Diabetes Updates: A Comprehensive Update in the Management of T1DM and T2DM

Disclosures

Objectives

1. Discuss new treatment options for diabetes management.

2. Review advancements in diabetes technology.

3. Discuss key updates from the ADA Standards of Care 2024.

4. (briefly) Examine new diabetes trends on the horizon.

Medication Updates

Bexagliflozin

Fifth SGLT-2i to market with FDA approval in January 2023
Dosing: 20mg PO q AM – available in 20mg tablets
Not approved for use in T1DM
eGFR <30: avoid use
Hold 3 days before surgery/procedure; hold in times of prolonged fasting
Adverse reactions – same as additional agents in SGLT-2i class
BEST trial
Bexagliflozin in Stage 3a/3b CKD: An RCT of Safety and Effectiveness

Empagliflozin; Empagliflozin + Metformin

Approved for children age 10 years of age and older
DINAMO - Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin

Oral semaglutide

January 2023 – label updated to permit use as first-line medication in adults with T2DM
PIONEER PLUS trial

ADA T2DM Figure/Flowsheet

Teplizumab

FDA approval November 17, 2022 as the first disease-modifying therapy for impeding progression of T1DM
Approved to delay the onset of stage 3 T1DM in adults and pediatric patients 8 yrs of age and older who currently have stage 2 T1DM

Administered by IV infusion once daily for 14 days
Expected to cost in the region of $200,000 for the course of treatment
COMPASS program -- helps navigate insurance reimbursement +/- financial assistance

Adverse Reactions -- most common include decreased levels of certain white blood cells, rash, and headache; monitoring for cytokine release syndrome

Stages of Type 1 DM
T1DM Autoantibody Screening Options

ADA Standard of Care (SOC) updates: 3.2 and 3.15

Lantidra (donislecel)

The first allogeneic (deceased donor) pancreatic islet cell therapy for the treatment of adults with type 1 diabetes who do not achieve target glycated hemoglobin levels because of repeated episodes of severe hypoglycemia, despite current management

FDA approval June 2023

Administered as a single infusion into the hepatic portal vein

Dose may be repeated if initial dose ineffective

Two non-randomized studies (for efficacy and safety)

30 patients (adults) with T1DM - received between 1 and 3 infusions

At one year, 21/30 study participants no longer required insulin, 11/30 study participants did not require insulin for between one and five years, and 10/30 study participants did not require insulin for more than five years

Transition-T2D Study

60 patients, age 18-75

T2DM on basal/bolus MDI (at least 6 months), < 120u TDD

+/- metformin and/or SGLT-2i

Hba1c $\leq$ 7.5%

Primary outcome: proportion of patients achieving Hba1c of 7.5% or less at week 26

Secondary outcomes: mean changes in weight, daily insulin requirement, and diabetes treatment satisfaction – all at 26 weeks; also including cumulative number of hypoglycemic episodes and % of subjects needing to resume prandial insulin at week 26

ADA SOC 9.24

Label Updates

Rybelsus

Ozempic/Rybelsus/Wegovy

Cardio-renal Updates

ADA SOC 9.18

Tirzepatide – SURPASS CVOT

Phase 3 trial

13,299 participants

Randomized to dulaglutide once weekly or tirzepatide once weekly (? doses)

Primary outcome: time to first occurrence of component event of MACE – 3

Secondary outcomes: numerous
Estimated completion date Oct 17, 2024

Metformin and Cardiovascular Comorbidities

Metformin has been found to be safe and effective in lowering morbidity and mortality for heart failure. --however, more difficult to interpret as results are from observation studies and not CVOTs

10 year follow up landmark United Kingdom Prospective Diabetes Study (UKPDS)

Shortly after FDA approval, HF listed as an absolute contraindication to metformin use

Risk of lactic acidosis from negative experiences with phenformin and buformin

2006 – FDA removed absolute contraindication, but contraindication in acute or unstable HF remained in warming label

Currently, at a minimum, we know that metformin is not harmful to diabetes with concurrent HF and that it may even be beneficial in reducing CV mortality and morbidity.

