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ADA 82ND SCIENTIFIC SESSIONS New Orleans, 2022

Presents

AMERICAN DIABETES ASSOCIATION

82nd SCIENTIFIC SESSIONS

DAILY COVERAGE

TOP 7 SESSIONS: DAY–3

TOPIC OF CONTENT

SESSION-1 :
New Hope, Old Challenges in Heart Failure

Newer Guideline-Directed Medical Therapies (GDMT) are Underutilized in 2021 in Patients with Heart Failure with or Without Diabetes

Sunday, 5th June 2022

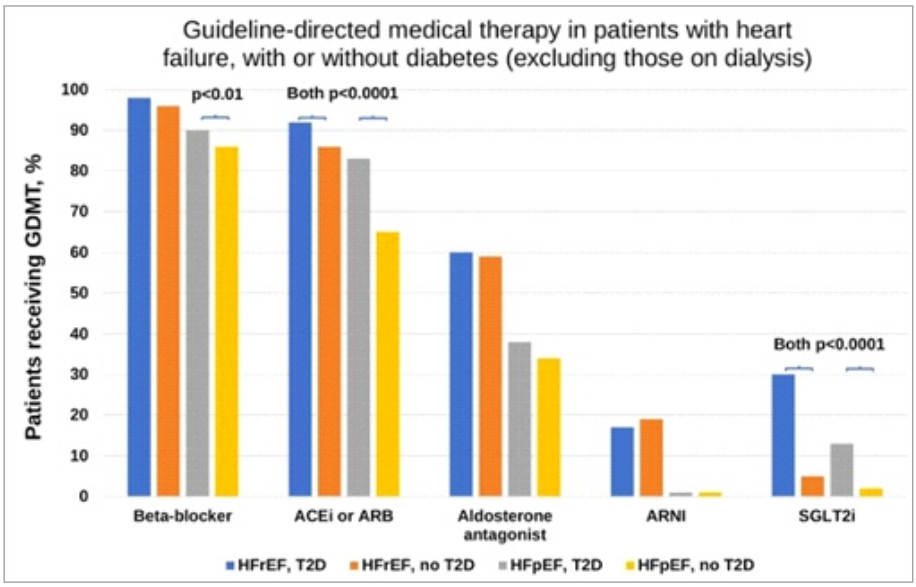
This paper was presented by Drs. Mario Enrico Canonico, Judith Hsia, Christopher P. Cannon, Marc P. Bonaca from Aurora, CO, Denver, CO, Boston, MA, as a part of the symposium "New Hope, Old Challenges in Heart Failure-New Heart Failure Clinical Trials" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Heart failure (HF) affects ~40% of patients with diabetes. In 2021, guidelines endorsed newer therapies such as angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) as first-line medications to improve clinical outcomes.

"We examined GDMT using claims data in a large health system which provides both rural and urban care. Patients with HF encounters during the 12 months preceding 18 Dec 2021 were extracted from the Univ of Colorado health system (UCHealth) TriNetX database. GDMT use was compared by chi square."

Among 10170 patients with HF encounters, 3356 (33%) had reduced (HFrEF) and 2980 (29%) preserved ejection fraction (HFpEF), 13% mixed and 25% other types or unspecified HF. Mean age was 71+14y, 45% were female, 8% Black, 10% Latino; 43% had T2D and 44% eGFR<59. Older GDMT such as beta-blockers and RAASi were widely prescribed (Figure); patients with T2D were more likely to receive ACEi/ARB and those with HFpEF and T2D were more likely to receive beta blockers. In contrast, use of ARNI and SGLT2i was less frequent. Patients with T2D were more likely to receive SGLT2i than those without T2D.

Demographic and clinical characteristics were consistent with the US population. ARNI and SGLT2i use even in 2021 was infrequent among patients with HF; SGLT2i use was particularly low in those without T2D.



Machine-Learning Models to Predict CKD and HF in Type 2 Diabetes Patients Without Diabetes

Sunday, 5th June 2022

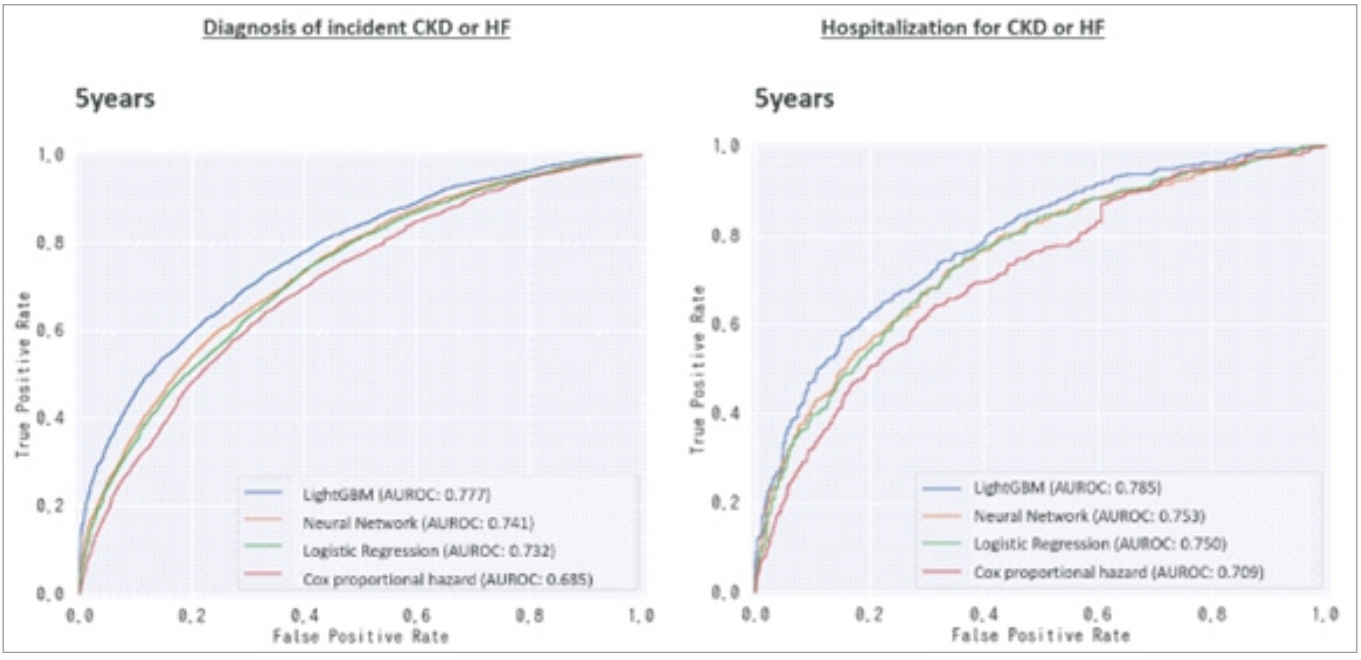
This paper was presented by Drs. Hiroo Tsubota, Atsushi Suzuki, Masaki Makino, Eiichiro Kanda from Oyoake, Japan, Kurashiki, Japan, Tokyo, Japan, as a part of the symposium "New Hope, Old Challenges in Heart Failure-New Heart Failure Clinical Trials" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Chronic kidney disease (CKD) and heart failure (HF) are the first and most frequent, and life-threatening comorbidities in type 2 diabetes (T2D) patients. Early intervention is important to prevent CKD and HF onset and to improve prognosis of these patients; however, the risk assessment of CKD and HF remains to be established.

