What’s New in Diabetes?

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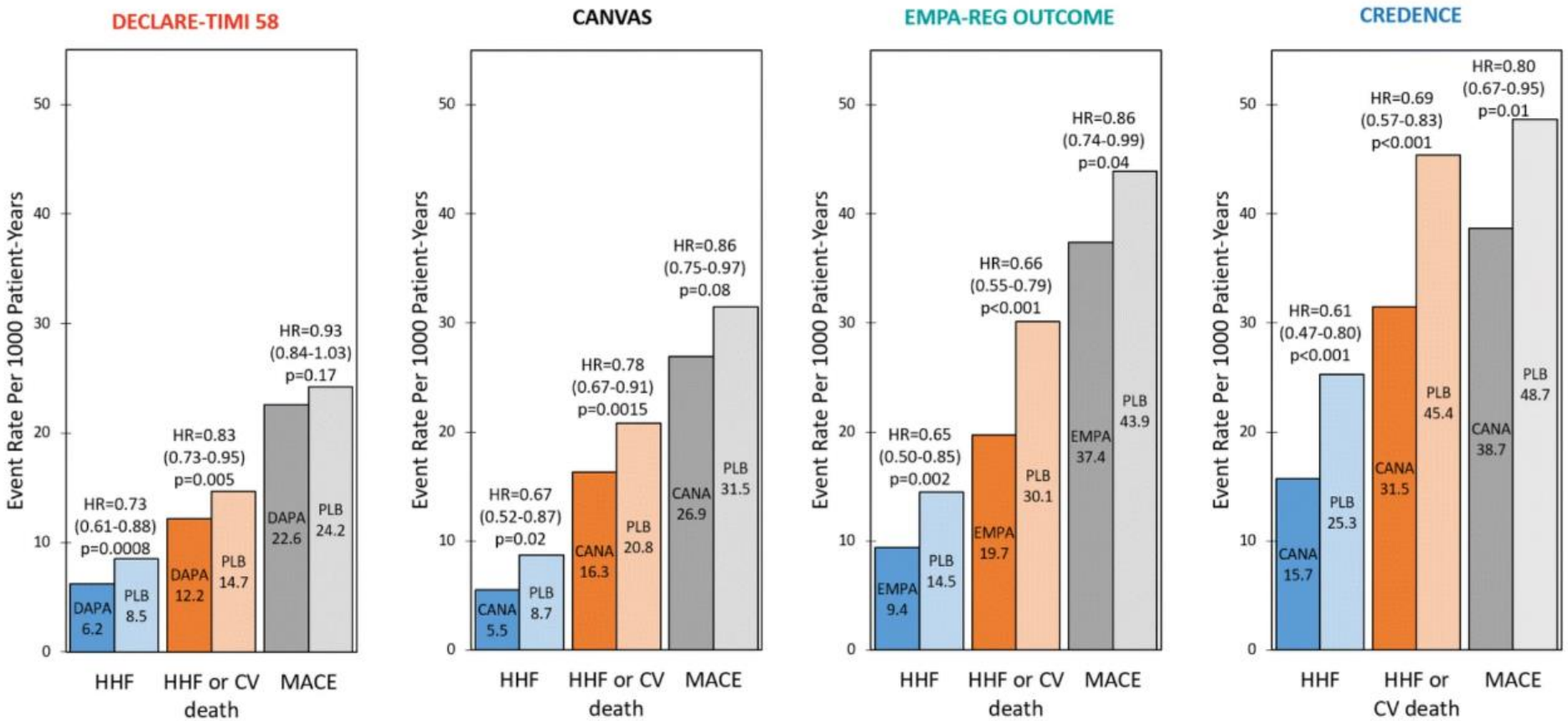
I have no relevant disclosures.

Presentation Overview

- SGLT-2 Inhibitors
- GLP-1 agonists
- Diabetes technology advances
  - Insulin pumps
  - CGMs
- Rescue Medications

