown. Forward-selection logistic regression models were used to identify biomarkers that were each independent determinant of one cluster versus the others, among 233 selected cardiometabolic proteins measured at baseline. Models were adjusted for age, sex, ethnicity, C-peptide level, diabetes duration.

A total of 13, 2, 7 and 10 biomarkers were independent determinants of DM subtypes 2 to 5 respectively (all P<4.3x10-5). A combination of 5 biomarkers that were distinctively associated with clusters (fig), showed a diagnosis performance, through AUC-ROC curves, of 0.71, 0.86, 0.88, 0.82 to respectively distinguish cluster 2 to 5 from the others. No biomarkers other than GAD antibodies were determinants of cluster 1.

"We identified 5 serum biomarkers, as independent determinants of DM subtypes, that could be used as a diagnosis test for DM subtyping. Although this requires further validation in an independent population."

Interleukin-6 and Cardiovascular Outcomes in Patients with Type 2 Diabetes: A Post Hoc Analysis of CANVAS Trial

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Michael K. Hansen, Hiddo L. Heerspink from Sydney, Australia, Spring House, PA, Groningen, Netherlands.

The sodium glucose co-transporter 2 inhibitor (SGLT2i) canagliflozin (CANA) reduced cardiovascular (CV) outcomes in patients with type 2 diabetes (T2D) at high CV risk in the CANVAS Program. CANA has been shown to reduce markers of inflammation in small

clinical studies. Higher interleukin-6 (IL-6) levels, a key inflammatory mediator, are associated with increased CV risk. We assessed the association between IL-6 and CV outcomes in patients with T2D and determined the effects of CANA on IL-6 levels over time.

Patients were randomly assigned to CANA (100 or 300 mg/day) or placebo. Plasma IL-6 was measured at baseline and 1, 3, and 6 years after randomization. Outcomes were a composite CV endpoint of non-fatal myocardial infarction, non-fatal stroke, or CV death; a composite of CV death or heart failure hospitalization (hHF); or hHF alone. Multivariable adjusted Cox proportional hazard regression model was used to estimate the associations between baseline IL-6 and CV outcomes. The effect of CANA versus placebo on IL-6 levels over time was assessed with a repeated measures mixed effect model.

Of 4,330 CANVAS trial participants, 3,503 (80.9%) had available IL-6 measurements at baseline. In multivariable adjusted models, each doubling of baseline IL-6 was associated with 14% (95% CI 4-24%), 24% (13-37%), or 35% (16-57%) increased risk for the composite CV endpoint, CV death or hHF, or hHF alone, respectively (all $p<0.01$). Compared with placebo, CANA reduced IL-6 levels by 4.4% (95% CI 1.3-9.9%; $p=0.01$) during follow-up. The proportion of the effect of CANA on the composite CV, CV death or hHF, and hHF endpoints explained by the change in IL-6 was 16.5% ($p=0.02$), 28.5% ($p=0.34$), and 11.4% ($p=0.05$), respectively.

In patients with T2D at high CV risk, increased IL-6 is associated with a higher risk of CV outcomes. CANA reduced IL-6 levels over time which may partly explain its protective effect.

Effects of Time-Restricted Eating vs. Low-Carbohydrate Diet on Mean Glucose in Type 2 Diabetes Patients

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Alexander Carbonel, Estephany Velis, from Vallejo, CA, Stanford.

Time restricted eating(TRE) and Low Carbohydrate Diets (LCD) have become popular dietary patterns with potential metabolic benefits for T2DM patients. The objective of this study is to evaluate TRE on glucose control compared to LCD for individuals with T2DM after completing a 72 hour medically supervised induction fast.

Participants completed a 72 hour medically supervised induction fast and were randomized to TRE (n=14, 8-hour daily feeding period) or LCD (n=10, <45 grams total per day) for 4 weeks. Blood glucose was captured by FreeStyle Libre pro continuous glucose monitors (CGM). GMI at 1 month post fast was compared to A1C values measured within 6 months prior to treatment.

A total of 24 participants completed the protocol (mean age = 53.9, range 35-72). GMI was reduced from 8.99% to 7.30% ($p=0.002$) in TRE and 7.99% to 6.77% in LCD ($p=0.001$). Reductions in GMI range were greater in the first 2 weeks compared to last 2 weeks. The TRE group spent less time within the target range (67.7% vs. 74.8%, $p=0.32$), more time hyperglycemic (29.4% vs. 21.0% $p=0.25$), and less time hypoglycemic (2.8% vs. 4.2%, $p=0.42$). Hypoglycemia was numerically less common in the TRE group (3/14 participants) compared to the LCD(6/10 participants) in CGM data beyond the induction fast. Glucose variability

was similar in TRE (28.6%) and LCD (28.2%). There were no SAEs experienced in either group. When surveyed, participants believed TRE and LCD were realistic nutritional therapies.

These results suggest that both TRE and LCD supplemented by a medically supervised induction fast are efficacious and safe nutritional therapies to improve blood glucose in patients with T2DM. The participants will be followed for 12 months to analyze long-term effects.

SESSION-3 : Mitigating ASCVD Risk in Diabetes: Role of Kidney in ASCVD

Discontinuation of Renin Angiotensin System Inhibitor and Cardiovascular-Renal Events in Advanced Diabetic Kidney Disease

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Juliana C. Chan, Elaine Chow from Hong Kong, China.

Whether angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) should be discontinued in advanced diabetic kidney disease (DKD) remains controversial. "We examined the association of discontinuation of ACEi/ARBs when estimated glomerular filtration rate (eGFR) reached <30 ml/min/1.73m^2 with risk of death, major adverse cardiovascular events (MACE), and end-stage-kidney-disease (ESKD) defined as dialysis and/or eGFR <15/ml/min/1.73m^2 in Chinese patients with type 2 diabetes (T2D)."

"We performed a prospective analysis of a register including 11,323 patients stratified by continuation of ACEi/ARBs within 6 months of reaching eGFR <30 ml/min/1.73m^2 in 2002-2018 followed up until 2019. We used Cox model with time-dependent exposure and covariates to estimate the hazard ratio (HR) of outcomes in the overlap propensity score weighted cohort."

Of 11,323 ACEi/ARBs users with new-onset eGFR<30 ml/min/1.73m^2, 2,055 (18.5%) discontinued ACEi/ARBs within 6 months whereas 9,268 (81.5%) had continuation of ACEi/ARBs. During a mean follow-up of 4.3 years, 13.5% and 28.4% had incident MACE and ESKD respectively, and 36.2% died. Compared to ACEi/ARBs continuation, discontinuation of ACEi/ARBs was associated with higher risk of MACE (HR=1.26, 95% CI: 1.15-1.39) and ESKD (HR=1.26, 95% CI: 1.14-1.40), and neutral risk of death (HR=0.96, 95% CI: 0.89-1.04). Results were consistent when modeling ACEi/ARBs as a time-dependent exposure using a marginal structural model.

