CVOT with Drugs for Type 2 Diabetes: Articles may have shifted during flight

Leonard Zemel, MD
ROME Conference
3.6.2020

Conflicts/Disclosures

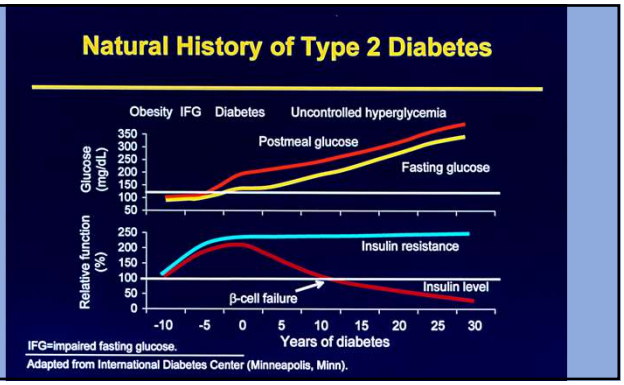
- I have no conflicts and nothing to disclose

Overview

- Review FDA approved drug classes for T2DM
- Certain classes reducing CV, Renal, HF risk
- New paths in DM management

Type 2 Diabetes and studies may include:

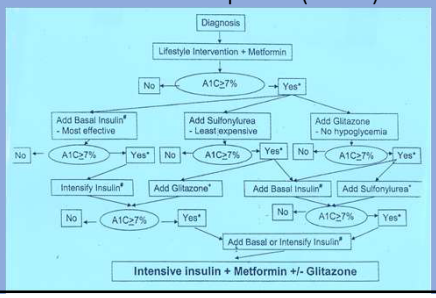
- Typical, Older, CV risk/Metabolic syndrome, Overweight
- MODY
- Glucose toxicity
- Other forms of adult diabetes: Chronic pancreatitis, Pancreatic toxins, Secondary causes
- Overlap with insulin deficiency, LADA



Multiple organs are involved in diabetic disease state

- Different contributions to cause disease physiology
- Damage from disease
- Drug development to address:
  - Diabetic syndrome
  - Damage from disease state (non-vascular)
  - Micro and Macrovascular disease
- Proliferation of drugs since the 1990's

ADA Algorithm From Time Capsule (2006)

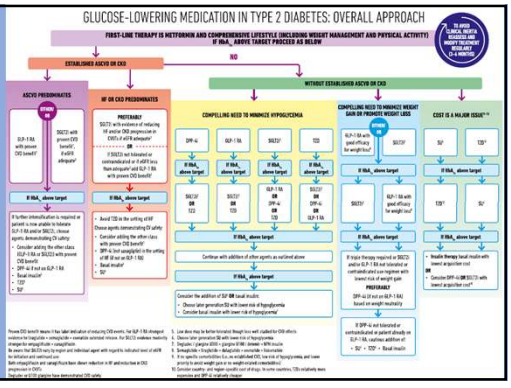


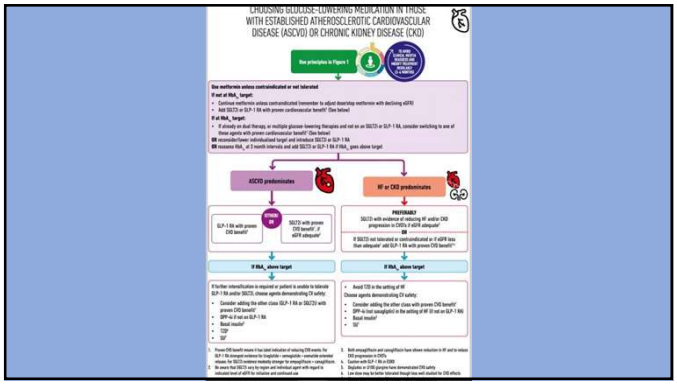
Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Diabetes Care Publish Ahead of Print, published online October 4, 2018

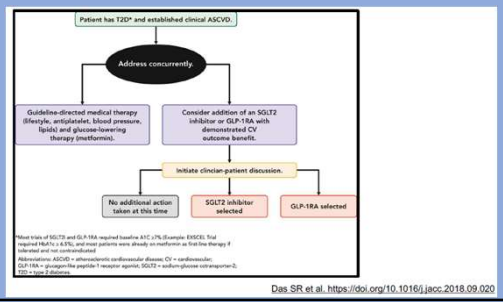
Current Algorithm (2018)