Fig. 2

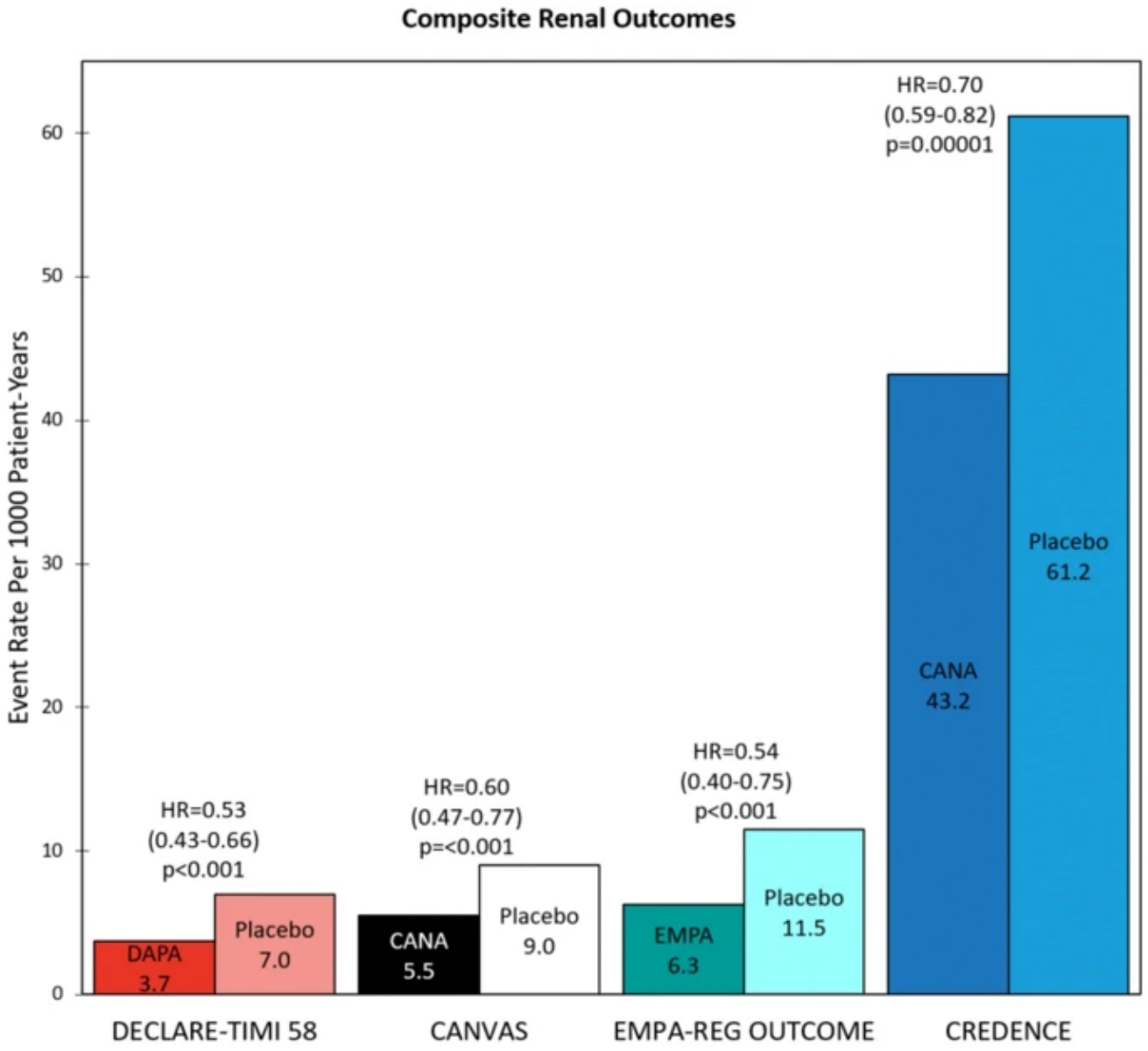
From: Class effects of SGLT2 inhibitors on cardiorenal outcomes



Heart failure hospitalization (HHF), HHF and cardiovascular (CV) death, and major adverse cardiovascular event (MACE) event rates per 1000 patients in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA–REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Statistical outcomes displayed as hazard ratio, 95% confidence interval, p-value. *HR* hazard ratio, *DAPA* dapagliflozin, *CANA* canagliflozin, *EMPA* empagliflozin, *PLB* placebo

Kluger, A.Y., Tecson, K.M., Lee, A.Y. *et al.* Class effects of SGLT2 inhibitors on cardiorenal outcomes. *Cardiovasc Diabetol* **18,** 99 (2019). https://doi.org/10.1186/s12933-019-0903-4

Fig. 3



Kluger, A.Y., Tecson, K.M., Lee, A.Y. *et al.* Class effects of SGLT2 inhibitors on cardiorenal outcomes. *Cardiovasc Diabetol* **18,** 99 (2019). https://doi.org/10.1186/s12933-019-0903-4

Credence Trial (Canagliflozin)

- Double Blind, Randomized Trial
- 4400 patients, 2.6 yrs
- Type 2 DM with CKD (GFR 30-90 ml/min) with macro-albuminuria.
- Canagliflozin 100 mg vs Placebo

- Outcome: ESRD, Doubling of Creatinine, Death from renal or CV disease
- Relative Risk of Primary Outcome: 30% ⬇
- Lower risk of CV death, MI, Stroke, hospitalization for Heart Failure
- No differences in fractures or amputations.

- Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy, Vlado Perkovic, M.B., B.S., Ph.D, et al. N Engl J Med 2019; 380:2295-2306
DOI: 10.1056/NEJMoa1811744

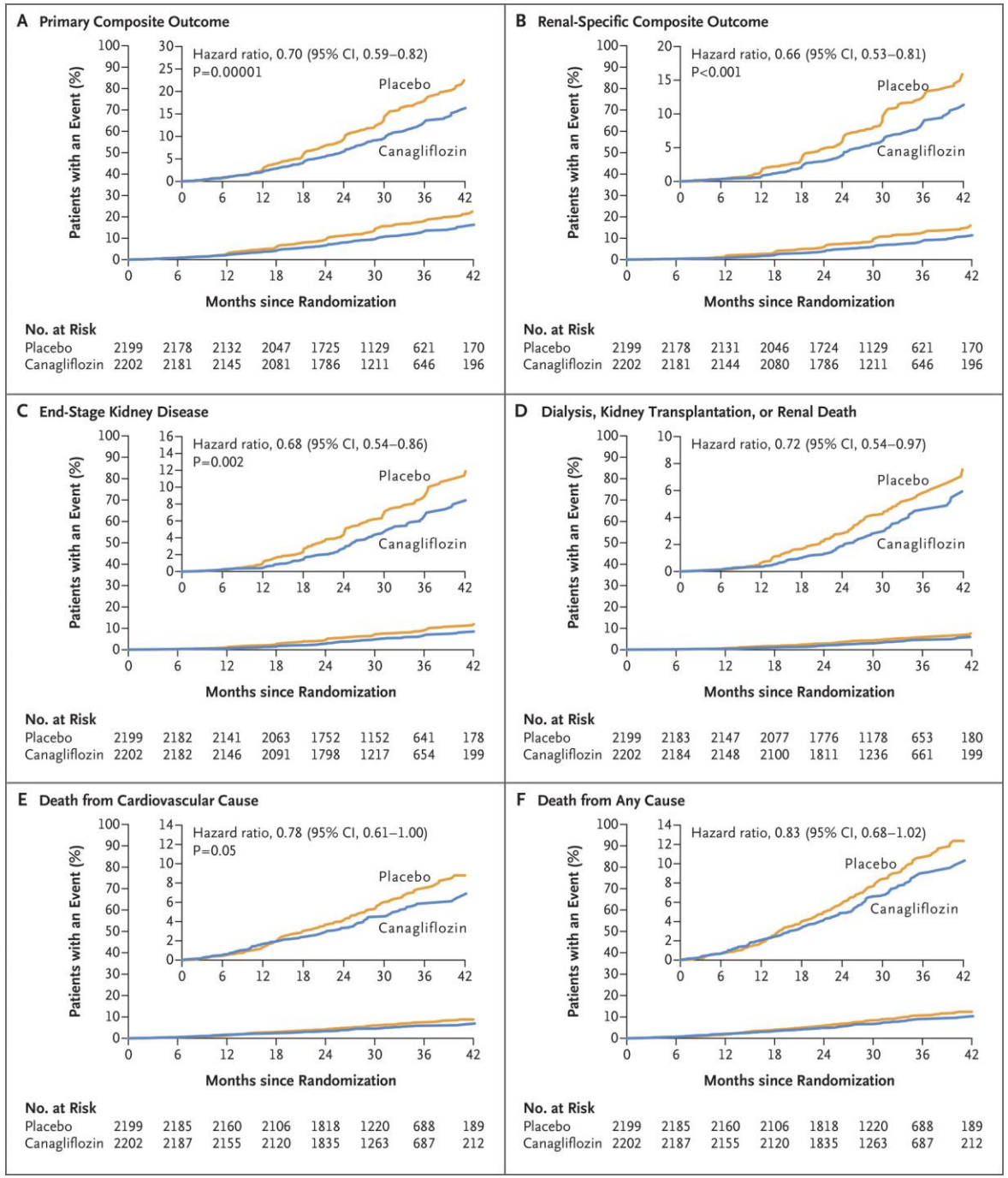


Figure 1: Perkovic et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 2019; 380:2295-2306
DOI: 10.1056/NEJMoa1811744