Blood Pressure Variability Is Associated with Risk of Heart Failure, Elevated NT-proBNP, and High-Sensitivity Troponin: Results from MESA

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Jin Zhou, Juraj Koska, Chike Nwabuo, Alain Bertoni, Steven Shea,

Peter Reaven from Phoenix, AZ, Los Angeles, CA, Aurora, CO, Winston-Salem, NC, New York, NY.

The association between blood pressure variability (BPv) and heart failure (HF) is incompletely studied. This association, and its links with biomarkers of HF and cardiac injury, were examined in the community-based Multi-Ethnic Study of Atherosclerosis (MESA). Resting seated BP was measured thrice; the average of the last two measures was used for analysis, and visit-to-visit BPv (coefficient of variation-CV) was assessed over 5 visits. Biomarkers of HF (N-terminal B-type natriuretic peptide: NT-proBNP) and cardiac injury (high-sensitivity troponin-T: hs-cTnT), respectively, at exams 1, 3 and 5 were ascertained.

With 9.4 years median follow-up in 6,785 individuals, 385 HF events occurred. In adjusted time-dependent models including CVD risk factors, BMI, BP medications, and cumulative mean BP, BPv (CV-SBP and CV-DBP) was associated with risk of clinical HF (e.g., CV-SBP HR=1.16, p=0.03). Similar patterns were seen regardless of T2D status. The associations were stronger for HF with reduced ejection fraction (EF) vs. preserved EF. When excluding those with baseline NT-proBNP >450 pg/mL or hs-cTnT >14 ng/L, the association between BPv and HF became stronger. CV-SBP and CV-DBP were also associated with elevated exam 5 NT-proBNP (>450 pg/mL: OR=1.74, and OR = 1.32, p<0.001).

"We saw a positive relationship between CV-SBP and exam 1 to exam 5 changes in NT-proBNP (p=0.001) and hs-cTnT (p<0.001) as well as elevated hs-cTnT (>14 ng/L; OR=1.18, p<0.001). Our data strongly support an association between BPv and both clinical HF and elevated NT-proBNP, and the association was greater in those with reduced vs. preserved EF. The association between BPv and clinical HF was related to deleterious changes in sub-clinical markers of myocardial injury and heart failure."

Cardiovascular Effectiveness of SGLT-2 Inhibitors and GLP-1 Receptor Agonists in Routine Care of Frail People with Type 2 Diabetes

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Alexander Kutz, Chandrasekar Gopalakrishnan, Dae H. Kim, Elisabetta Patorno from Boston, MA Phoenix, AZ, Los Angeles, CA, Aurora, CO, Winston-Salem, NC, New York, NY.

Frailty is important in diabetes management but its impact on the cardiovascular (CV) effectiveness of SGLT-2i and GLP-1 RA as used in routine care is unexplored. Using Medicare claims data, we identified three pairwise 1:1 propensity score (PS) matched cohorts of people with type 2 diabetes who initiated a SGLT-2i, a GLP-1 RA, or a DPP-4i between 04/2013-12/2018. The primary outcome was a composite of major adverse CV events (MACE) including acute myocardial infarction, ischemic stroke, hospitalization for heart failure, or all-cause mortality.

"We estimated hazard ratios (HR) and absolute rate differences (RD) per 1000 person-years, with their 95% CI, in each PS-matched cohort by level of frailty, using a validated claims-based frailty index (3 strata: non-frail, <0.15; pre-frail, 0.15-0.24; frail, ≥0.25), controlling for >150 baseline covariates. We used the Wald test for homogeneity to assess treatment heterogeneity across strata."

The HR for MACE associated with SGLT-2i vs. DPP4i (n=91141 PS-matched pairs) was 0.82 (95% CI 0.72 to 0.93) in frail, 0.71 (0.67 to 0.75) in pre-frail, and 0.78 (0.71 to 0.86) in non-frail people (p for homogeneity=0.033). The HR for MACE associated with GLP-1 RA vs. DPP4i (n=90988 pairs) was 0.84 (0.76 to 0.93) in frail, 0.77 (95% CI 0.73 to 0.81) in pre-frail, and 0.82 (0.74 to 0.91) in non-frail people (p for h.=0.150). The HR for MACE associated with SGLT-2i versus GLP-1 RA (n=67067 pairs) was 0.87 (0.75 to 1.01) in frail, 0.93 (95% CI 0.87 to 1.01) in pre-frail, and 0.90 (0.79 to 1.03) in non-frail people (p for h.=0.692). Compared to DPP-4i, the absolute benefit of either SGLT-2i or GLP-1 RA was largest in frail people [RD, -25.0 (-42.1 to -7.9), p for h.<0.001, NNT=20; and RD, -24.9 (-39.0 to -10.7), p for h.<0.001, NNT=21; respectively].

While, compared to DPP4i, SGLT-2i and GLP-1 RA were associated with similar relative risk reductions in MACE among people with and without frailty, their absolute benefits were largest in frail people.

Cardiovascular Effectiveness of SGLT2 Inhibitors: Head-to-Head Comparisons

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Devin Abrahami, Elvira

Table. Pooled hazard ratios and 95% confidence intervals for cardiovascular outcomes and mortality comparing individual SGLT2i

	Pooled‡ crude incidence rate* (95% CI)	Pooled‡ weighted hazard ratio (95% CI)
MI/stroke		
Canagliflozin	9.21(4.55-13.88)	1.00 [reference]
Dapagliflozin	8.78 (4.34-13.22)	0.96 (0.81-1.14)
Empagliflozin	9.60 (5.58-13.61)	0.95 (0.81-1.11)
HHF		
Canagliflozin	1.42 (1.24-1.59)	1.00 [reference]
Dapagliflozin	2.76 (0.07-5.46)	1.07 (0.85-1.34)
Empagliflozin	2.60 (0.49-4.72)	0.73 (0.57-0.94)
MI		
Canagliflozin	5.88 (3.77-7.98)	1.00 [reference]
Dapagliflozin	5.29 (3.43-7.15)	0.91 (0.78-1.05)
Empagliflozin	6.00 (4.65-7.36)	0.95 (0.76-1.20)
Stroke		
Canagliflozin	3.41 (0.82-5.60)	1.00 [reference]
Dapagliflozin	3.47 (0.63-6.30)	1.09 (0.79-1.51)
Empagliflozin	3.59 (0.88-6.30)	1.01 (0.73-1.40)
All-cause mortality		
Canagliflozin	5.01 (0-10.91)	1.00 [reference]
Dapagliflozin	5.37 (0-11.83)	1.13 (0.95-1.34)
Empagliflozin	6.16 (0-12.70)	1.20 (0.91-1.59)

Abbreviations: SGLT2i: sodium-glucose cotransporter-2 inhibitor; CI: confidence interval; MI: myocardial infarction; HHF: hospitalization for heart failure.
Empagliflozin users: 116,240; Dapagliflozin users: 62,675; Canagliflozin users: 135,562.
‡ Data were pooled from 3 US healthcare claims databases: Optum Clinformatics Data Mart Database, IBM MarketScan and Medicare fee-for-service using random-effects models with inverse variance.
* Per 1,000 person-years
All baseline characteristics were well balanced after weighting, with standardized differences below 0.1.
Patients were followed using an on-treatment exposure definition starting one day after their cohort entry prescription, until the earliest of a cardiovascular event or mortality, treatment discontinuation (allowing a 60-day grace period), add-on or switch to the comparator drug, or censored due to death, bariatric surgery, end of enrollment, or end of the study period.