Metformin – cardioprotective mechanisms

Myocardium
- Altered mitochondrial bioenergetics
- Altered substrate utilization
- Reduced cardiocyte apoptosis

Vasculature
- Increased endothelial function
- Decreased coagulability
- Decreased oxidative stress
- Decreased inflammation
- Decreased monocyte adhesion
- Decreased neointima formation
- Decreased reduced glycol-oxidaton

Gut
- Altered microbiome

DAN-HEART trial
VA-IMPACT
SMART-EST study

ADA SOC – 10.46

COORDINATE-Diabetes

1049 adults with T2DM and ASCVD

High intensity statin, ACEi or ARB, SGLT-2i and/or GLP-1 RA

Randomized to intervention clinic vs usual clinic

Primary outcome: proportion of patients who were prescribed all 3 agents

Participants in the intervention group were more like to be prescribed all 3 agents: usual care group (173/457 [37.9%] vs 85/588 [14.5%] – a difference of 23.4%

Finerenone

FIDELIO-DKD

Examine long-term effects on kidney and cardiovascular outcomes

Patients with T2DM and CKD

Eligible patients:

Urinary albumin-to-creatinine ratio of 30 to less than 300, an estimated eGFR of 25 to less than 60ml/min/1.73m2, and diabetic retinopathy

Urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of 25 to less than 75ml/min/1.73m2

All patients treated with renin-angiotensin system blockade

Primary composite outcome: assessed in a time-to-event analysis, was kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes.

Key secondary composite outcome: assessed in a time-to-event analysis, was death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization from heart failure

FIGARO-DKD

Examined whether treatment with finerenone would lead to lower risks of cardiovascular events and death from cardiovascular causes among patients with either stage 2 to 4 CKD and moderately elevated albuminuria or stage 1 or 2 CKD with severe increased albuminuria

Eligible patients:

Urinary albumtin-to-creatinine ratio of 30 to less than 300 and an eGFR of 25 to 90 ml/min/1.73m2 (stage 2 or 4 CKD)

Urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of at lest 60 ml/min/1.73m2 (stage 1 or 2 CKD)

Primary outcome:

Assessed in a time-to-event analysis – composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization from heart failure

Secondary outcome: composite of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR, or death from renal causes.

FIDELITY

Cardiovascular and Kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis

Conclusion: finerenone reduced the risk of clinically important cardiovascular and kidney outcomes vs placebo across the spectrum of CKD in patients with T2DM

Screening for albuminuria to identify at-risk patients among patients with T2DM facilitates reduction of both cardiovascular and kidney disease.

ADA – Chronic Kidney Disease and Risk Management Figure

Finerenone Dosing Guidelines

ADA SOC Updates – 10.43, 10.45d, 11.5c, 11.5d

ADA SOC Updates – 9.19, 10.39a, 10.39b

Sotagliflozin – what does it mean for our diabetic patients?

Dual SGLT-2 and SGLT-1 inhibitor

FDA approved May 26, 2023; 200mg or 400mg PO daily

Indication: indicated to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:

Heart failure (across the EF spectrum)

Type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors

Sotagliflozin is not indicated for glycemic control

Renal dosing:

eGFR > 90: no adjustment

eGFR 25-90: not defined, cautions advised***

eGFR <25: not defined

Contraindicated with dialysis

SOLOIST WHF

1222 patients – T2DM, recently hospitalized for worsening HF

Safety and efficacy of SGLT-2i initiated soon after an episode of decompensated heart failure

Sotagliflozin vs placebo

Primary endpoint: total number of deaths from cardiovascular causes and hospitalizations and urgent visits for HF

Found that in patients with T2DM and worsening HF, sotagliflozin therapy initiated before or shortly after discharge resulted in significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for HF than placebo.

SCORED

10, 584 patients – T2DM, CKD, and risk of CV disease

Sotagliflozin vs placebo

Primary endpoint: composite of the total number of deaths from CV causes, HHF, and urgent visits for HF

Found that patients with diabetes and chronic kidney disease, with or without albuminuria, sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo but was associated with adverse events.