Canagliflozin Dosing

- > 60 ml/min/m2: 100-300 mg daily
- 45-60 ml/min/m2: 100 mg daily
  - Macroalbuminuria or hyperglycemia
- 30-45 ml/min/m2 with macroalbuminuria: 100 mg daily
- < 30 ml/min/m2: Contraindicated for hyperglycemia
  - But can continue 100 mg daily for macroalbuminuria

Type 1 DM and SGLT-2 Inhibitors

- InTandem Trial
  - Multicenter, Double Blind
  - 1400 + patients
  - Type 1 DM on insulin therapy
  - Sotagliflozin vs Placebo
  - 24 weeks
- Primary End Point:
  - A1c < 7.0%
  - No DKA or hypoglycemia
- Results
  - 28.6% vs 15.2% achieved goal
  - Similar severe hypoglycemia rate
  - Overall lower hypoglycemia
  - DKA higher
    - 3.0% vs 0.6%
- Approved for use in Europe
- Not FDA approved

Garg, et al. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. N Engl J Med 2017; 377:2337-2348. DOI: 10.1056/NEJMoa1708337

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Liraglutide in Children and Adolescents

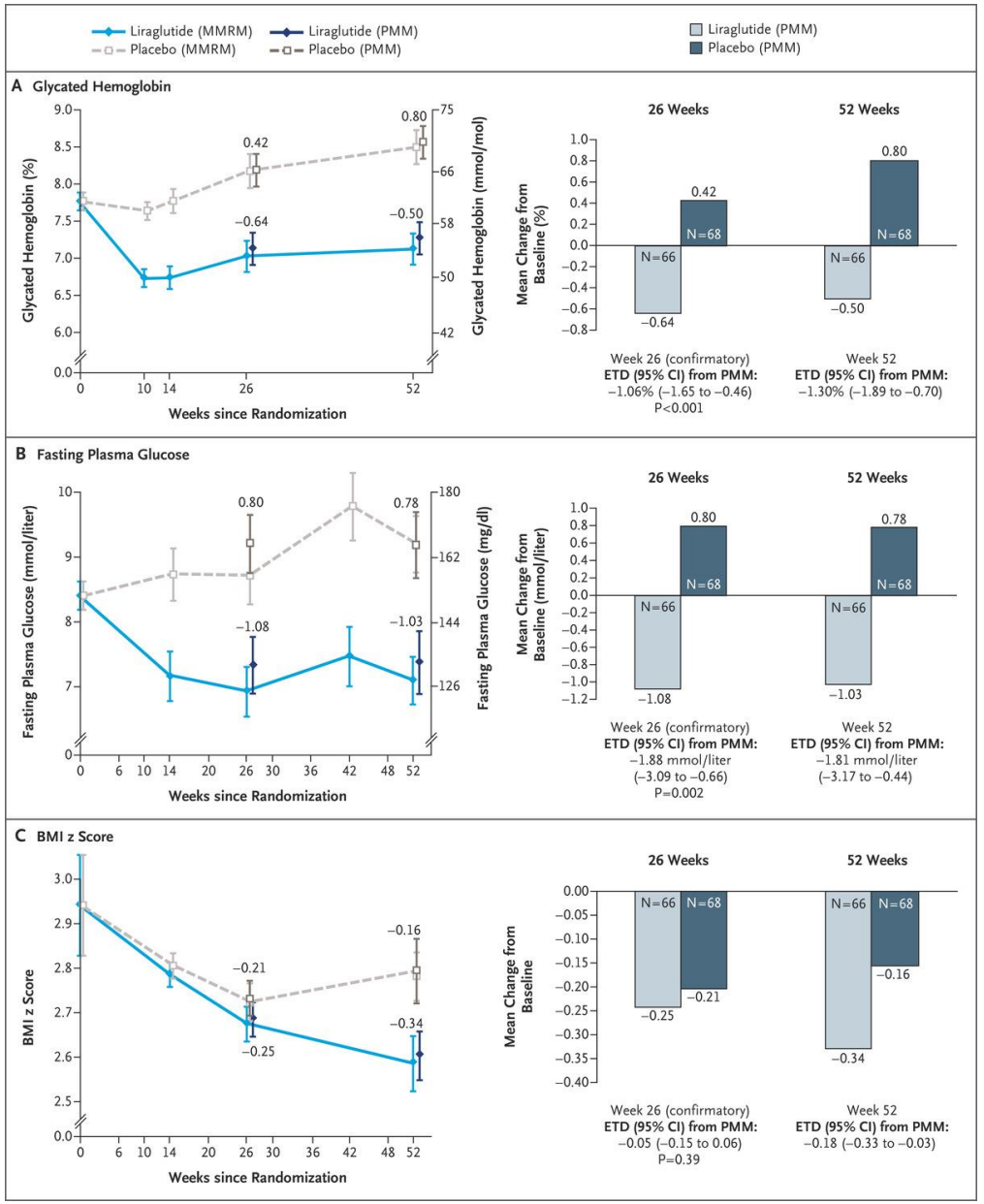
- Trial Design
  - Randomized, Double Blind
  - 26 week trial + 26 week open label
- Ages 10-17
  - BMI > 85th percentile
  - A1c: 7-11
    - Diet and exercise only
  - A1c: 6.5-11
    - Metformin monotherapy
  - All patients received metformin