D'andrea, Julie M. Paik, Deborah J. Wexler, Brendan M. Everett, Seoyoung C. Kim, Elisabetta Patorno, from Boston, MA Phoenix, AZ, Los Angeles, CA, Aurora, CO, Winston-Salem, NC, New York, NY.

In placebo-controlled cardiovascular (CV) outcome trials, SGLT2 inhibitors (SGLT2i) reduced the risk of CV events in patients with T2D and CV disease. However, not all trials showed consistent CV benefits across individual SGLT2i. We assembled a cohort of adults with T2D (median age 62, 57% male), newly treated with an SGLT2i (canagliflozin, dapagliflozin, empagliflozin) from Medicare and two US commercial healthcare claims databases (4/2012 - 12/2020).

"We assessed the risk of a composite event of myocardial infarction (MI) or stroke (MI/stroke), its individual components, hospitalization for heart failure (HHF), and mortality. To account for differences between initiators of different SGLT2i, we reweighed each group using inverse probability of treatment weights, adjusting for >130 baseline characteristics. In each database, hazard ratios (HRs) and 95% CI were estimated using Cox proportional hazards models and results were pooled using random-effects models. Compared to canagliflozin, the most frequently used SGLT2i during the study period, dapagliflozin and empagliflozin had a similar risk of MI/stroke, though empagliflozin was associated with a reduced risk of HHF [HR (95% CI) = 0.73 (0.57-0.94)], over a median 0.65 years of follow-up. Individual SGLT2i showed a similar risk of other outcomes (Table). This study suggests that SGLT2i have similar effectiveness on most CV outcomes and mortality in patients with T2D.

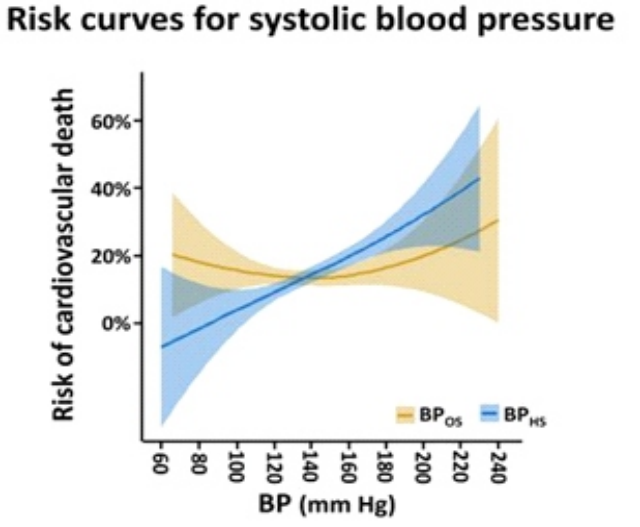
Value of Blood Pressure Measurement Earlier vs. Later in Life to Predict Cardiovascular Mortality

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Andreas Leiherer, Hanno Ulmer, Axel Muendlein, Christoph H. Saely, from Bregenz, Austria, Triesen, Liechtenstein, Feldkirch, Austria, Philadelphia, PA.

"We here aimed at comparing the value of systolic blood pressure (BP) earlier versus later in life to predict cardiovascular mortality. In a cardiovascular observation study (OS) we prospectively recorded fatal cardiovascular events over up to 19 years in 1282 patients of whom 570 had the Metabolic Syndrome (MetS) at baseline."

These patients had participated in a health survey (HS) 15 years prior to the OS baseline. BP was measured both at the HS and at the



Risk curves are calculated for blood pressure (BP) assessed at the health survey (HS) and at the baseline of the cardiovascular observation study (OS) according to loess (LOcally WEighted Scatter-plot Smoother) fitting with 95% confidence intervals for cardiovascular death during follow up.

baseline of the OS. We found that the increase in cardiovascular mortality matched the increase of BP in the HS in a linear way but this is not the case for BP assessed at the OS (figure). A cox regression analysis revealed that each millimeter of mercury (mm Hg) increased the risk for cardiovascular death by 2% (HR = 1.02 [1.01-1.03], p<0.001).

"Applying a stratification for the presence of MetS, we found that in both groups BP was a significant predictor of cardiovascular mortality (HRMetS = 1.02 [1.01-1.02], p<0.001 and HRnoMetS = 1.02 [1.01-1.03], p<0.001)."

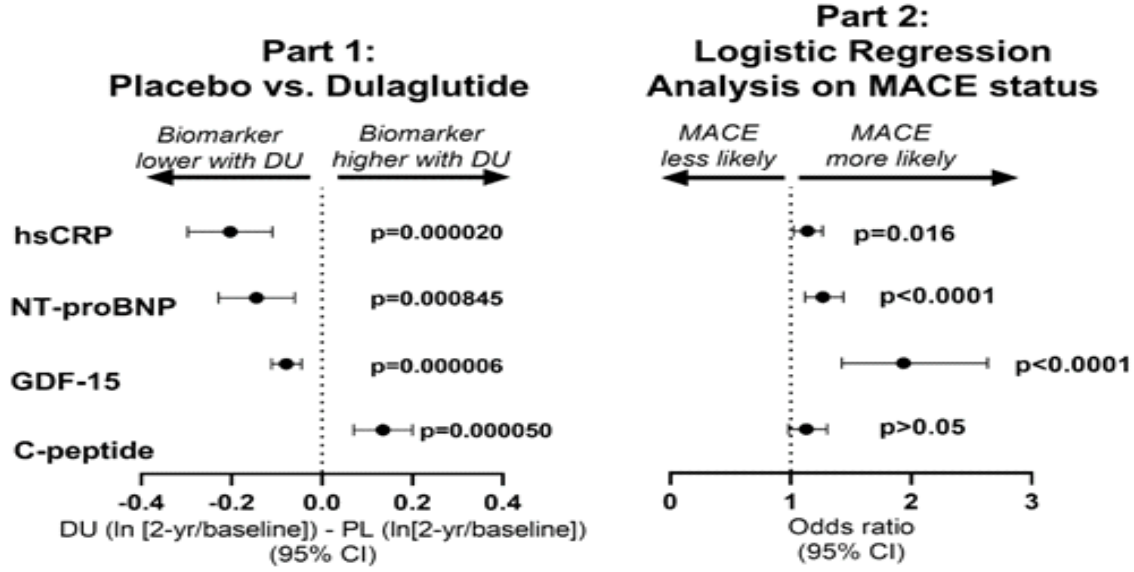
In contrast, BP as measured at the baseline of the OS was not significantly associated with cardiovascular death during follow-up neither in the total population nor in any subgroup (HR = 1.00 [0.99-1.01], p=0.652; HRMetS = 1.00 [0.99-1.01], p=0.468 and HRnoMetS = 1.00 [0.99-1.01], p=4.66). We thus conclude that BP assessed earlier in life is a better predictor of cardiovascular mortality than BP assessed later in life.