- No drug left behind
- CVOT guidance appears



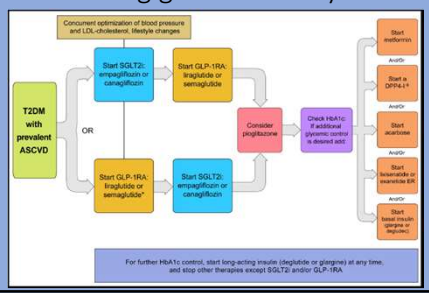


Updated decision pathway



Das SR et al. https://doi.org/10.1016/j.jacc.2018.09.020

Disrupting Care for patients with T2DM and ASCVD: Removing glucocentricity



Now there are 13 Classes of FDA Approved drugs for Type 2 DM

- Biguanides
- Sulfonylureas
- TZD's
- Alpha glucosidase inhibitors
- Meglitinides
- GLP-1's
- DPP-4's
- Bromocriptine
- Welchol
- Pramlintide
- Insulin injected
- Insulin inhaled
- SGLT-2's
- Combos of all sorts

Classes to save $

- Sulfonylureas
- Biguanides
- Older Insulins – NPH, Regular, 70/30

Classes associated with best A1C lowering

- Sulfonylureas
- Metformin
- TZD's
- GLP-1's
- Insulins
- Combinations

Classes associated with weight loss

- GLP-1's
- SGLT-2's

Classes you'll likely not use

- Bromocriptine
- Welchol
- Meglitinides
- Alpha glucosidase inhibitors

Controversial classes

- TZD's

Controversies within SGLT-2 class

- Bone loss
- Fracture
- Amputations

Classes you may not know exist

- Pramlintide
- Inhaled insulins

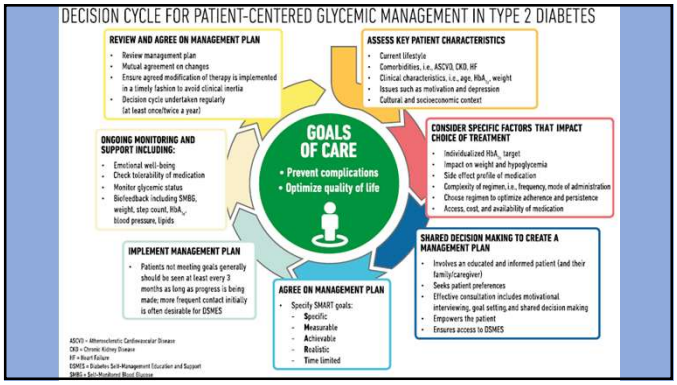
Metformin variations

- IR
- XR
- DR – to get gut peptide effect
- Glumetza

CVOT/Renal protection

(may change the algorithm)

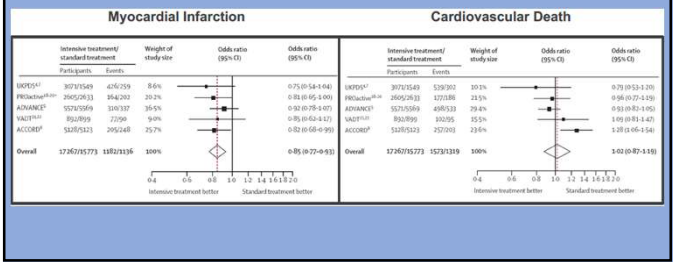
- GLP-1's
- SGLT-2's



Outcomes – Early studies with glucoentric focus

- ACCORD – Risks of tight control too late

Effects of more vs less intensive glycemic control on CV outcomes



Early major trials evaluating the effects of intensive glycemic control of diabetes

Study	Diabetes type	CV composite		MI		CV mortality		All-cause mortality	
DCCT/EDIC (17,26,27)	Type 1	↔	↓	—	—	—	—	↔	↓
UKPDS	Type 2								
Main randomization (SU or insulin vs. conventional therapy) (18,28)		—	—	↔	↓	—	—	↔	↓
Additional randomization of overweight patients (metformin vs. SU vs. conventional therapy) (19,28)		—	—	↓*	↓*	—	—	↓*	↓*
ACCORD (20,30)	Type 2	↔	↔	↓	↔	↑	↑	↑	↔
ADVANCE (21)	Type 2	↔†		↔		↔		↔	
VADT (22,29)	Type 2	↔	↓	↔	↔	↔	↔	↔	↔

Left columns show initial results; right columns show long-term follow-up. ↔, Neutral effect; ↓, decrease; ↑, increase; —, not assessed/reported; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; SU, sulfonylurea. Adapted from Bergenstal et al. (97).

*Metformin group only.

†A decrease was reported in a combined CV/microvascular composite but was found to be mostly attributable to nephropathy.