- Key Results
  - A1c: -0.6% in liraglutide group,
  - A1c: + 0.4% in placebo group at 26 weeks
  - Net Change
    - -1.0% at 26 weeks
    - -1.3% by 52 weeks
  - + GI side effects

- Dosing: 1.8 mg daily in addition to metformin
- CI: Medullary thyroid cancer, History of MEN

Tamborlane, William MD. Liraglutide in Children and Adolescents with Type 2 Diabetes. N Engl J Med 2019; 381:637-646. DOI: 10.1056/NEJMoa1903822

Figure 2



WV Tamborlane et al. N Engl J Med 2019;381:637-646.

Oral Semaglutide

- Sept 2019—Approved by FDA as first oral GLP- Agonist
- Type 2 Diabetes
  - Contraindications:
    - Medullary thyroid cancer
    - MEN2
    - Type 1 DM
    - Pancreatitis ?
    - Diabetic retinopathy ?
- Dosing
  - Take 3o min prior to first meal of day
    - 3 mg, 7 mg, 14 mg doses.

Oral Semaglutide Comparison

26 week trial

VS Placebo

- A1c Reduction
  - 7 mg: -1.2%
  - 14 mg -1.4%
  - Placebo: -0.3%
- Patients achieving < 7%
  - 7 mg: 69%
  - 14 mg: 77%
  - Placebo: 31%

VS Empagliflozin 25 mg

- Patients on Metformin
- A1c Reduction
  - 14 mg: -1.3%
  - Empa 25 mg: -0.9%
- Patients achieving < 7%
  - 14 mg: 67%
  - 25 mg: 40%

Oral Semaglutide in combination with metformin +/- SGLT2i

VS liraglutide 1.8 mg or placebo with baseline A1c ~8.0

- A1c change
  - Placebo: -0.2%
  - Liraglutide 1.8 mg: -1.1%
  - Semaglutide 14 mg: -1.2%
- Patients achieving < 7% goal
  - Placebo: 14%
  - Liraglutide 1.8 mg: 62%
  - Semaglutide 14 mg: 68%

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Smart Pens

- Integrates diabetes pump technology in insulin delivery pen
- Has programmed correction factors, carbohydrate ratios
- Records time and dosing of insulin for easy download
- ½ unit increments
- Takes into account insulin on board
- Limitations
  - 30 unit max bolus
  - Some rapid acting insulin not available in cartridges

Closed Loop Systems in Type 1 Diabetes

- 6 month trial.
- 168 patients
- 2:1 assignment (Closed loop: sensor augmented pump)
- Primary outcome:
  - % Time in Range (TIR)
  - TIR defined: Blood glucose 70-180 mg/dL
  - 11% increase in TIR in Closed loop Group, no change in Sensor augmented group

Brown, S. et al. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. N Engl J Med 2019; 381:1707-1717. DOI: 10.1056/NEJMoa1907863.

Closed Loop Systems in Type 1 Diabetes

- Secondary outcomes:
  - % time BG > 180 mg/dL
  - Mean glucose level
  - A1c
  - % time BG <70 mg/dL

- All favored Closed Loop Group

Control IQ Insulin Pump

- FDA approved in December 2019
- Integrates an alternate controller-enabled pump to an integrated continuous glucose monitor (iCGM)
- Based on CGM, Automatically
  - Increases insulin delivery
  - Decreases insulin delivery
  - Suspends insulin delivery
  - Adjusts insulin based on predicted high or low glucose thresholds