Protein Biomarkers Associated with Dulaglutide and Cardiovascular Events in REWIND

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Jonathan M. Wilson, Guillaume Pare, Shun Fu Lee, Helen M. Colhoun, Hui-Rong Qian, Valentina Pirro, Anastasia Hoover, Mark Lakshmanan, Giacomo Ruotolo, Kevin L. Duffin, Hertzel C. Gerstein from Indianapolis, IN, Hamilton, ON, Canada, Edinburgh, United Kingdom.

In the REWIND trial, dulaglutide (DU) reduced the risk of CV outcomes compared with placebo (PL) (Major Adverse Cardiovascular Event [MACE]-3 hazard ratio 0.88). This post hoc analysis studied circulating protein biomarkers associated with CV events to better understand how DU reduces CV risk.



Left panel: For Part 1, 4 biomarkers of 19 tested were associated with DU as shown by the difference (DU minus PL) in the natural log (ln) of biomarker changes from baseline to 2 years of treatment to an ANCOVA model with model terms of treatment, biomarker baseline level, and CV risk factors (age, sex, A1C, eGFR, previous CVD, current smoking, albuminuria, LDL-C, BMI, SBP, and race as white/non-white); p <0.0026 was significant. **Right panel:** For Part 2, the ln of 2-year/baseline value for the 4 biomarkers were tested in a logistic regression model for MACE case/control, adjusting for DU treatment, and CV risk factors previously listed (right panel). Odds ratios per unit change of ln(2-year/baseline) are shown. No adjustment for multiple testing was made for the logistic regression analysis. The 907 cases with MACE and 907 non-MACE controls were matched for treatment, gender, baseline age, systolic blood pressure, LDL-C, statin use, and A1C.
(Abbreviations: A1C=glycated hemoglobin A1C; BMI=body mass index; hsCRP=C-reactive protein; CVD=cardiovascular disease; DU=dulaglutide; eGFR=estimated glomerular filtration rate; GDF-15=Growth/Differentiation Factor-15; LDL-C=low-density lipoprotein cholesterol; ln=natural logarithm; MACE=major adverse cardiovascular event; NT-proBNP=N-terminal prohormone of brain natriuretic peptide; PL=placebo; SBP=systolic blood pressure; yr=year).

Patients ≥50 years of age with T2D, A1C ≤9.5%, BMI ≥23 kg/m^2, and CV risk were treated DU (1.5 mg weekly) or PL. This case/control study matched 907 cases with MACE with 907 non-MACE controls. A total of 19 protein biomarkers were measured by immunoassay in plasma and serum. Biomarkers associated with DU were first identified by fitting the natural log (ln) of biomarker changes from baseline to 2 years of treatment to an ANCOVA model; the p value cutoff was 0.0026 after Bonferroni correction. Then, the identified biomarkers were fit to a logistic regression model for MACE case/control to test possible impact on CV outcome.

Four biomarkers were associated with DU: C-reactive protein (hsCRP), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and Growth/Differentiation Factor-15 (GDF-15) had attenuated increases over 2 years for DU vs. PL, and C-peptide had a greater increase over 2 years for DU vs. PL. Logistic regression analyses showed that patients with smaller increases in hsCRP, NT-proBNP, and GDF-15 were less likely to have MACE. C-peptide levels did not significantly impact MACE occurrence.

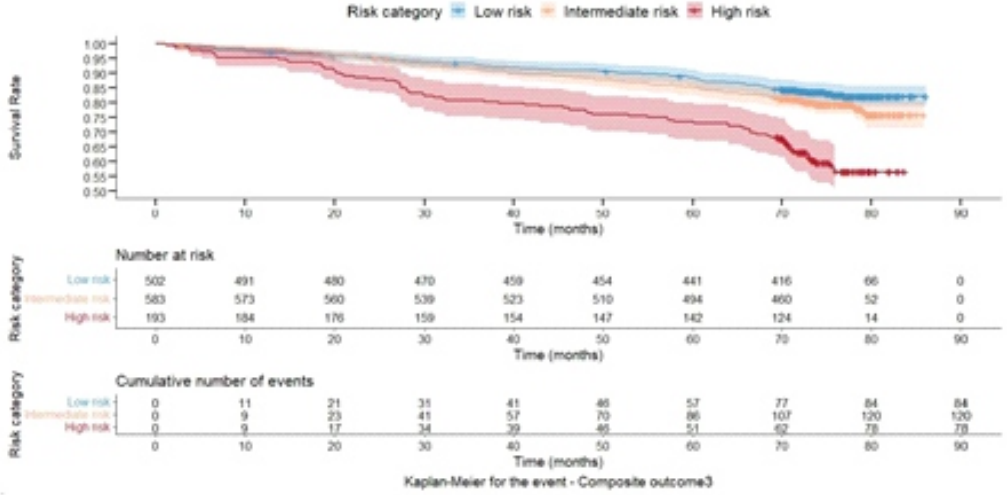
KidneyIntelX Association with Clinical Outcomes in Diabetic Kidney Disease

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Fergus Fleming, Hiddo L. Heerspink, Steven Coca from Stanford, CA, Raritan, NJ, Spring House, PA, Groningen, Netherlands.

Individuals with diabetic kidney disease (DKD) are at risk for progression, heart failure, and death. We assessed the association of KidneyIntelX, a bioprognostic test validated for DKD progression, with a composite time-to-event endpoint of 57% eGFR decline, kidney failure, heart failure hospitalization (HFH), or death in a posthoc analysis of a subgroup of CANVAS participants with DKD. sTNFR-1, sTNFR-2, and KIM-1 were measured via proprietary assays, and KidneyIntelX scores were calculated using the existing algorithm.

Figure 1. Kaplan-Meier Curves for the Composite Event Stratified by KidneyIntelX Risk Strata



The figure above shows the composite event rate over time stratified by KidneyIntelX risk category (High, Intermediate and Low). The table below shows the number at risk at different time points.