FDA Regulatory guidance for drugs for T2DM

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
December 17, 2008

Media Inquiries:
Karen Riley, 301-796-4674
Consumer Inquiries:
888-INFO-FDA

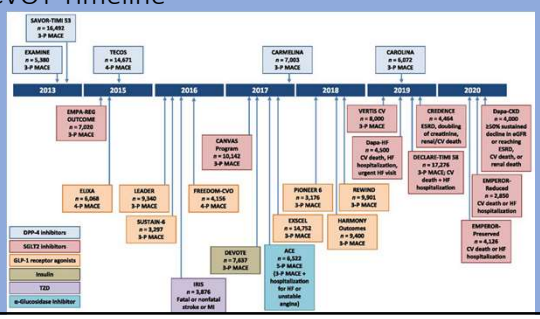
FDA Announces New Recommendations on Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes

The U.S. Food and Drug Administration recommended today that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack. The recommendation is part of a new guidance for industry that applies to all diabetes drugs currently under development.

"We need to better understand the safety of new antidiabetic drugs. Therefore, companies should conduct a more thorough examination of their drugs' cardiovascular risks during the product's development stage," said Mary Parks, M.D., director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research (CDER), FDA. "FDA's guidance outlines the agency's recommendations for doing such an assessment."

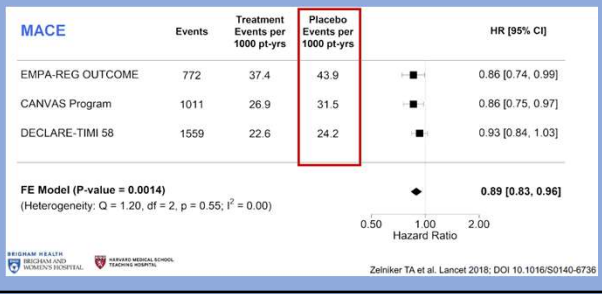
Requires ~15,000 pt-yrs of exposure

CVOT Timeline

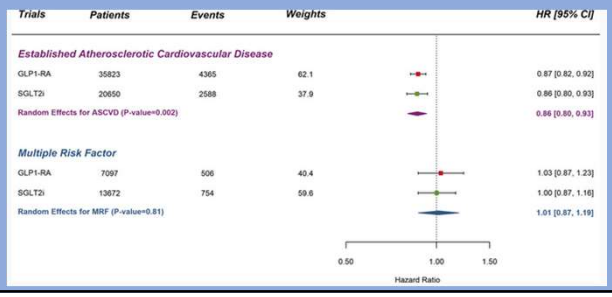


Cardiovascular Protection

Meta-analysis of SGLT-2 CVOTs

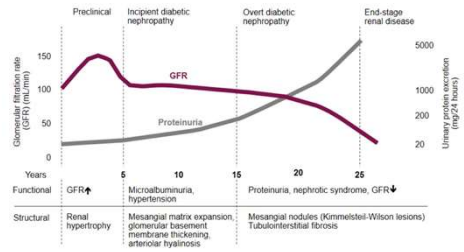


Primary and Secondary CV prevention by GLP-1 and SGLT-2



Renal Protection

Progression of Chronic Kidney Disease in Diabetes

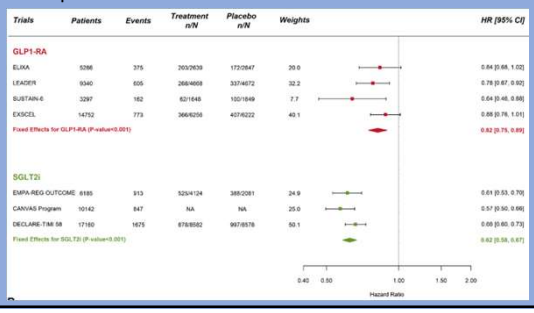


37 Williams ME. *Med Clin North Am*. 2013;97:75-89. © AstraZeneca 2019

Product labeling regarding eGFR for SGLT-2's glucocentric effect

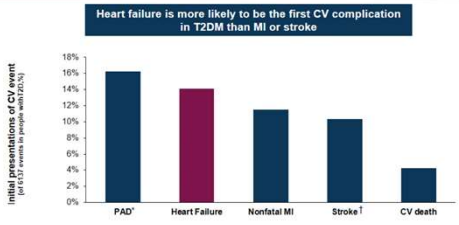
Drug	eGFR labeling
empagliflozin	Contraindicated eGFR <45ml/min/1.73m²
canagliflozin	Contraindicated eGFR <45ml/min/1.73m²; Only use 100mg daily for eGFR <60ml/min **Will update with new labelling**
dapagliflozin	Contraindicated for eGFR <60ml/min/1.73m²
ertugliflozin	Not recommended for eGFR eGFR <45ml/min/1.73m²; Contraindicated for eGFR <30ml/min/1.73m²

Renal protection from GLP-1 and SGLT-2



Heart Failure Protection

Heart Failure is the Second Most Common Initial CV Event in Patients with Type 2 Diabetes



Cohort study of patients with T2D evaluating initial manifestations of cardiovascular disease.
*Defined as intermittent claudication, limb ischemia, gangrene; †Not further specified
T2DM = type 2 diabetes mellitus
Shah AD et al. Article and supplementary material. *Lancet Diabetes Endocrinol*. 2015;3:105-113.