"We aimed to build a machine learning model to predict the risk of CKD or HF onset in the early-stage T2D patients without a history of CKD or cardiovascular diseases (CVD). We developed prediction models using light gradient boosting machine (LightGBM), neural network, logistic regression, and Cox proportional hazards model."

The model was derived and validated in a sample of 217,054 T2D patients aged ≥18 years without a history of CKD or CVD extracted from a Japanese hospital-based administrative claims data. The outcomes used for the prediction model were diagnosis of incident CKD or HF and hospitalization for CKD or HF in 1, 2, 3, and 5 years. Based on the importance, 60 characteristics and laboratory data were selected and used for models.

LightGBM outperformed other models in all outcomes, with AUROCs 0.777 for diagnosis of incident CKD or HF, and 0.785 for hospitalization for CKD or HF in 5years. (Figure) The present study demonstrated successful development of prediction algorithms to support identifying T2D patients with high-risk of CKD or HF onset, which will contribute to improvement of patient prognosis.



SESSION-2 :
Emerging Directions in Diabetic Neuropathy

24-Month Results for 10-kHz Spinal Cord Stimulation (SCS) in Treating Painful Diabetic Neuropathy (PDN)

Sunday, 5th June 2022

This paper was presented by Drs. Erika Petersen, Thomas G. Stauss, James A. Scowcroft, from little Rock, AR, Milawaukee, WI, Lees Summit, MO, Orlando, FL, as a part of the symposium "Emerging Directions in Diabetic Neuropathy" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

PDN can lead to severe deterioration in quality of life. While published data demonstrate 10kHz SCS provides substantial refractory pain relief and neurologic improvement for PDN patients, here we report durability of these outcomes.

"Prospective, multicenter, RCT to document the impact of 10kHz SCS on PDN. Participants had PDN symptoms ≥12 months (M), refractory to medications, lower limb pain intensity ≥5cm (0-10cm visual analog scale [VAS]), and hemoglobin A1c ≤10%. Patients (N=216) were allocated 1:1 to 10kHz SCS (Nevro Corp.) plus conventional medical management (CMM) or CMM alone with optional crossover at 6 M."

The 10kHz SCS patients maintained substantial pain relief from 3 M, averaging 81.9% (95%CI 77.3 - 86.5) decrease at 24 M. At 6 M follow up, 0% of 10kHz SCS participants but 93% of eligible CMM patients elected to crossover. After SCS, both groups reported similar significant improvements in pain, sleep disturbance, and in pain interference with mood and daily activities (see Figure 1). There were no stimulation-related neurological deficits and 6 total explants (3.9%), 5 due to procedure-related infections and 1 as a precaution for endocarditis.

The largest RCT to date of SCS management of PDN demonstrates safety, durable pain relief and neurologic improvement over 24 months with 10 kHz SCS.

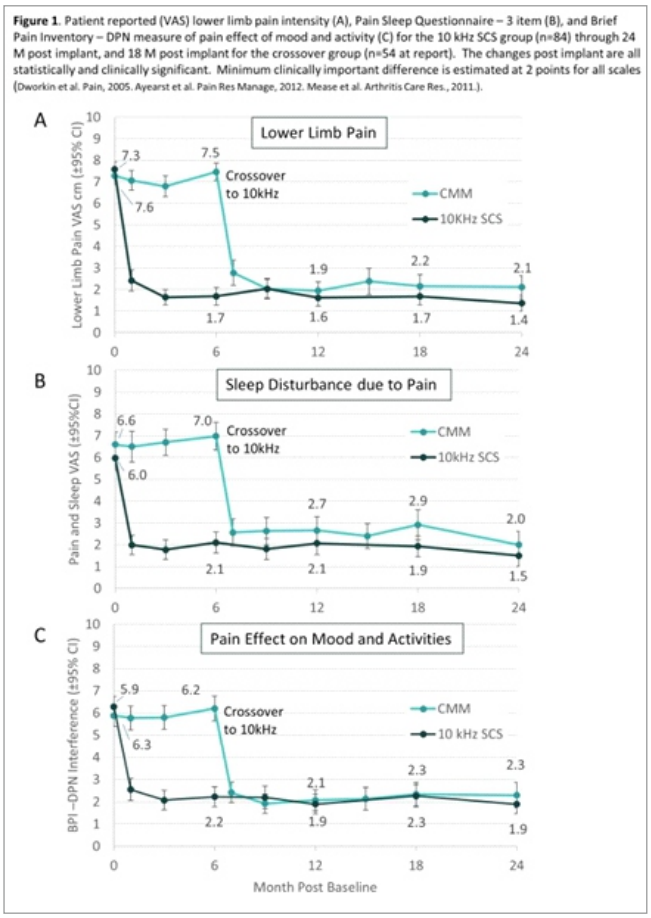


Figure 1. Patient reported (VAS) lower limb pain intensity (A), Pain Sleep Questionnaire – 3 item (B), and Brief Pain Inventory – DPN measure of pain effect of mood and activity (C) for the 10 kHz SCS group (n=84) through 24 M post implant, and 18 M post implant for the crossover group (n=54 at report). The changes post implant are all statistically and clinically significant. Minimum clinically important difference is estimated at 2 points for all scales (Dworkin et al. Pain, 2005. Ayearst et al. Pain Res Manage, 2012. Mease et al. Arthritis Care Res., 2011.).

Artificial Intelligence Approach to Treatment Classification in Painful Diabetic Neuropathy

Sunday, 5th June 2022

This paper was presented by Drs. Kevin Teh, Iain D. Wilkinson, Gordon P. Sloan, Solomon Tesfaye, Dinesh Selvarajah, Sheffield, United Kingdom as a part of the symposium "Emerging Directions in Diabetic Neuropathy" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

"Our study predicted treatment responses in patients with painful DPN (diabetic peripheral neuropathy) by developing a deep learning model using resting state functional magnetic resonance imaging (fMRI) neuroimaging datasets."

Forty-three consecutive patients who received intravenous lidocaine treatment for painful DPN were assessed. All subjects (responders n=29 and non-responders n=14) underwent detailed clinical and neurophysiological assessments to phenotype their pain sensory profile. Subjects also underwent brain resting-state fMRI. After pre-processing we performed a group concatenated independent component analysis (ICA) set to 30 components and automatically chose 7 highly correlated ($p<0.05$) ICA components. A 3D convolutional neural network (CNN) classification framework was trained using a VoxNet based architecture. This deep learning architecture compared models using (1) 7 correlated ICA networks 2) all 30 ICA networks generated 3) pre-processed resting state images.

The deep learning treatment response classification in a ten-fold cross validation experiment using 7 ICA spatial maps has a mean AUC of 0.85 and an F1-Score of 0.90. However, with the extra information of all 30 ICA maps the mean AUROC increased to 0.97 with an F1-Score of 0.95. Using only pre-processed resting-state fMRI data achieved suboptimal F1-Score of 69% and AUC score of 44%.

Through the use of our deep learning model, we have demonstrated high classification performance. Our method improves painful DPN treatment efficiency by stratifying patients to receive the correct treatment from the outset. We believe to our knowledge this is the first study utilising deep learning methods to classify treatment response in painful DPN.