Hazard ratios for high vs. low-risk strata for the composite outcome were adjusted for age, sex, race, treatment arm, baseline CVD, HbA1c, SBP, DBP, LDL, BMI). During 5.6 years follow-up, 282 (22%) of the 1278 CANVAS participants with DKD experienced the outcome (57% decline in eGFR/ESKD 3%, HFH 6%, death 16%). The adjusted HR for the composite outcome in KidneyIntelX high-risk group was 2.7 (95% CI 1.9 to 3.8) vs. the low-risk group. Canagliflozin reduced the risk for the composite event vs. placebo, with larger absolute risk reductions for the high-risk stratum (11%), compared to intermediate (6%) or low-risk strata (4%) ($p<0.01$).

In conclusion, KidneyIntelX successfully risk-stratified adults with DKD for clinical outcomes. Absolute risk reductions with canagliflozin were greatest in the high-risk stratum, thereby potentially allowing its use to identify patients most likely to benefit from treatment.

SESSION-4 :
From Paper to Practice: Preventing Diabetes Foot Complications

Innovations in Diabetes Foot Complication Translational Research

Friday, 3rd June 2022

Laura Shin, DPM, PhD, Assistant Professor of Clinical Surgery, Keck Medicine of University of Southern California.

Dr. Shin discussed some of the translational research their team is conducting at USC evaluating the diabetic foot and treatment and imaging modalities. She highlighted during her talk the relationship and significance of bench research and how it can translate that into therapies for patient populations.

This topic is important for advancing the bench to bedside therapies to help combat diabetic foot complications & preventing amputations.

"During the COVID lockdown, not only did we have shutdowns for the different clinics around the area, but also the emergency rooms were virtually impossible for these patients to get to," Dr. Shin said. "The pandemic lockdowns included cancelation of a lot of our outpatient hospital services. This included lab work, vascular studies, and radiology. So getting care to these high-risk patients who are not only at high risk for developing complications related to COVID, but also have complications related to diabetic foot was really quite challenging."

As part of the care team's strategy to expand the use of telemedicine in the acute care setting, Dr. Shin said information packets were provided to patients, families, and caregivers that included instructions for a "three-minute foot exam" to assist providers in prescribing care and identifying high-risk limbs.

"Comprehensive foot exams are highly recommended and really vital to improve outcomes. So just like in the doctor's office, we had patients fill these out, or the caregivers fill them out and let us know what patients were at the highest risk," she said. "A large part of us being able to treat these patients as best we could, especially with using different telemedicine technologies, was the 'foot selfie.' If they were flexible or agile enough, they could take the pictures themselves using their cell phones, or have a family member or caregiver take the pictures."

Providing comprehensive, user-friendly resources and maintaining open lines of communication were the keys to providing optimal care to patients and preventing severe complications during the pandemic, Dr. Shin said.

"With COVID-19, we have learned a lot about accessing patients," she said. "Utilizing different tools and avenues for telemedicine was extremely helpful for us and for our patients with diabetes and diabetic foot care needs. And although it's not a replacement for inpatient visits, I think we were still able to manage to keep a lot of these patients safe, keep them out of the hospital, and keep them moving in the world."

SESSION-5 : What is New in Diabetic Retinopathy Screening and Grading?

How Should Artificial Intelligence Influence Screening Intervals?

Friday, 3rd June 2022

Tunde Peto, MD, PhD.

The lifestyle of modern society has changed significantly with the emergence of artificial intelligence (AI), machine learning (ML), and deep learning (DL) technologies in recent years. Artificial intelligence is a multidimensional technology with various components such as advanced algorithms, ML and DL. Together, AI, ML, and DL are expected to provide automated devices to ophthalmologists for early diagnosis and timely treatment of ocular disorders in the near future. In fact, AI, ML, and DL have been used in ophthalmic setting to validate the diagnosis of diseases, read images, perform corneal topographic mapping and intraocular lens calculations. Diabetic retinopathy (DR), age-related macular degeneration (AMD), and glaucoma are the 3 most common causes of irreversible blindness on a global scale. Ophthalmic imaging provides a way to diagnose and objectively detect the progression of a number of pathologies including DR, AMD, glaucoma, and other ophthalmic disorders. There are 2 methods of imaging used as diagnostic methods in ophthalmic practice: fundus digital photography and optical coherence tomography (OCT). Of note, OCT has become the most widely used imaging modality in ophthalmology settings in the developed world. Changes in population demographics and lifestyle, extension of average lifespan, and the changing pattern of chronic diseases such as obesity, diabetes, DR, AMD, and glaucoma create a rising demand for such images. Furthermore, the limitation of availability of retina specialists and trained human graders is a major problem in many countries. Consequently, given the current population growth trends, it is inevitable that analyzing such images is time-consuming, costly, and prone to human error. Therefore, the detection and treatment of DR, AMD, glaucoma, and other ophthalmic disorders through unmanned automated applications system in the near future will be inevitable. The presentation provided an overview of the potential impact of the current AI, ML, and DL methods and their applications on the early detection and treatment of DR, AMD, glaucoma, and other ophthalmic diseases.

Novel methods of retinal imaging for ocular telehealth programs

Recent technological advances in diabetic retinopathy screening fall into three categories: image capture, image analysis, and risk assessment. Novel methods of image capture include the use of scanning (laser) confocal ophthalmoscope-based cameras with ultrawide field imaging or conventional cameras with improvements, such as the use of handheld mobile devices. Automated image analysis and use of artificial intelligence can make an important contribution in teleophthalmology not only for the automated detection of diabetic retinopathy but also to identify patients at risk of cardiovascular or neurodegenerative dis-

eases. New methods for risk assessment include the use of alternative methods for screening (e.g., tear film and potentially mRNA and genetic information) and visual function data. However, before implementation of these new technologies, evidence is needed for their clinical effectiveness and cost-effectiveness. The use of scanning confocal ophthalmoscopy (with lasers or a white-light light-emitting diode illuminator), particularly with ultrawide field imaging technology, can potentially improve image quality and the field of view without the need for pupillary dilation. In a nationwide teleophthalmology program for diabetic retinopathy in the setting of the Indian Health Service-Joslin Vision Network program (which serves American Indian and Alaska Native communities at 97 sites across 25 states), it was shown that non-mydriatic ultrawide field imaging was able to considerably reduce the rate of ungradable images and substantially increase not only the detection of diabetic retinopathy, but also of referable diabetic retinopathy, compared with non-mydriatic multifield fundus imaging.

Additionally, the presence of predominantly peripheral lesions seen only with ultrawide field images was shown in one study to enable the identification of a more severe level of diabetic retinopathy in 7.2% of eyes (9.6% of patients), suggesting an increased risk of retinopathy progression in these eyes. These findings support the substantial potential advantages of ultrawide field imaging for large diabetic retinopathy screening teleophthalmology programs. Approaches to retinal image analysis and prediction of retinopathy progression. The use of artificial intelligence models for retinal image interpretation in the screening of diabetic retinopathy is a rapidly evolving field.