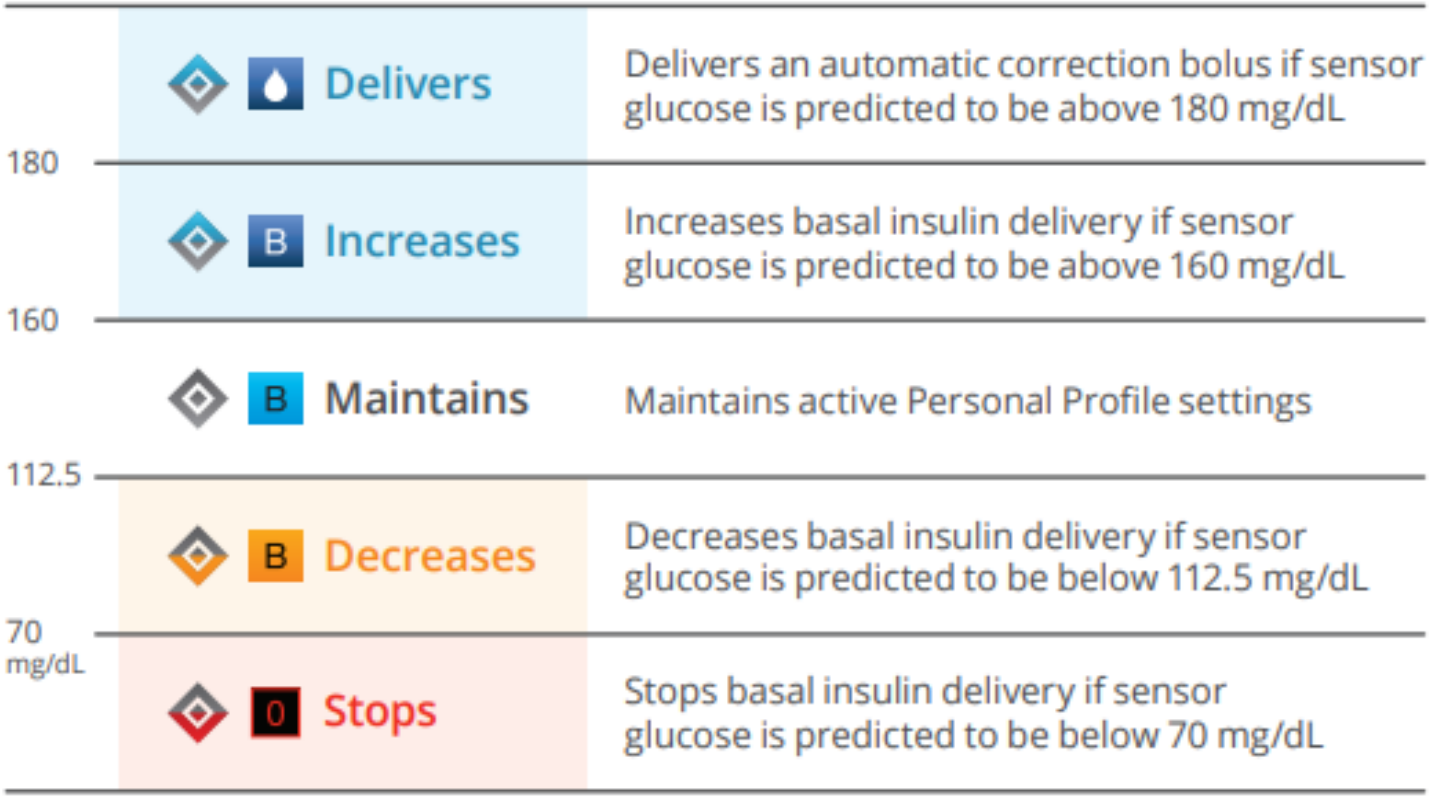
FDA authorizes first interoperable, automated insulin dosing controller designed to allow more choices for patients looking to customize their individual diabetes management device system, FDA news release, December 13, 2019.

Control IQ Clinical Trial

- 168 participants with Type 1 Diabetes
- Randomized to Control IQ or Pump plus CGM groups
- Findings:
  - The controller could safely determine and command insulin delivery
  - The controller could safely communicate to all parts of the system

How Does Control-IQ Technology Work?

Control-IQ™ technology is designed to help increase time in range (70—180 mg/dL)* using Dexcom G6 continuous glucose monitoring (CGM) values to predict glucose levels 30 minutes ahead and adjust insulin delivery accordingly, including delivery of automatic correction boluses (up to one per hour).