Results

METRIC	7 COMPONENTS	30 COMPONENTS	Resting State
Accuracy	0.75	0.83	0.47
AUC	0.62	0.87	0.57
Precision	0.75	0.87	0.4
Recall	0.8	0.8	0.45
Lidocaine Responders	0.92	0.85	0.36
Lidocaine Non Responders	0.6	0.8	0.57

Transdermal Microneedle Device Delivery of Adipocyte-Specific AAVs to Overexpress Adipose Tissue Neurotrophic Factors in the Treatment of Diabetic Peripheral Neuropathy

Sunday, 5th June 2022

This paper was presented by Drs. Magdalena Blaszkiewicz, Kristy L. Townsend from Columbus, OH, as a part of the symposium "Emerging Directions in Diabetic Neuropathy" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Diabetes is the leading cause of peripheral neuropathy (PN), which results in loss of nerve supply in tissues like skin, adipose and muscle. While there are currently few treatments for PN, early mitigation in the pre-diabetic state with tissue neurotrophic factors may improve nerve function in metabolically important tissues like adipose. We used an adipocyte-tropic adeno-associated virus (AAV; serotype Rec2) to deliver neurotrophic factors directly to scWAT using a transdermal microneedle device that we developed.

This approach avoids potential off-target effects and aberrant axon outgrowth in skin that may increase pain. Using both the BTBRob/ob and C57BL/6J diet-induced neuropathy mouse models, we have demonstrated that AAVRec2-BDNF (brain derived neurotrophic factor, which we have implicated in controlling adipose innervation) delivery to scWAT with our device increased tissue innervation 14 days after treatment, marked by increased protein expression of pan-neuronal marker PGP9.5 and sympathetic nerve marker tyrosine hydroxylase (TH). Longer periods of dietary obesity (25+ wks vs 16 wks) blunted the ability of AAVRec2-BDNF to increase innervation in scWAT, despite these mice showing an initial decrease in body weight compared to controls. This indicates there may be a critical window for therapy delivery during the progression to diabetic neuropathy during which interventions are more advantageous.

Treatment with AAVRec2-NGF (nerve growth factor) also increased scWAT innervation in obese mice at 8 weeks post-treatment, as evidenced by increased protein expression of PGP9.5, TH and markers of axon outgrowth (Gap43, Vasp). Thermal imaging above inguinal scWAT revealed an increase in temperature only in AAVRec2-NGF treated mice, supporting the idea that NGF-responsive nerves drive tissue browning and/or thermogenesis. Taken together, we have developed a novel treatment approach for delivering adipocyte-tropic AAVs to overexpress neurotrophic factors as a means to mitigate diabetes-associated PN.

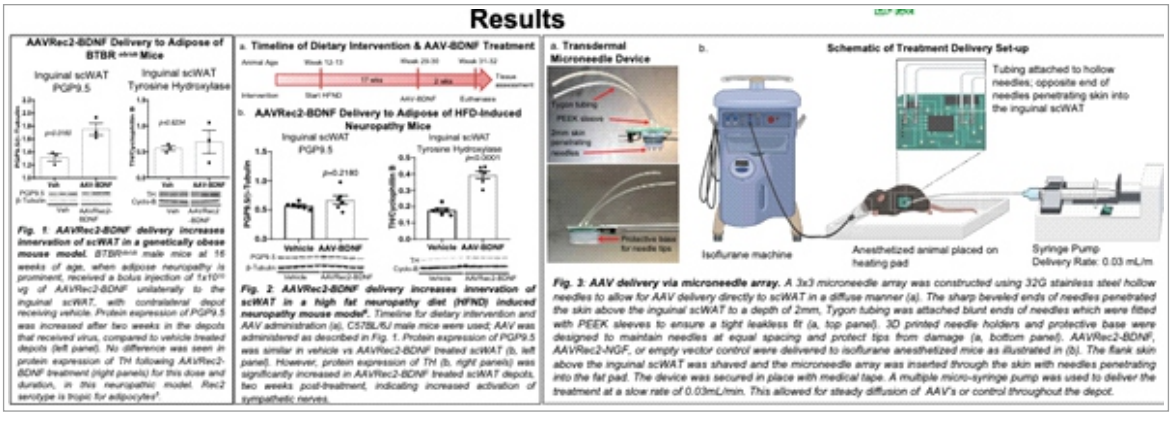


Fig. 1: AAVRec2-BDNF delivery increases innervation of scWAT in a genetically obese mouse model. BTBR ob/ob male mice at 16 weeks of age, when adipose neuropathy is prominent, received a bolus injection of 1x10^11 vg of AAVRec2-BDNF unilaterally to the inguinal scWAT, with contralateral depot receiving vehicle. Protein expression of PGP9.5 was increased after two weeks in the depots that received virus, compared to vehicle treated depots (left panel). No difference was seen in protein expression of TH following AAVRec2-BDNF treatment (right panels) for this dose and duration, in this neuropathic model. Rec2 serotype is tropic for adipocytes[1].

Fig. 2: AAVRec2-BDNF delivery increases innervation of scWAT in a high fat neuropathy diet (HFND) induced neuropathy mouse model[2]. Timeline for dietary intervention and AAV administration (a). C57BL/6J male mice were used; AAV was administered as described in Fig. 1. Protein expression of PGP9.5 was similar in vehicle vs AAVRec2-BDNF treated scWAT (b, left panel). However, protein expression of TH (b, right panels) was significantly increased in AAVRec2-BDNF treated scWAT depots, two weeks post-treatment, indicating increased activation of sympathetic nerves.

Fig. 3: AAV delivery via microneedle array. A 3x3 microneedle array was constructed using 32G stainless steel hollow needles to allow for AAV delivery directly to scWAT in a diffuse manner (a). The sharp beveled ends of needles penetrated the skin above the inguinal scWAT to a depth of 2mm, Tygon tubing was attached blunt ends of needles which were fitted with PEEK sleeves to ensure a tight leakless fit (a, top panel). 3D printed needle holders and protective base were designed to maintain needles at equal spacing and protect tips from damage (a, bottom panel). AAVRec2-BDNF, AAVRec2-NGF, or empty vector control were delivered to isoflurane anesthetized mice as illustrated in (b). The flank skin above the inguinal scWAT was shaved and the microneedle array was inserted through the skin with needles penetrating into the fat pad. The device was secured in place with medical tape. A multiple micro-syringe pump was used to deliver the treatment at a slow rate of 0.03mL/min. This allowed for steady diffusion of AAV's or control throughout the depot.

SESSION-3 :
Complication Compendium: The Overlooked Offenders

The Effect of Surgical Weight Loss on Diabetic Complications in the Severely Obese

Sunday, 5th June 2022

This paper was presented by Drs. Evan L. Reynolds, Maya Watanabe, Melissa Elafros, Eva L. Feldman, Brian C. Callaghan from Ann Arbor, MI as a part of the symposium "Recent Advances in the Management of Obesity & T2D in Youth" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

The aim of this study was to determine the effect of surgical weight loss on chronic kidney disease (CKD), retinopathy, and cardiovascular autonomic neuropathy (CAN) in people with severe obesity.

"We completed a prospective cohort study of participants with severe obesity who underwent bariatric surgery. At baseline and at 2 years following bariatric surgery, participants had outcome measurements and underwent metabolic phenotyping. The updated National Cholesterol Education Program (NCEP) criteria were used to define the metabolic syndrome (MetS) and its individual components.

The primary outcome for CKD was the estimated Glomerular Filtration Rate (eGFR), retinopathy was mean deviation on frequency doubling technology testing, and CAN was the expiration/inspiration (E/I) ratio.