Historically, artificial intelligence systems have relied on so-called hard-coded image processing and specific lesion-detection algorithms. In the past decade, computing advances have led to impressive results with deep learning processes that enable artificial intelligence systems to self-learn and improve with the increasing number of images assessed. Leveraging current image databases tens of thousands to hundreds of thousands of images, deep learning algorithms have now surpassed traditional machine-learning methods. The use of deep learning has led to substantial improvements in diabetic retinopathy detection, achieving significantly higher sensitivity (87–90%) and specificity (98%).

In traditional machine learning, features needed to be extracted manually with specific feature-detection algorithms before being incorporated into the machine algorithm. By contrast, deep learning mainly relies on large datasets to generate data representations rather than feature-specific algorithms. This approach allows deep learning algorithms to program autonomously by learning from a large set of examples that demonstrate the desired behaviors. The need to specify rules explicitly is thereby removed, allowing unsupervised learning as the relevant features are automatically learned. One widely used deep learning model is convolutional neural networks (CNNs). CNNs can take in an input image and assign importance to various features to achieve the desired outcome and behavior. Several studies have shown increased sensitivity and specificity when CNNs were used for the detection of diabetic retinopathy. Using a CNN in microaneurysm detection shows a sensitivity value of 0.8 for every mean of more than six false positives per image. The automated analysis of retinal color images for diabetic retinopathy detection has been studied extensively, with systems in clinical use in both Europe and the USA. Apart from fundus images, CNN models have been used in spectral domain optical coherence tomography segmentation models to identify hyperreflective foci that surpass the accuracy of traditional methods.

Initially, automated retinal image analysis algorithm development was confined to small (usually start-up) software firms. The potential

market size and growth potential, however, have led to a myriad of entrants— including industry-leading players such as Google and IBM—investing considerable resources into these developments. Currently, systems for the automated and computer-assisted detection, classification, and diagnosis of diabetic retinopathy vary greatly in design, validation, degree of autonomy, and clinical use. Several automated and computer-assisted approaches can be used to detect diabetic retinopathy and monitor patients who are at risk for diabetic retinopathy progression and vision loss. Nevertheless, while artificial intelligence technologies are in the process of resolving clinical and cost-effectiveness challenges as well as image acquisition and quality concerns, the extent of acceptance by both patients and health-care professionals, as well as unresolved medicolegal questions, limit implementation in most countries at present.

Predictive risk models for diabetic retinopathy progression

Models for predicting the risk of developing diabetic retinopathy and its progression are based on the creation of a learning system that enables aggregation and analysis of the great wealth of diverse patient conditions and treatment approaches taken by eye-care providers. The increased use of electronic medical records has resulted in the creation of large high-resolution health information databases that can be used in the development of deep learning or artificial intelligence models. This approach has resulted in the concept of a more personalized medicine with the goal of providing the right treatment to the right patient at the right time. With the use of predictive modelling, a wide array of factors (e.g., clinical care, genomics, metabolomics, proteomics, imaging, etc.) and a highly complex physician decision-making process will be integrated. Such work can potentially optimize care of complex chronic diseases such as diabetes and predict the risk of developing diabetic retinopathy in a personalized way. Application of predictive modelling promises several innovative approaches that use a multidisciplinary approach to diabetes care, leveraging the clinical expertise of eye-care providers to potentially facilitate the use of the model in day-to-day clinical practice. Unique and complex clinical scenarios that would not be easily examined or not financially available in randomized clinical trials can be addressed through this collaborative clinician–engineer process.

Conclusion

Health-care affordability, quality, and accessibility for diabetic retinopathy screening are important factors in the prevention of blindness in populations at risk. The combination of automated retinal image analysis and telemedicine has the potential to substantially improve how diabetes eye care is delivered by providing automated real-time assessment in a more personalized way. Additionally, the introduction of new technologies for diabetic retinopathy screening will improve its cost-effectiveness. Finally, the possibility of using retinal examination to help to identify patients at risk of cardiovascular disease and cognitive impairment could change the concept of diabetic retinopathy screening, with benefits beyond the prevention of sight-threatening disease.

SESSION-6 : Hypoglycemia, CGM Metrics & HbA1c: Patient and Clinician Perspectives

Continuous Glucose Monitoring Measures Impact Cognitive Function in Long-Duration Type 1 Diabetes

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Hetal Shah, Marc Gregory Yu, Tahani Boumenna, John Gauthier, Regina Tham, Atif Adam, George L. King, from Boston, MA .

As people with type 1 diabetes (T1D) live longer, they are increasingly presented with greater health risks tied to aging-related cognitive decline. "We previously reported that participants of the Joslin 50-year Medalist Study ("Medalists"), with T1D ≥50 years, have impaired cognitive function compared to controls without diabetes, and similar to those with type 2 diabetes."

While glycemic control has been shown to impact cognitive function, the impact of day-to-day continuous glucose monitoring (CGM) measures is unclear. CGM provides measures of glycemic variability uncaptured by HbA1c alone. A 2-week block of CGM data was procured from a subset of Medalists (n=64) who also had undergone a cognitive battery testing psychomotor function (Grooved Pegboard), verbal learning and memory (RAVLT- immediate and delayed recall), working memory (Wechsler) and executive function (WASI). In a cross-sectional study, log-transformed CGM metrics were tested for associations with cognitive domains in linear regression models adjusted for duration of diabetes, education status and sex. Better psychomotor function was associated with a higher time in range 70 - 180 mg/dL (p=0.04), and with lower: glucose coefficient of variation (p=0.02), time above range (TAR) >180 -250 mg/dL (p=0.01), TAR > 250 mg/dL (p=0.07), mean glucose (p=0.07) and glucose management indicator (p=0.07). Better delayed recall associated with lower time below range < 70 mg/dL (p=0.02) and better immediate recall with lower TAR > 180 -250 mg/dl (p=0.08). Lower HbA1c previously associated with better executive function in the Medalists, but not with other cognitive domains.

This CGM study shows that glucose variability and hyperglycemia impact psychomotor function, while hypoglycemia impacts verbal learning and memory. Thus, better day-to-day glucose management in conjunction with long-term HbA1c control, are potentially important to prevent cognitive decline in aging populations with long-duration T1D.

Algorithmic Identification of Atypical Diabetes in Electronic Health Record (EHR) Systems

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Victoria Chen, Sara Jane Cromer, Christopher Han, William G. Marshall, Shekina Emongo, Tim Majarian, Jose C. Florez, Josep M. Mercader, Miriam Udler from Boston, MA, Providence, RI, Cambridge, MA, from Hamilton, ON, Canada, Helsinki, Finland, Frankfurt, Germany.

Understanding atypical forms of diabetes may lead to personalized treatment regimens and discovery of novel pathophysiologic mechanisms of diabetes. We aimed to create a high-throughput method for identifying patients with atypical diabetes in large electronic health record (EHR) databases and validate this method in the Mass General Brigham (MGB) Biobank.