*As measured by CGM.

https://www.tandemdiabetes.com/docs/default-source/general-guides/ml-1004929_a---print-flyer-quick-reference-sheet-control-iq-technology.pdf?sfvrsn=d9dc04d7_6

Treatment values in Control-IQ technology

		Control-IQ	Sleep Activity	Exercise Activity
Delivers	Delivers an automatic correction bolus if sensor glucose is predicted to be above ____ mg/dL	180	--	180
Increases	Increases basal insulin delivery if sensor glucose is predicted to be above ____ mg/dL	160	120	160
Maintains	Maintains active Personal Profile settings when sensor glucose is between ____ - ____ mg/dL	112.5 - 160	112.5 - 120	140 - 160
Decreases	Decreases basal insulin delivery if sensor glucose is predicted to be below ____ mg/dL	112.5	112.5	140
Stops	Stops basal insulin delivery if sensor glucose is predicted to be below ____ mg/dL	70	70	80

https://www.tandemdiabetes.com/docs/default-source/general-guides/ml-1004929_a---print-flyer-quick-reference-sheet-control-iq-technology.pdf?sfvrsn=d9dc04d7_6

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New Intranasal Glucagon Powder

- Indicated for severe hypoglycemia for adults and children > 4 years old.
- Contraindications
  - Pheochromocytoma
  - Insulinoma
  - Allergy to glucagon
- Adverse reactions
  - Nausea
  - Vomiting
  - Headache
  - Upper respiratory tract symptoms
- Doses
  - 3 mg one time use device

“Ready to Use” Glucagon

- FDA approved in Sept 2019 for severe hypoglycemia
  - Adults and children > 2 years old
- Premixed glucagon injector pen
- 2 year shelf life
- Contraindications
  - Pheochromocytoma
  - Insulinoma
  - Allergy to glucagon
- Adverse Reactions
  - Nausea
  - Vomiting
  - Headache
  - Upper respiratory tract symptoms
- Doses
  - 0.5 mg/0.1 ml dose for children
  - 1 mg/0.2 mL dose for adolescents and adults.

Thank You

- QUESTIONS?

What's New in Male Hypogonadism?

Steven L Brown DO

Endocrinologist

I have no relevant financial disclosures.

Overview

- Current Guidelines
- Current Therapies
- Management of fertility in male hypogonadism

Male Hypogonadism Guidelines

- Diagnosis
  - Symptoms and signs of low testosterone
  - **Consistently** low serum total or free testosterone
- Evaluation
  - Primary vs Secondary (FSH, LH)
  - Further Evaluation
    - Prolactin, Iron saturation, Other pituitary hormones
    - Karyotype
    - MRI Brain with pituitary protocol
      - Panhypopituitarism
      - Hyperprolactinemia
      - Total testosterone < 150 ng/dL
      - Symptoms of tumor mass effect

Bhasin S, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 5, May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229

Treatment of Hypogonadism

- Recommended treatment to:
  - Maintain secondary sex characteristics
  - Treat symptoms of low testosterone

- Recommended against treating:
  - Near-term fertility
  - History of **Breast or Prostate Cancer**
  - Palpable **prostate nodule**
  - **PSA > 4 or PSA > 3 with high risk**
  - **Elevated H/H,**
  - OSA
  - Uncontrolled Heart Failure or **MI within 6 months.**
  - Thrombophilia

Bhasin S, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 5, May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229

Special Treatment Groups

- 2.4- Against prescribing all men over age 65
  - Symptoms of low testosterone, anemia, etc.
- 2.5-Treat HIV infected males with short term course of testosterone
  - Low testosterone and weight loss
- 2.6- Against treating men with diabetes to improve glycemic control

Bhasin S, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 5, May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229

Testosterone Treatments

- Injections
- Transdermal Gels
- Axillary Solutions
- Transdermal Patches
- Pellets
- Buccal Testosterone
- Nasal Testosterone

Testosterone cypionate/enanthate injections

- Starting dose
  - 150-200 mg IM every 2 weeks
  - 75-100 mg IM every week
- Pharmacokinetics:
  - Instant rise after injection
  - Often hypogonadal before next injection
- Advantages
  - $
  - Self Administered
- Disadvantages:
  - IM injection, peaks and valleys

Transdermal Gels

- Starting Doses
  - 50-100 mg of 1% gel
  - 20.25-81 mg of 1.62% gel
- Pharmacokinetics
  - Gradual increase to physiological range
- Advantages
  - Less erythrocytosis than injections
  - Ease of administration
- Disadvantages
  - Cross-contamination, Skin irritation

Testosterone Axillary Solution

- Starting Doses
  - 60 mg dose applied to axillae
- Pharmacokinetics
  - Gradual increase of testosterone levels
- Advantages
  - Better skin tolerability
- Disadvantages
  - Cross contamination
  - Variable doses application to application