Among 138 baseline participants, 80 (mean (standard deviation) age: 45.6 (11.2) years, 72.5% female) completed 2 years of follow-up. Participants lost 31.9 (17.5) kg. All metabolic syndrome components improved with the exception of blood pressure. CKD worsened (eGFR: baseline: 85.6 (19.7), 2-year: 82.6 (23.1), p=0.04), retinopathy was stable (mean deviation: baseline: -1.2 (4.3), 2-year: -1.6 (4.2), p=0.53), and CAN was stable (E/I ratio: baseline: 1.18 (0.12), 2-year: 1.18 (0.11), p=0.95) following bariatric surgery. Greater reduction in fasting glucose was associated with significant improvements to primary CKD (eGFR: point estimate (PE): -0.22, 95% Confidence Interval (CI): -0.38, -0.06) and retinopathy (mean deviation: PE: -0.04, 95% CI: -0.08, -0.004), after adjusting for age, sex, and baseline BMI.

Surgical weight loss was associated with improvements in all metabolic parameters except blood pressure. Despite the improvement to metabolic risk factors, CKD significantly worsened during follow-up, whereas retinopathy and CAN outcomes remained stable. This stability may be an improvement compared to the natural progression of these conditions; however controlled trials are needed to confirm.

The DERMIS Study — Preliminary Evaluation of Skin Changes at Continuous Subcutaneous Insulin Infusion (CSII) Sites in Type 1 Diabetes (T1D)

Sunday, 5th June 2022

This paper was presented by Drs. Jesica D. Baran, Dori Khakpour, Andrea Kalus, Michi Shinohara, from Seattle, WA, as a part of the symposium "Complication Compendium the Overlooked Offenders" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

CSII is used with increased frequency; however, there are no studies evaluating human skin histology related to its use. Objectives: 1) to investigate the skin histology and metabolite changes at CSII sites and 2) associate possible changes with clinical characteristics in a cohort of patients with T1D.

We conducted a cross-sectional study which included individuals with T1D using CSII. Skin and blood samples in addition to clinical data were collected. Histological, immunohistochemical (IHC), and metabolomic analyses were performed using skin biopsies from three sites: 1) current 2) recent and 3) never used site (control) for CSII.

A total of 30 participants were enrolled in the study (age 48.3 ± 17.9 years, female 66.7%, diabetes duration 30.4 ± 16.0 years, insulin pump use 15.7 ± 11.7 years, BMI 25.3 ± 3.4 kg/m2, HbA1c 6.66 ± 0.79%, mean glucose from CGM 150.7 ± 26.4 mg/dL, coefficient of variation 31.2 ± 4.4%, insulin dose 0.53 ± 0.17 IU/kg). Histologic data showed a significant increase in inflammation, fibrin, fat necrosis, vascularity, eosinophils, and IHC staining of IGF-1 and TGF 3 at both CSII sites compared to control sites (all $p<0.001$). Targeted tissue analysis demonstrated an increase in critical metabolites at current sites compared to control, including histamine ($p=0.013$), uracil ($p<0.001$), and a trend in UDP-GlcNAc ($p=0.063$). Inflammation is positively correlated with insulin dose ($p=0.005$), in addition to mean glucose ($p<0.01$) and coefficient of variation ($p<0.01$) from the CGM.

Biologic changes were observed in skin histology and metabolites at CSII sites that may be associated with inflammation, oxidative stress response, protein synthesis and wound healing. These could have a clinical impact on insulin availability and diabetes control.

Effects of Finerenone in Patients with CKD and T2D are Independent of HbA1c at Baseline, HbA1c Variability, and Duration of Diabetes

Sunday, 5th June 2022

This paper was presented by Drs. Janet B. Mcgill, Rajiv Agarwal, Stefan Anker et al from St. Louis, MO, Indianapolis, IN, Chicago, IL, as a part of the symposium "New Hope, Old Challenges in Heart Failure-New Heart Failure Clinical Trials" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Finerenone reduced the risk of cardiovascular (CV) and kidney outcomes, without affecting HbA1c, in CKD and T2D patients in the FIDELITY prespecified pooled analysis of the FIDELIO-DKD and FIGARO-DKD studies. Here, we evaluate the effect of finerenone by baseline HbA1c, HbA1c variability, and diabetes duration.

Patients with T2D and CKD (UACR ≥30-≤5000 mg/g and eGFR ≥25 mL/min/1.73 m^2) were randomized to finerenone or placebo. Effects of finerenone vs. placebo on CV (CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) and kidney (kidney failure, sustained ≥57% eGFR decline from baseline, or renal death) composite outcomes were analyzed by baseline HbA1c quartiles, HbA1c variability (first year of treatment), and diabetes duration quartiles.

In 13,026 patients included in the analysis, mean baseline HbA1c was 7.7% and diabetes duration was 15.4 years. Higher baseline HbA1c quartiles had longer diabetes duration and more diabetes-related complications. Risk reductions in the CV and kidney composite outcomes with finerenone vs. placebo were

consistent across HbA1c (p-interaction 0.52 and 0.09, respectively) and diabetes duration (p-interaction 0.12 and 0.75) quartiles. HbA1c variability in the first year of treatment was associated with higher cardiorenal risks; each 1 unit increase in mean absolute residual of HbA1c was associated with a 20% increased risk of a CV event (HR 1.20; 95% CI 1.07-1.35; p=0.0016) and a 36% increased risk of a kidney event (HR 1.36; 95% CI 1.21-1.52; p<0.001). The CV and kidney benefits of finerenone were not modified by HbA1c variability (p-interaction 0.48 and 0.09, respectively).

Greater variability in HbA1c was associated with increased risks of cardiorenal outcomes. Risk reductions in the CV and kidney outcomes with finerenone in patients with CKD and T2D were not modified by baseline HbA1c, HbA1c variability, or duration of diabetes.

SESSION-4 : Improving Diabetes Care for Older Adults

Time in Range and Time Below Range in Insulin-Treated Older Adults with Type 2 Diabetes

Sunday, 5th June 2022

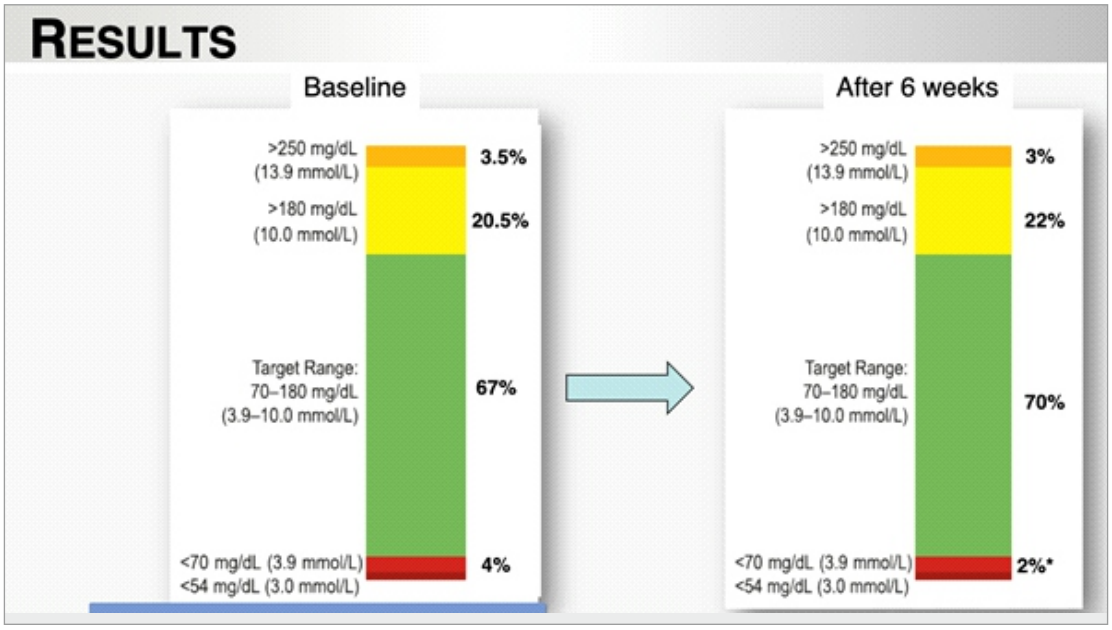
This paper was presented by Drs. Silmara A.O. Leite, Michael Silva, Ana C.R. Lavalle, Murilo Bastos, Maria C. Bertogy, Suelen C. Vieira, Guillermo E. Umpierrez from Curitiba, Brazil, Rio Grande, Brazil, Guarapuava, Brazil, Atlanta, GA as a part of the symposium "Improving Diabetes Care for Older Adults" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Hypoglycemia is the key limiting step for optimizing glycemic control in older adults. Continuous glucose monitoring (CGM) technology has not been well-evaluated in insulin treated older patients with type 2 diabetes (T2D).