Patients with likely type 2 diabetes (T2D) were identified using a validated machine-learning (ML) algorithm. "Typical" T2D was filtered out through a "base algorithm" that excluded individuals with body mass index (BMI) ever >30 kg/m^2, HDL values ever < 50 mg/dL, and triglycerides ever >150 mg/dL. To remove people with typical type 1 diabetes (T1D), we tested six additional "branch algorithms," relying on clinical characteristics, including autoantibodies, medication usage, and T1D diagnosis determined by ML algorithm, resulting in six overlapping cohorts. Charts were then manually reviewed, and diabetes type was classified by two endocrinologists into one of three categories: atypical, not atypical, and indeterminate due to missing information.

"We identified 119 potentially atypical cases, of whom 16 individuals were confirmed to have atypical diabetes after expert review, across the six branch algorithms. The branch algorithm which excluded T1D by removing patients who had ever used outpatient insulin had the highest percentage yield (13 of 27; 48.2%) of atypical diabetes ."

The 16 atypical cases had significantly lower BMI and higher HDL compared to an unselected group of individuals with T1D or T2D diagnosis by ML algorithm. Compared to the ML T1D group, the atypical group had a significantly higher T2D polygenic score and lower hemoglobin A1c.

"In summary, we designed an algorithm to identify individuals with atypical diabetes within an EHR database with up to 48% yield which may shed light on the heterogeneity of T2D and help generate cohorts of atypical cases for studies, such as the Rare and Atypical Diabetes Network (RADIANT)."

Effectiveness and Safety of Empagliflozin in Routine Care: Results from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Phyo T. Htoo, Helen Tesfaye, Julie M. Paik, Deborah J. Wexler, Mehdi Najafzadeh, Robert Glynn, Anouk Deruaz-Luyet, Soulmaz F. Fazeli Farsani, Lisette Koeneman, Sebastian Schneeweiss, Elisabetta Patorno from Boston, MA, Ingelheim am Rhein, Germany, Ingelheim, Germany, AL.

EMPRISE is a 5-year monitoring program that evaluates the effectiveness and safety of empagliflozin (EMPA) using Medicare and 2 U.S. commercial claims [2014-2019 (2018 for Medicare)].

"We identified 190,226 patients ≥18 years with type 2 diabetes initiating EMPA or a dipeptidyl peptidase-4 inhibitors (DPP-4i), and followed them up for heart failure hospitalization in primary (HHF-Specific) or any discharge positions (HHF-Broad), a composite of myocardial infarction (MI) and stroke, and all-cause mortality (ACM) (Medicare only). Safety outcomes were lower-limb amputations (LLA), non-vertebral fractures, diabetic ketoacidosis (DKA), acute kidney injury (AKI), renal and bladder cancers (CA). We estimated pooled HR

(95% CI) after propensity score matching, adjusting for 143 baseline covariates."

Compared to DPP4i, EMPA was associated with a reduced risk of HHF [HHF-Specific: 0.47 (0.41, 0.55); HHF-Broad: 0.67 (0.62, 0.72)], a similar risk of the composite of MI or stroke [0.92 (0.84, 1.02)], and a reduced risk of ACM [0.56 (0.46, 0.68)]. EMPA was associated with a reduced risk of AKI [0.73 (0.68, 0.78)], an increased risk of DKA [1.88 (1.51, 2.34)], and a similar risk of LLA, fractures, and renal and bladder CA.

"Our findings support the cardiovascular effectiveness of EMPA in routine care with a safety profile in line with documented information."

Table 1. Pooled patient characteristics and outcomes in 1:1 PS-matched population from 3 databases[1]

	Empagliflozin (N =95,113)	DPP-4i (N =95,113)	
Pooled patient characteristics[2]	Mean (SD) or n (%)	Mean (SD) or n (%)	Stand. Diff.
Age, mean (SD)	60.5 (11.94)	60.4 (11.94)	0.005
Gender female, n (%)	42,248 (44.4%)	42,392 (44.6%)	0.003
Baseline cardiovascular diseases[3], n (%)	27,982 (29.4%)	27,982 (29.4%)	0.000
Combined comorbidity score, mean (SD)	1.1 (1.78)	1.1 (1.78)	0.003
Acute MI, n (%)	1,895 (2.0%)	1,870 (2.0%)	0.002
Heart failure, n (%)	6,617 (7.0%)	6,609 (6.9%)	0.000
Ischemic Stroke, n (%)	6,084 (6.4%)	6,112 (6.4%)	0.001
Chronic kidney disease, n (%)	8,870 (9.3%)	9,012 (9.5%)	0.005
Baseline use of insulin; n (%)	21,487 (22.6%)	21,261 (22.4%)	0.006
HbA1C, %, mean (SD)[4]	9.0 (2.33)	8.9 (2.32)	0.016
eGFR, mean (SD)[4]	81.2 (13.0)	80.0 (22.2)	0.068
Pooled Outcomes	N events (IR/1000 PY)	N events (IR/1000 PY)	HR (95% CI)
HHF-Specific[5]	238 (3.6)	495 (7.9)	0.47 (0.41, 0.55)
HHF-Broad[6]	1,137 (17.3)	1673 (26.8)	0.67 (0.62, 0.72)
Myocardial infarction or stroke	763 (11.6)	806 (12.8)	0.92 (0.84, 1.02)
Myocardial infarction	484 (7.3)	541 (8.6)	0.87 (0.77, 0.98)
Ischemic or hemorrhagic stroke	286 (4.3)	269 (4.3)	1.05 (0.89, 1.23)
All-cause mortality (Medicare only)	162 (11.0)	297 (19.6)	0.56 (0.46, 0.68)
Lower-limb amputation	197 (3.0)	181 (2.9)	1.05 (0.86, 1.29)
Bone fracture	239 (3.6)	226 (3.6)	1.02 (0.85, 1.22)
Renal cancer	54 (0.8)	66 (1.1)	0.78 (0.54, 1.12)
Bladder cancer	59 (0.9)	48 (0.8)	1.20 (0.82, 1.75)
Hospitalization for diabetic ketoacidosis	237 (3.6)	122 (1.9)	1.88 (1.51, 2.34)
Acute kidney injury	1,373 (20.9)	1,845 (29.6)	0.73 (0.68, 0.78)

PS: propensity score; DPP4i: dipeptidyl peptidase-4 inhibitors; Stand. Diff.: standardized difference; SD: standard deviation; HbA1c: Hemoglobin A1c; eGFR: estimated glomerular filtration rate; IR: Incidence rate; PY: person-years; HR: hazard ratio; CI: confidence interval
Median as-treated follow-up ranged from 5.1-5.5 months
[1]Follow-up started on the day following treatment initiation and ended at the occurrence of a study outcome, insurance disenrollment, treatment switch/discontinuation, or end of study period, whichever came first.
[2]Patient characteristics were measured during the 12 months (365 days) preceding (and including) date of treatment initiation
[3]Included atherosclerotic cardiovascular diseases or heart failure at baseline
[4]Available for a subset (~25-27%) of patients, thus not included in in the PS model
[5]Defined as a discharge diagnosis of heart failure in the primary position
[6]Defined as a discharge diagnosis of heart failure in any position