ADA SOC Updates – 10.42a

GLP-1 RA Suggested Nephroprotective Mechanisms

Indirect

Direct

KDIGO 2022 guidelines

Table with GLP-1RA + GLP/GIP meds, dosing, and renal recommendations

FLOW trial

Will be the first study to investigate effects of GLP-1 RA on primary kidney outcomes
Estimated completion date 2024
3000 patients with T2DM and moderate/advanced CKD and albuminuria
Primary renal outcome:
Persistent ≥ 50% reduction in eGFR or a persistent eGFR ≤ 15 mL/min/1.73m2, initiation of RRT, or death from kidney disease or CVD

SOUL trial

CVOT to evaluate the hypothesis that oral semaglutide lowers the risk of CV events in T2DM patients at high risk for CVD
Composite renal endpoint is a secondary outcome: persistent ≥50% reduction in eGFR or a persistent eGFR < 15mL/min/1.73m2, initiation of RRT, and renal death.

REMODEL trial

ADA SOC Updates – 9.20 and 9.21

Technology

ADA SOC Updates – 7.3

Insulin pumps – timeline of updates for 2023

Medtronic Minimed 780G system

Self-adjusting basal insulin pump system with new autocorrection dosing
Three components:
Insulin pump
Receives data from CGM every 5 minutes
Makes automatic adjustments and correction to insulin delivery

Medtronic Extended infusion set
For wear up to 7 days

Continuous glucose monitor – Guardian Sensor 4
Measures glucose values 288 times per day, every 5 minutes
No fingersticks required
Sends values automatically to your insulin pump

Omnipod Go Insulin Delivery Device

First of its kind basal-only, stand-alone insulin pod
Alternate option to daily insulin injections
Not for patients requiring intensive insulin regimen (i.e. basal-bolus)
Cleared for use with patients with T2DM age 18 or older
Provides a fixed rate of continuous rapid-acting insulin for 72h; 7 different pre-programmed daily rates

Range 10u to 40u per day
10u/24h, 15u/24h, 20u/24h, 25u/24h, 30u/24h, 35u/24h, 40u/24h
Operates without the need for a handheld device to control the pod
Approved U-100 rapid acting insulin: Novolog, Fiasp, Humalog, Admelog, Lyumjev
Supported through pharmacy benefit; select geographics*

iLet Bionic Pancreas

Automated insulin delivery system that:
Eliminates need for CHO counting
Uses estimate of CHO: usual for me, more, less
Eliminates need for correction factors
Automatic correction for BG trends
Eliminates need for CHO ratios
Does not require pre-set basal rates
iLet algorithms communicate with Dexcom G6 or G7 CGM

Approved for use in adults with T1DM and children age ≥ 6 years with T1DM
Does not use any information from previous insulin regimen – doses determined by body weight alone
Basal insulin algorithm, bolus correction insulin algorithm, and meal announcement insulin algorithm
user is not able to edit doses

Mobi Insulin pump

Tandem
Smallest AID system
Compatible with Dexcom G6; anticipated G7 Quarter 2, 2024
Uses control IQ technology
Also has a button to allow a quick bolus

Phone controlled
Wireless charging
200u cartridge
Remote software updates

Accu-chek Solo Micropump

FDA approval August 2023 – unknown launch time in US
Tubeless insulin pump + wireless handheld controller
Approved for T1DM age 2 yrs and older
5 parts:
Adhesive pump holder
Disposable adhesive infusion cannula
Disposable 200 unit reservoir
Reusable pump base
Reusable handheld diabetes manager

Features:

Can deliver bolus without handheld device

Compatible with: Humalog, Novolog, Apidra, and Fiasp

Downfalls:

No AID technology

No smartphone app

CGMs/apps/etc.