This prospective observational cohort study assessed of glycemic control using the FreeStyle Libre Flash CGM in insulin treated older adult patients with T2D. Subjects >65 years with T2DM on insulin therapy and HbA1c between 7% and 9%, with or without oral agents, were identified from a public hospital and a private diabetes clinic and invited by phone to participate (n= 462). Patients treated with GLP1 agonists; eGFR <30 ml/min; Hb <11g/dL; ALT> 3x ULN; glucocorticoid use in the previous 3 months, and active malignancy were excluded. Participants worn the CGM continuously during a 6-weeks study period. They returned to clinic every 2 weeks for CGM data downloaded and new CGM placement, assessment of glycemic control and hypoglycemia. The investigators adjusted insulin treatment at each visit as needed. The first 2 weeks of CGM was considered baseline point and the last 2 weeks was the endpoint. The differences on time in range (TIR 70-180, mg/dl) and time below range (TBR, < 70 mg/dl) was tested using the Wilcoxon Signed-rank test with p <0.05.

A total of 125 patients were randomized and 49 patients completed the 6 weeks follow-up (women=53.9%; age=72.8 ± 5.0 years; BMI=28.3±3.6 Kg/m^2; eGFR=62.4 ± 16.6; ml/min A1c=8.0 ± 0.57%; GMI=7.1 ± 0.8%. The patients had a median TIR of 65% (min= 7%, max= 94%) at the baseline and 68% (min= 4%; max= 97%) at the endpoint. The median TBR was 3% (min= 0%, max= 23%) at the baseline and 2% (min= 0%; max= 18%) at the end of study. The TBR was significantly reduced after 6 weeks of CGM (p<0.01).

An individualized approach may be possible using FreeStyle Libre Flash CGM to avoid overtreatment and undertreatment of older adults with T2D. CGM is a useful tool to reduce hypoglycemia in insulin older adults with T2D.



Assessing the Relationship Among Multimorbidity, Psychosocial Factors, and Clinical Outcomes in Older Adults Living in Rural Appalachia

Sunday, 5th June 2022

This paper was presented by Drs. Brittany L. Smalls, Adebola Adegboyega, Patience Simon-Okube, Philip Westgate, Nancy Schoenberg from Lexington, KY as a part of the symposium "Improving Diabetes Care for Older Adults" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Type 2 diabetes (T2DM) is a significant public health burden in rural Appalachian Kentucky, with an estimated one in four older adults diagnosed with T2DM. To determine factors associated with T2DM, we assessed the relationship between multimorbidity (MM), psychosocial factors, and clinical outcomes among 148 older adults with T2DM along with one or more comorbid conditions, living in rural Appalachian Kentucky.

A community-based sample of Appalachian residents provided data on diabetes knowledge, chronic conditions in addition to T2DM, demographics, and clinical measures (HbA1c, blood pressure) using point-of-care methods. The sample population (N=148) had an average age of 72.2 years (± 5.4) and were mostly women (66%) and White (98%), reflecting the region's demographics. The average HbA1c was 7.6 (±1.3) and systolic and diastolic blood pressure were 145.2 (±20.8) mmHg and 81.9 (±12.6) mmHg, respectively. Participants reported having 2.3 (±1) chronic conditions in addition to T2DM. As for psychosocial factors, participants reported average score stress 20.7 (±9.1), distress 26.7 (±10.7), and social support 115.0 (±15.9). There was a significant relationship between MM and HbA1c ($\beta=0.27$, SE=0.13, $p=0.04$) and stress ($\beta=0.23$, SE=0.08, $p=0.004$). However, distress, social support, disability, and depression did not have significant relationships with MM in this sample. These findings elucidate the burden of MM in older adults who are living with T2DM in a rural environment.

Though MM is not unique to the aging population, understanding how MM effects clinical outcomes and T2DM related psychosocial factors is important. In most cases, properly managing T2DM could reduce (or prevent)

severity and complications of comorbid conditions. Thus, identifying psychosocial factors that are associated with clinical outcomes provides a pathway for targeted interventions to improve health outcomes for this vulnerable population.

Sample Characteristics: The sample population (N=153) had an average of 72.2 years (SD 5.4) and were mostly women (66%), White (98%), married (51.7%), retired (61.4%), insured (100%), and indicated that they "have just about enough to get by" financially (45%.3).

Regression Results (Adjusting for Covariates).

- Stress and MM had significant relationship (β=0.24; SE 0.08; p=0.01)
- There was no statistically significant relationship between HbA1c, blood pressure, diabetes distress, or social support.

SESSION-5 : Recent Advances in the Management of Obesity & T2D in Youth

Glycine and Branched-Chain Amino Acids (BCAA) Metabolic Signature in Youth with Obesity and Type 2 Diabetes

Sunday, 5th June 2022

This paper was presented by Drs. Heba El Ayash, Mahmoud A. Mohammad, Reem S. Shawar, Rupa S. Kanchi, Susan Sharma, Maurice R. Puyau, Cristian Coarfa, Fida Bacha from Houston, TX as a part of the symposium "Recent Advances in the Management of Obesity & T2D in Youth" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

BCAAs are associated with increased risk for T2D in adults, while glycine (Gly) appears to be having an inverse relationship. β-cell function is central to the development of T2D in youth. The relationship of Gly and BCAA to β-cell function in youth is not clear.

We investigated the relationship between Gly vs. the BCAA: Leucine (Leu), Isoleucine (Ile) and Valine (Val), to insulin sensitivity (IS) and β-cell function in youth across the spectrum of glycemia.

Adolescents (65 female/62 male; 15.5±1.9 y.o.; 30 with normal weight normal glucose tolerance (NW-NGT), 33 obese-NGT, 34 prediabetes, and 30 T2D) underwent assessment of AA concentrations (mass spectrometry), fasting and at steady state (SS) of a 3-hr hyperinsulinemic-euglycemic clamp (in-vivo IS); insulin secretion by 2-hr hyperglycemic clamp; adipokines, body composition (DXA) and visceral fat (MRI). The disposition index (DI) (measure of β-cell function) = first phase insulin x IS per fat free mass (DIFFM). We performed analysis of variance (adjusting for sex, race-ethnicity and Tanner stage) and correlation analyses.