SESSION-7 :
Heterogeneity of Diabetes

American Diabetes Association Symposium to Bring to Light the Impact of Suicide and Depression on Adolescents with Type 1 Diabetes

Friday, 3rd June 2022

A symposium presented by international research group, RESCUE (REducing SuiCide rates amongst individUals with diabEtes) Collaborative Community, will address the ongoing connection between suicide and people with type 1 diabetes, with the goal of highlighting available resources and key takeaways for the field. The symposium comes at a time when adolescents and young adults with type 1 diabetes are 61% more likely to say they feel suicidal than those without diabetes. **Suicide and Self-Injury—Unveiling and Addressing the Hidden Nightmare in Diabetes was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, LA.**

Suicide is a leading cause of death among young people ages 20 to 24 in the United States, and the risk is even higher in individuals with type 1 diabetes. In fact, up to 7% of deaths in individuals with type 1 diabetes are a result of suicide. However, current screening tools for depression and suicide often miss individuals at risk of suicide and the risk among the type 1 diabetes patient population is greatly underestimated.

The symposium will highlight the work of RESCUE and address solutions for two distinct uncertainties faced by health care providers in the management of people with type 1 diabetes at risk of suicide: how to identify those at risk and the best way to prevent and reduce that risk.

Discussion topics will include:

- Depression, Suicidal Ideation, and Self-Harm among Adults with Diabetes—Unmet Needs and How to Address Them
- Partnership Among RESCUE, Advocacy, and Industry to Address Suicide and Self-Harm in Diabetes
- Educational Support Needs for Addressing Suicide and Self-Harm in Diabetes

"Suicide and self-harm is an all-too-common reality for young adults with type 1 diabetes, but it doesn't have to be. With a multi-pronged approach to awareness, education, and identification, we have the opportunity to intervene on the link between suicide and diabetes," said Professor Katharine Barnard-Kelly, PhD., RESCUE Collaborative Community. "With this symposium, it is our hope that we can reach stakeholders with awareness and arm them with messages that can ultimately save a young person's life if adopted in clinical practice and through mental health screenings."

Persistent and Heterogeneous Long-Term Effects of the Diabetes Prevention Program (DPP) Intensive Lifestyle (ILS) Intervention on Diabetes Incidence

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. William C. Knowler, Sharon Edelstein, Peter H. Bennett, Dana Dabelea, from Phoenix, AZ, Rockville, MD, Aurora, CO, Seattle, WA, Baltimore, MD.

During the three years of the DPP, ILS reduced incidence of diabetes compared with placebo in high-risk adults. Diabetes was defined using ADA criteria based on 1) annual OGTT or semi-annual fasting glucose (the primary DPP outcome, diab-G, hazard ratio (HR)=0.42 and rate difference (RD)= -6.2 cases/100 person-years) or 2) annual HbA1c ≥ 6.5% (diab-A1C, HR=0.51 and RD = -4.2).

After DPP ended, participants were unmasked, placebo was discontinued, and all participants were offered group-based ILS and followed in the DPP Outcomes Study. We now compare the original ILS and placebo groups over a mean of 21 years since randomization.

"We test heterogeneity across subgroups defined by demographics and baseline glucose, HbA1c, BMI, and history of gestational diabetes and express it by interaction p-values (P-het)." During the total follow-up, ILS, compared with placebo, significantly reduced incidence of diab-G: HR=0.76 (95% CI=0.68, 0.85), RD= -1.62 (-2.28, -0.97) and of diab-A1C: HR=0.80 (0.70, 0.92), RD= -1.67 (-2.24, -1.10). Effects on diab-G were homogenous across subgroups except for fasting glucose (P-het <0.01) and HbA1c (P-het <0.02) with greater effects at higher baseline values.

By contrast, ILS reduced incidence of diab-A1C more in older than younger persons (P-het <0.02), and more in men than women (P-het <0.03). Notably, ILS was highly effective in reducing incidence of diab-A1C if baseline HbA1c was already elevated (HbA1c=6.0-6.4%: HR=0.62, RD= -3.27) but ineffective if baseline HbA1c was normal by ADA criteria (HbA1c <5.7%: HR=1.09, RD= +0.19; P-het <0.001). In sum, ILS effects on reducing incidence of diab-G and diab-A1C persisted but decreased during total follow-up from that observed during DPP (i.e., HRs and RDs closer to 1 and 0). ILS effects on diab-G were greater in those with higher baseline fasting glucose or HbA1c. Effects on diab-A1C were greater in men, older participants, and those with higher baseline HbA1c.

Perspectives of People with Diabetes and Caregivers Experiencing Insulin Pump Infusion Set Failure (IPISF): A Qualitative Study

Friday, 3rd June 2022

This paper was presented on June 3rd 2022 at the 82nd Scientific Sessions held by the American Diabetes Association® (ADA) in New Orleans, by Drs. Luis E. Blanco, Lisanne M. Vanengelen, John C. Gray, John H. Wilcox, from Memphis Tennessee.

IPISF can be a life-threatening complication and remains a serious issue for individuals who utilize automated insulin delivery (AID) systems. This study assessed the emotional burden of IPISF and how infusion failure affects sentiment towards insulin pump use.

50 follow-on interviews (10/2020 - 05/2021) were performed with Caregivers (CG) and People with Diabetes (PWD) from the 2020 Diatech Diabetes - T1D Exchange Insulin Pump Infusion Set Failure Management Survey. Participants consented to a 1-hour video call interview covering topics related to insulin pump use and experiences with infusion set failures. Audio recordings were transcribed using Trint Software and qualitative interview data was analyzed using thematic analysis, R, and Python.

39 PWD and 11 CG were interviewed (PWD age 40.1±20.9 years, CG age 46.2±6.3 years, 72% female, 72% white, 50% household income ≥$100K/year, CSII use for 11.5±8.2 years, 48% use AID, HbA1c 6.9±1.4%, TIR 69.9±18.9%, infusion set wear time 2.9±0.8 days, 62% having ≥1 IPISF/month). Participants shared quotes on how IPISF is "a direct correlation to my level of happiness...kind of irks me and just makes me angry...because as the caregiver, it's my responsibility to make sure that it goes right" and technology that reduces IPISF and improves detection "would probably be the first step in making me even reconsider going back on the pump." Identified themes showcase the burden of diagnosing and managing infusion failures when overcoming existing alarm fatigue, trusting care team input, and general stress of CSII therapy.

IPISF's clinical impact is associated with hyperglycemia and DKA, yet IPISF can also affect the mental health of people who use CSII therapy. CSII users heavily rely on hyperglycemia to detect IPISF and can have issues identifying true IPISF from other confounding factors, thus increasing the risk of CSII therapy and justifying the need for better IPISF detection.

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New Orleans, 2022

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