Transdermal Testosterone Patch

- Starting Doses
  - 1-2 patches delivering 2-4 mg/24 hours
- Pharmacokinetics
  - Gradual increase of testosterone levels
- Advantages
  - Ease of application
- Disadvantages
  - Irritation at skin site
  - Patches non-adherent
  - Difficultly obtaining physiological levels of testosterone

Testosterone Pellets

- Starting Doses
  - 600-1200 mg subcutaneous implant
- Pharmacokinetics
  - Peak testosterone at 1 month
  - Gradual decline over next 3-6 months
- Advantages
  - Infrequent administration
- Disadvantages
  - Surgical procedure
  - Infection, protrusion of pellet, hematoma
  - Fairly permanent

Buccal Testosterone

- Starting Doses
  - 30 mg controlled release tablets twice daily
- Pharmacokinetics
  - Absorbed from buccal mucosa to gradually increase levels
- Advantages
  - Convenient and discrete
- Disadvantages
  - Gum-related adverse events

Injectable Long Acting Testosterone Undecanoate

- Starting Doses
  - 750 mg initial dose
  - 750 mg at 4 weeks
  - 750 mg every 10 weeks
- Pharmacokinetics
  - Similar to IM injections, but more stable levels
- Advantages
  - Dosing interval
- Disadvantages
  - Large dose
  - Coughing episode after injections in some men

Nasal Testosterone Gel

- Starting Doses
  - 11 mg two to three times daily
- Pharmacokinetics
  - Slow increase into normal range
- Advantages
  - Rapidly absorbed
  - Avoids 1st pass metabolism
- Disadvantages
  - Dosing intervals
  - Local side effects

The “Not FDA Approved” List

- Clomid and Tamoxifen
  - Selective Estrogen Receptor Modulator (SERM)
  - Used for Hypogonadotropic Hypogonadism without pituitary mass
  - Can increase both sperm counts and testosterone levels

- Anastrozole
  - Often used to inhibit estrogen conversion

American Urological Association: Evaluation and Management of Testosterone Deficiency (2018). Table 6

HCG

- Dosing
  - 500-4000 IU SQ or IM three times a week
- Indications
  - Male hypogonadism with/without low sperm counts
  - Pediatric patients with cryptorchidism
- Disadvantages
  - Injections 3 times a week
  - Cost
- Adverse Reactions
  - Headache, Mood changes, fatigue, edema, gynecomastia

American Urological Association: Evaluation and Management of Testosterone Deficiency (2018). Table 6

Testosterone Enanthate SQ Injection

- Starting Doses
  - 50 mg, 75 mg, 100 mg subcutaneous injection weekly
- Indications
  - Male hypogonadism
  - > 18 yrs old
- Advantages
  - Fast, Almost Pain Free
  - Single-use injection device 27 gauge needle
- Disadvantages
  - Hypertension
  - Typical testosterone side effects.

Trial Details

- Evaluation of testosterone enanthate auto-injector
- Primary Outcome: % patients with serum testosterone 300-1100 ng/dL
- Inclusion:
  - > 18 yr old with hypogonadism
  - Total Testosterone < 300 ng/dL X 2
  - Good general health
- Study: 137 patients, 12 weeks, 1 intervention group
  - Dosed 50, 75 or 100 mg testosterone
- Results: 98.5% achieved primary goal

https://clinicaltrials.gov/ct2/show/results/NCT02159469. **Subcutaneous Testosterone Replacement Efficacy and Safety in Adult Men Diagnosed With Hypogonadism (STEADY)**

Oral Testosterone Undecanoate

- Starting Doses
  - 158mg, 198mg, and 237mg strength capsules
- Indications
  - Male hypogonadism
  - > 18 yrs old
  - Not for Age related hypogonadism
- Advantages
  - Oral Medication
  - No injections
- Disadvantages
  - Hypertension
  - Typical testosterone side effects.
- **FDA approves new oral testosterone capsule for treatment of men with certain forms of hypogonadism March 27, 2019.** https://www.fda.gov/news-events/press-announcements/fda-approves-new-oral-testosterone-capsule-treatment-men-certain-forms-hypogonadism

Trial Overview

- Randomized 4 month trial
- Oral Testosterone vs Topical Testosterone solution (3:1)
- 237 mg twice daily dose with dose adjustments up to 396 mg twice daily
- Primary Endpoint: Normal Testosterone level
- Results:
  - 87% of patients reached goal
  - https://clinicaltrials.gov/ct2/show/study/NCT02722278. A Study of Oral Testostserone Undecanoate (TU) in Hypogonadal Men (inTUne)

Questions?