Fasting and SS-Gly were lower and SS-BCAA higher in the groups with obesity compared with NW with post-hoc significant differences in T2D vs. NW ($p<0.001$ for fasting and SS-Gly, SS-Ile, and $p=0.02$ for SS-Val) and in prediabetes vs. NW (for Gly, Val and Ile). Fasting and SS-Gly negatively and SS-BCAA positively associated with %body fat, waist/hip, and visceral fat, while Gly positively and BCAA negatively related to adiponectin. Fasting and SS-Gly ($r=0.4$, $p<0.001$) positively and SS-BCAA ($r=-0.4$ for Val, Leu, Ile, $p<0.001$) negatively related to ISFFM. Gly positively ($r=0.27$, $p=0.005$), SS-Ile ($r=-0.26$, $p=0.006$) inversely related to DIFFM.

Gly is positively related to IS and β-cell function and negatively to adiposity measures, with

opposite relationships observed for BCAA. A metabolic signature of low Gly and elevated BCAA may constitute a biomarker to identify youth at risk for β-cell failure.

Obesity and Type 2 Diabetes in Patients with NAFLD Are Independently Associated with the Risk of Liver Fibrosis, Insulin Resistance, and Atherogenic Dyslipidemia

Sunday, 5th June 2022

This paper was presented by Drs. April Mathews, Srilaxmi Kalavalapalli, Eddison Godinez, Romina Lomonaco, from Tallahassee, FL, Gainesville, FL, as a part of the symposium "Recent Advances in the Management of Obesity & T2D in Youth" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Obesity (OB) and type 2 diabetes (T2D) are associated with NAFLD and a worse cardiometabolic profile. However, their independent contribution to steatosis, fibrosis, insulin resistance (IR) and atherogenic dyslipidemia are controversial. To this end, we examined the prevalence of NAFLD and hepatic fibrosis in 199 patients (64 with T2D, 135 without T2D) screened from outpatient endocrinology and primary care clinics.

NAFLD/fibrosis was assessed by transient elastography (liver fat by controlled attenuation parameter/CAP; fibrosis by liver stiffness measurement/LSM). Patients were divided into groups either with or without obesity (OB) or T2D. Within each group, patients were well matched for age, BMI, A1c and AST/ALT. The impact of obesity was best observed on the prevalence of steatosis, that increased from pts without OB or T2D (controls = C) to OB/no-T2D (OB) and OB/T2D (C: 40% vs. OB: 64% vs. OB/T2D: 86%, both $p<0.01$ vs. C). The impact of T2D was best observed by the increasing prevalence of liver fibrosis (C: 4% vs. OB: 9% vs. OB/T2D: 25%; $p=0.30$, 0.01, respectively vs. C). HOMA-IR (primarily hepatic IR, C: 2.5±0.3 vs. OB: 4.3±0.5 vs. OB/T2D: 6.0±0.6, $p<0.01$ vs. C) and adipo-IR (adipose tissue IR, C: 2.8±0.3 vs OB: 4.3±0.6 vs. OB/T2D: 5.4±0.6, $p<0.01$ vs. C) followed the worsening impact of OB and T2D. Finally, there was an independent, stepped worsening of HDL-C with obesity and T2D (C: 58±18 vs. OB: 50±11 vs. OB/T2D: 44±10 mg/dL; $p<0.01$) and a worsening trend of TG with T2D (C: 110±78 vs. OB: 110±62; $p=0.98$, and OB/T2D: 148±79 mg/dL; $p<0.01$ vs. C). LDL-C did not follow this pattern as closely.

In conclusion, obesity and T2D increase the prevalence of NAFLD (more driven by OB) and hepatic fibrosis (more driven by T2D). This is associated with a continuous worsening of IR and of atherogenic dyslipidemia. The clinical implication is that both factors need to be addressed for the prevention of cirrhosis and of cardiovascular disease in NASH.

A Scoping Review on Diabetes Management in People with Mild Cognitive Impairment (MCI): Glycemic Control, Medications, and Onset of Alzheimer's and Related Dementias (ADRD)

Sunday, 5th June 2022

This paper was presented by Drs. Sumaya Abuloha, Alaa A. Alshehri, Naykky Singh Ospina from Gainesville, FL, as a part of the symposium "Complication Compendium the Overlooked Offenders" on Sunday, June 5th

2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Controversy exists in diabetes management after the onset of MCI, and the ideal treatment goals and medication use in this population remain inconclusive. This review aimed to comprehensively summarize the existing literature on diabetes management after MCI onset, focusing on the change of A1c goals, medication choices, and the risk of ADRD onset.

We conducted a systematic literature search in PubMed (2000.1.1-2021.9.30) to identify studies related to mild cognitive impairment, glycemic goal, and medication use after MCI onset. Study types include guidelines, clinical trials, and observational studies. A standard literature searching process including title/abstracts screening, duplication removal, eligibility assessment, and data extraction was conducted by two reviewers independently.

We have identified 30 studies addressing the management of diabetes in patients with MCI. The study contents were categorized into two main focuses; glycemic control (moderate vs. intensive) and the role of medications in delaying ADRD onset. Most guidelines recommend individualized goal setting to a relaxed glycemic target to avoid hypoglycemia after MCI onset. On the other hand, existing evidence linked improved glycemic control with a lower risk of ADRD onset. Observational studies and small-sized trials found the use of metformin, TZD, DPP4, and GLP-1 receptor agonists may be able to slow down the cognitive function decline. However, whether such effects were attributable to improved glycemic control or other mechanisms such as neutral protective effect is inconclusive. The risk-benefit tradeoff in glycemic control is vital in diabetes population with MCI. A large gap exists in understanding the underlying mechanism for the potential protective effect of cognitive function from glucose-lowering medications.

SESSION-6 : Health Disparities, Risk of Hypoglycemia & Treatment Options

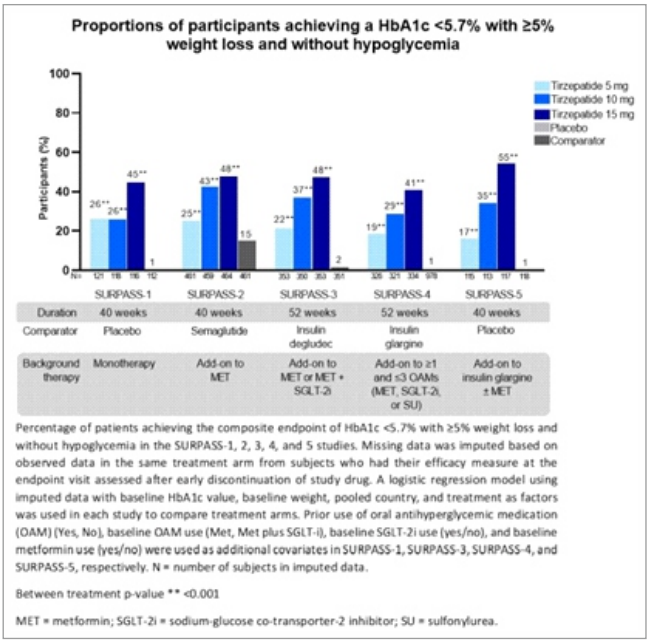
Patients Achieving an HbA1c <5.7% with =5% Weight Loss and Without Hypoglycemia: A Post Hoc Analysis of SURPASS 1 to 5

Sunday, 5th June 2022

This paper was presented by Drs. Alice Y. Cheng, Ildiko Lingvay, Pratik Choudhary, Elisa Gomez-Valderas, from Mississauga, ON, Canada, Dallas, TX, as a part of the symposium "Health Disparities, Risk of Hypoglycemia & Treatment Options" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

In the phase 3 SURPASS studies of tirzepatide (TZP), a novel dual GIP/GLP-1 receptor agonist developed for the treatment of type 2 diabetes, 23%-62% of TZP-treated participants achieved a HbA1c <5.7% and 54%-88% achieving ≥5% weight loss. This post hoc analysis evaluated the proportion of participants who achieved the triple endpoint of HbA1c <5.7%, ≥5% weight loss, and no clinically significant or severe hypoglycemia.