March 2023: Libre 2 and Libre 3 -> clearance granted to allow both devices to be used with AID systems and by children as young as age 2

Freestyle libre 2 plus CGM – compatible with Tandem t:slim x2 insulin pump with control IQ technology

March 2023: Android app for Bigfoot Unity diabetes management system -> connected smart cap for insulin pens

April 2023: Freestyle libre 3 reader now available

July 2023: Aspyre Rx digitally delivered cognitive behavioral therapy

December 2023: updated t:slim x2 insulin pump software with Dexcom G7

COMISAIR

7 year study

Longest prospective real-world CGM study ever conducted

Continues to show significant reduction of Hba1c with the use of real-time CGM by patients with T1DM compared to self-monitoring blood glucose

Findings are seen regardless of insulin delivery method (MDI vs pump)

Study shows further substantial reduction in Hba1c when real-time CGM is connected to an AID system

High CGM adherence over 7 years – 88.8% for CGM + MDI and 91.9% for CGM + AID

ADA SOC Table 7.4 – Continuous Glucose Monitoring Interfering Devices

Miscellaneous Updates

ADA SOC Updates - 6.11a, 6.11b, and 6.11c

ADA SOC Table 6.5 – Assessment of hypoglycemia risk among individuals treated with insulin, SU, or metaglinides

ADA SOC Updates – 9.6

What's to Come?

Insulin icodec – once weekly basal insulin

Weekly Icodec versus Daily Glargine U100 in Type 2 Diabetes without Previous Insulin – ONWARDS 1

Switching to once-weekly insulin icodec versus once-daily insulin degludec in individuals with basal insulin-treated type 2 diabetes (ONWARDS 2): a phase 3a, randomised, open label, multicentre, treat-to-target trial

Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults With Insulin-Naive Type 2 Diabetes. The ONWARDS 3 Randomized Clinical Trial

Switching to once-weekly insulin icodec versus once-daily insulin glargine U100 in individuals with basal-bolus insulin-treated type 2 diabetes (ONWARDS 4): a phase 3a, randomised, open-label, multicentre, treat-to-target, non-inferiority trial

Once-Weekly Insulin Icodec With Dosing Guide App Versus Once-Daily Basal Insulin Analogues in Insulin-Naive Type 2 Diabetes (ONWARDS 5) : A Randomized Trial

Once-weekly insulin icodec versus once-daily insulin degludec as part of a basal-bolus regimen in individuals with type 1 diabetes (ONWARDS 6): a phase 3a, randomised, open-label, treat-to-target trial

Effect of Verapamil on Pancreatic Beta Cell Function in Newly Diagnosed Pediatric Type 1 Diabetes -A Randomized Clinical Trial - CLVer study

Does once-daily oral verapamil preserve pancreatic beta cell function in children and adolescents with newly diagnosed type 1 diabetes?

88 patients, children and adolescents with newly diagnosed T1DM

Age 7 to 17 years

Randomly assigned 1:1 – once daily oral verapamil or placebo

Primary outcome: area under the curve values for Cpeptide level stimulated by a mixed meal tolerance test at 52 weeks from diagnosis of T1DM

30% higher Cpeptide level at 52 weeks with verapamil

Cpeptide level 0.2 or greater 95% verapamil group, 71% placebo group

Hba1c 6.6% verapamil group, 6.9% placebo group

Adjusted between-group difference, −0.3% [95% CI, −1.0% to 0.4%]

Retatrutide (LY3437943) - TRIUMPH – novel triple hormone receptor agonist GIP/GLP/glucagon

Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA

Orforglipron (LY3502970) – ACHIEVE trials – oral GLP-1 RA

Tirzepatide (LY3298176) – SURPASS PEDS

Tirzepatide (LY3298176) - SURPASS SWITCH

Insulin Efsitora Alfa (LY3209590) – QWINT studies

A Research Study to See How Much CagriSema Lowers Blood Sugar and Body Weight Compared to Tirzepatide in People With Type 2 Diabetes Treated With Metformin With or Without an SGLT2 Inhibitor

A Research Study to See How Well CagriSema Compared to Semaglutide, Cagrilintide and Placebo Lowers Blood Sugar and Body Weight in People With Type 2 Diabetes Treated With Metformin With or Without an SGLT2 Inhibitor

COMBINE 3 phase 3a trial successfully completed with once-weekly IcoSema demonstrating non-inferior reduction in HbA1c versus daily basal-bolus treatment (insulin glargine U100 and insulin aspart) in people with type 2 diabetes