We compared the proportion of participants achieving the triple endpoint between the TZP (5, 10, or 15 mg) and respective comparator groups using the efficacy analysis dataset without rescue medication. HbA1c and weight were evaluated at the end of the treatment period at week 40 (SURPASS 1, 2, 5) or week 52 (SURPASS 3, 4). Hypoglycemia included blood glucose level <54 mg/dL with symptoms or severe hypoglycemia at any time. Significantly



more participants treated with any dose of TZP achieved the triple endpoint compared to placebo or active comparators in SURPASS 1-5 (Figure).

Of the participants treated with TZP 15 mg, 45%, 48%, 48%, 41%, 55% reached the triple endpoint compared to 1% with placebo, 15% with semaglutide 1 mg, 2% with degludec, 1% with glargine U100, and 1% with placebo, in SURPASS 1-5, respectively. Significantly more participants treated with TZP achieved a HbA1c <5.7% with ≥5% weight loss and without hypoglycemia compared to placebo, semaglutide 1 mg, or basal insulin.

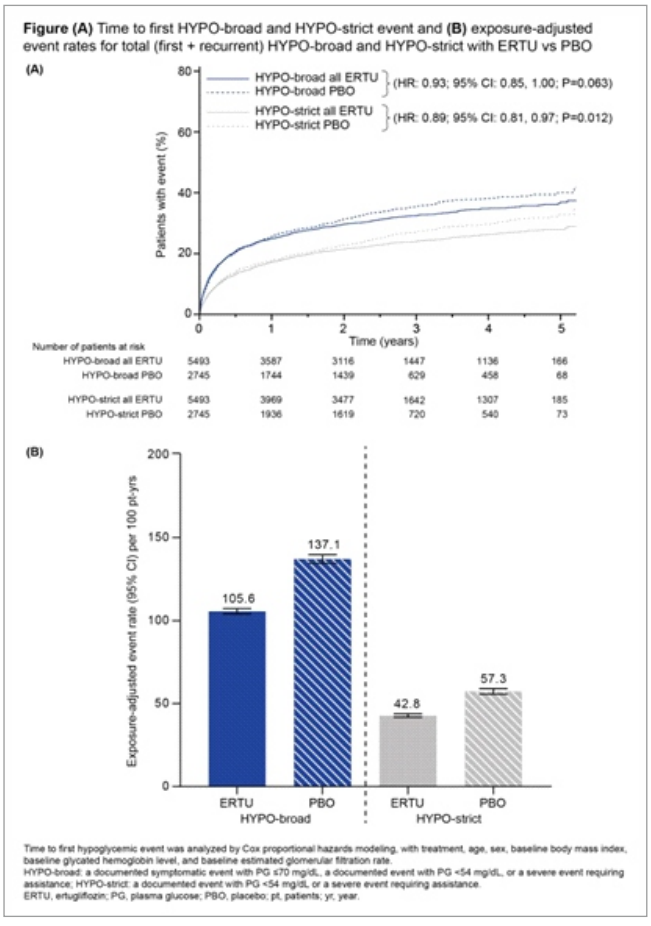
Long-Term Ertugliflozin Treatment and Incidence of Hypoglycemia: Analyses from VERTIS CV

Sunday, 5th June 2022

This paper was presented by Drs. Samuel Dagogo-Jack, Christopher P. Cannon, David Cherney, from Memphis, TN, Boston, MA, Toronto, ON, Canada, as a part of the symposium "Health Disparities, Risk of Hypoglycemia & Treatment Options" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

This analysis assessed the incidence and total events of hypoglycemia in VERTIS CV (NCT01986881), the cardiovascular (CV) outcome trial for ertugliflozin (ERTU) in patients (pts) with type 2 diabetes and atherosclerotic CV disease.

Hypoglycemia was categorized as level 1, a documented symptomatic event with plasma glucose (PG) ≤70 mg/dL (prespecified); level 2, a documented event with PG <54 mg/dL (post hoc); level 3, a severe event requiring assistance (prespecified). Time to first HYPO-broad (levels 1+2+3) and HYPO-strict (levels 2+3) were analyzed by a Cox proportional hazards model. Kaplan-Meier estimates were plotted. Exposure-adjusted event rates for total (first + recurrent) HYPO-broad and -strict were analyzed.



Overall, 8246 pts were randomized, mean follow-up was 3.5 yrs. The incidence rate (ERTU vs PBO) of first HYPO-broad was 14.3 vs. 16.2/100 pt-yrs; adjusted hazard ratio [aHR], 95% CI: 0.93 [0.85, 1.00] and HYPO-strict was 9.5 vs. 11.1/100 pt-yrs; aHR: 0.89 [0.81, 0.97] [Figure A]. Exposure-adjusted event rates were lower in ERTU vs PBO [Figure B]. The increase in percentage of insulin users (end of study vs. baseline) was less with ERTU (3.5% 5 + 15 mg) compared with PBO (6.2%).

In VERTIS CV, pts randomized to ERTU had a lower risk of hypoglycemia, including first and recurrent events, than PBO-treated pts. This may in part be due to the lesser increase in insulin users with ERTU vs. PBO.

Glycemic Control Across eGFR Categories with the Dual SGLT1 and 2 Inhibitor Sotagliflozin in SCORED

Sunday, 5th June 2022

This paper was presented by Drs. Silvio E. Inzucchi, Deepak L. Bhatt, Bertram Pitt, from New Haven, CT, Boston, MA, Ann Arbor, MI, as a part of the symposium "New Hope, Old Challenges in Heart Failure-New Heart Failure Clinical Trials" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

In cardiovascular (CV) outcome trials (OT) of glucose-lowering medications (GLM), glycated hemoglobin (A1c) is typically treated according to local standard of care, with aim of glycemic equipoise between the randomized groups. However, in SGLT inhibitor CVOTs, larger A1c reductions are consistently seen in the active therapy vs. placebo (PBO) groups, since the former has access to an additional class of GLM.

SCORED was a multicenter, double-blind, placebo-controlled CVOT of the dual SGLT1 and 2 inhibitor sotagliflozin (SOTA), which may have preserved antihyperglycemic effects even in those with advanced chronic kidney disease (CKD.)

"We assessed the association between A1c lowering and assignment to SOTA vs. PBO in the overall trial population and across various pre-specified subgroups, including CKD categories. 10,584 type 2 diabetes (T2D) (A1c ≥7%) patients with CKD (eGFR 25-60 mL/min/1.73 m2) and increased CV risk were randomized to SOTA vs. PBO and followed for a median of 15.9 months. We previously reported that the risk for the primary composite outcome of total CV deaths and hospitalizations or urgent visits for heart failure was reduced by 26% in the SOTA group (p<0.001)."

In the overall population, from a baseline A1c of 8.7%, the least-squares mean change in A1c was -0.60% with SOTA and -0.17% with placebo (mean difference [95% CI] = -0.42% [-0.47, -0.38]; p<0.0001). Differences were larger with increasing baseline A1C: <8%: -0.31%; 8-<9%: -0.40%; and ≥9%: -0.57% (all p<0.0001). The association between SOTA use and A1c lowering vs. placebo was consistent across strata of baseline eGFR, including those with CKD stage 4 (eGFR>45, 30-<45, and <30: -0.47%. -0.38%, and -0.31%, respectively [all p<0.001]).

These results were similarly consistent across age, sex, race/ethnicity, age, and BMI subgroups. In SCORED, SOTA consistently reduced A1c across all pre-specified subgroups, including patients with the lowest baseline eGFR, possibly reflecting SOTA's dual mechanism of action.

SESSION-7: Pancreas Transplantation in the 21st Century

Excellent Outcome of Solitary Pancreas Transplant Recipients with Brittle Diabetes and Without Advanced Nephropathy

Sunday, 5th June 2022

This paper was presented by Drs. Angelika Gruessner, from Brooklyn, NY, as a part of the symposium "Pancreas Transplantation in the 21st Century" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

In contrast to non-pancreatic transplantation, where nephrologists refer patients for kidney and hepatologists for liver transplantation, endocrinologists only rarely refer patients with brittle diabetes for solitary pancreas transplantation. While most pancreas transplants are performed in combination with a kidney graft, solitary pancreas transplants (PTA) without a previous kidney transplant accounted for only 6-7% of pancreas transplants per year although a PTA is the best treatment option to achieve long-term insulin-independence in patients with severe brittle diabetes.

The change in demographics and outcome of 1,636 primary PTAs were analyzed between 2001 and 2020 in 5-year intervals. Graft survival was defined as complete insulin-independence. Multivariate analysis was performed to assess factors that impacted outcome and the potential need for a subsequent kidney transplant.

Over time, recipient age increased, but donor age and preservation time decreased significantly. Most recipients received induction therapy and maintenance immunosuppression. These changes resulted in significant improvement in patient and pancreas graft survival. Three-year patient survival increased from 92% in 2001-05 to 96% in 2016-20. Three-year pancreas graft survival improved from 60% in 2001-05 to 77% in 2016-20 ($p<0.0001$). The most influential factors for this decrease were older recipient age and better immunosuppression.

The rate of a subsequent kidney transplant declined significantly. It was primarily contingent on native graft function at the time of transplant. If the GFR was as >70ml/min only 1% of patients required a kidney graft.

The results of PTA have significantly improved over the past 20 years. A PTA should be strongly considered in brittle diabetic patients before the development of advanced nephropathy.

The Best Insulin Delivery System Remains a Human Pancreas

Sunday, 5th June 2022

This paper was presented by Drs. Kasi R. Mccune, Geoffrey Dube, Lloyd E. Ratner from New York, NY, as a part of the symposium "Pancreas Transplantation in the 21st Century" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Patients referred for pancreas transplantation represent a subset of difficult to treat diabetics, who may have clinical factors preventing them from achieving a goal Hgb A1C of ≤7%. Advanced insulin delivery systems with continuous glucose monitor (CGM) have been developed to offer less invasive treatment options in this population. We wanted to see how pan-

creas transplant performed compared to alternative modalities.

"We conducted a retrospective review of pancreas transplantation at our institution from January 1, 2008 through August 1, 2021. All patients were ≥18 years who underwent either simultaneous kidney pancreas (SPK), pancreas after kidney (PAK), or pancreas transplant alone (PTA). Outcomes were assessed by HgbA1C level at evaluation (eval), at transplant (pre), between 3-5 months posttransplant (post) and the most recent (MR) (avg 62 months SD 75.4 months)."

133 patients underwent pancreas transplant during the study period, 85 SPK (62%) 39 PAK (30%) and 11 PTA (8%). 19 (14%) patients suffered graft loss in the first year and were excluded from analysis. Overall, 1, and 5-year pancreas graft survival was 86% and 82%. 96 (84%) had type 1 diabetes (T1D) and 18 (16%) had type 2 diabetes (T2D). Of the 114 patients, 33 (29%) utilized CGM with or without pump (CGM) prior to transplant and had a lower Hgb A1C (%) than those without (nonCGM) (8.18 SD 1.5 vs. 8.75 SD 1.9 p=0.04). Hgb A1C then improved for the nonCGM group during their time on the waitlist (8.75 to 8.36 SD 1.8 p=0.004) but not the CGM group (8.18 to 8.05 SD 1.3 p=0.24). Post-transplant saw significant improvement in CGM pre 8.05 to post 5.0 (SD.6 p=2.7E-17) and MR 5.3 (SD 0.7 p=9.9E-14) and in nonCGM pre 8.4 to post 5.2 (SD 0.62 p= 2.9E-29) and MR 5.4 (SD 0.7 p= 7.3E-29).

Considering the clinical challenges of staying in range for difficult to treat diabetes, leading to HgbA1C goal of ≥7%, solid organ pancreas transplantation offers superior glycemic control compared to advanced insulin delivery systems with CGM.

Response to COVID-19 Vaccination and Infection in Islet Transplant Recipients

Sunday, 5th June 2022

This paper was presented by Drs. Braden Juengel, Piotr J. Bachul, Angelica Perez-Gutierrez from Chicago, IL, as a part of the symposium "Pancreas Transplantation in the 21st Century" on Sunday, June 5th 2022 at the 82nd Scientific Sessions of the American Diabetes Association held in New Orleans.

Since response to COVID-19 vaccine among transplant recipients remains diminished comparing to general population, we decided to assess effect of COVID-19 specifically among islet transplant patients.

Response to COVID-19 infection and vaccine was assessed in a cohort of 20 islet transplant recipients: N=13 after islet transplant alone (ITx), N=7 with islet after kidney (IAK) or pancreas after islet transplantation (PAI). The median age was 48 years (25-62). Maintenance immunosuppression included tacrolimus and an antimetabolite in addition to 5mg of Prednisone in IAK and PAI recipients. Nine patients received booster.

Seven patients (38%) chose not to be vaccinated and 4 (57%) of them remained COVID-19 free with no SARS-CV-2 Spike total antibody (Spike ab) present in their blood. The other three patients (43%) developed only mild symptoms of infection with a high level of Spike ab (>2,500 U/ml) afterwards. In contrast, all remaining 13 patients (62%), who were vaccinated while on immunosuppression for a median of 7 years (0.5-16), remained COVID-19 free (p=0.11, Fischer). The level of Spike ab in response to vaccine varied: undetected- (N=4), in range 1-100U/ml (N=6), around 400U/ml (N=2), and above 2,500U/ml (N=1). Presence of 5mg of Prednisone did not affect the outcomes. Booster

was administered in 10 patients and increased the level of Spike ab above 100U/ml in all of them, in 7 (78%) to over 2,500 U/ml. One patient responded neither to vaccine nor to booster. There were no SAEs related to the vaccination or booster. Islet graft function remained stable in all but one patient after initial vaccination or COVID-19.

Nearly half of unvaccinated islet transplant recipients developed COVID-19, however, all of them presented only with mild symptoms. In contrast, none of vaccinated transplant patients developed COVID-19 infection with 69% rate of seroconversion. Booster increased level of the Spike ab in those patients who responded to the original vaccination.

within 3 months of receiving kidney transplants and initiating tacrolimus. Both responded well to IV fluids and insulin and were transitioned to SQ insulin by discharge. Risk factors for post-transplant de novo DKA and HHS common to both patients were African American ethnicity, high BMI, and tacrolimus treatment with elevated trough levels. Tacrolimus inhibits insulin secretion and is linked to increased rates of PTDM, which is often reversible with tacrolimus dosage reduction. Both of our patients were prescribed tacrolimus at reduced dosage and were scheduled for outpatient Endocrine clinic evaluation to determine whether they should continue insulin treatment.

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