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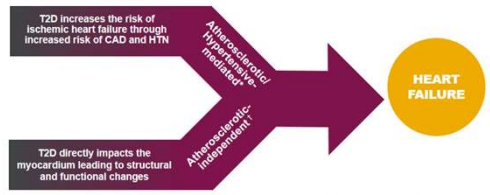
Diabetes can Lead to HF through Both Atherosclerotic-Mediated and Atherosclerotic-Independent Mechanisms[1-4]



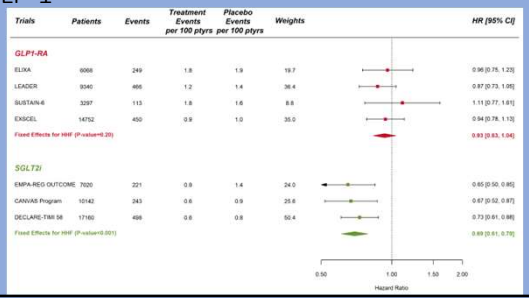
Diabetic cardiomyopathy is characterized by early diastolic dysfunction in the absence of CAD or hypertensive heart disease and can manifest as either HFpEF or HFrEF.[3,4]

*Ischemic and Hypertensive Cardiomyopathy; †Diabetic Cardiomyopathy

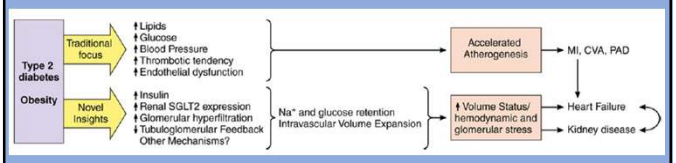
CAD = coronary artery disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction;; HTN = hypertension; T2D = type 2 diabetes

1. Ofstad AP et al. *Heart Fail Rev.* 2018;23:303–323. 2. Low Wang C et al. *Circulation.* 2016;133:2459-2502. 3. Seferović PM. et al. *Eur Heart J.* 2015;36:1718-1727. 4. Jia G. et al. *Diabetologia.* 2018;61:21-28.

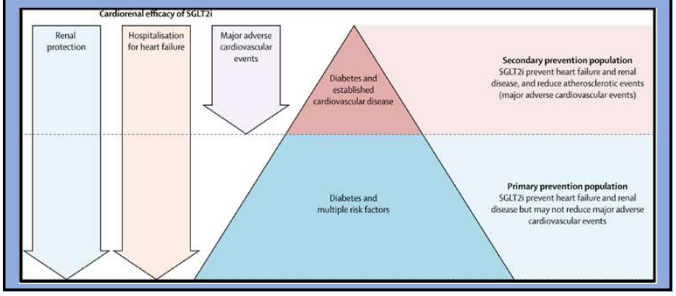
HF hospitalization protection from SGLT-2 and GLP-1



Redefining pathways to HF and kidney disease in T2DM



Pumps, Pipes, and Filter: Do SGLT-2's cover it all?



Conclusions on CVOT

- Regulatory requirements have dramatically altered the trial landscape of drug development for T2DM
  - > 300,000 patients enrolled/planned in CV outcomes trials
- 6 completed trials demonstrating CV safety
  - DPP4's: saxagliptin, alogliptin, sitagliptin, linagliptin
  - Labeled caution for HF for all DPP4's based on alogliptin and saxagliptin data
  - GLP1 RA: lixisenatide, exenatide ER
- 7 trials/programs have reported CV benefit
  - SGLT inhibitors: empagliflozin, canagliflozin, dapagliflozin
  - GLP1 RA: liraglutide, semaglutide, albiglutide, dulaglutide
- Trial results have directly impacted contemporary care for T2DM

Beyond Conclusions

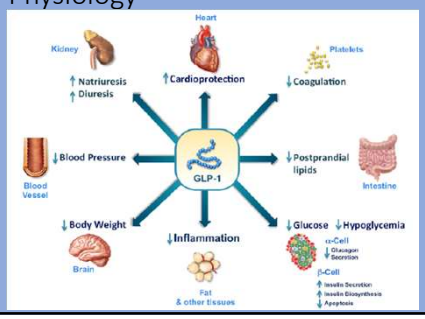
Cerebral/Dementia Protection

- Newer studies with cognitive testing

If there is a mechanism here, can these drugs help non-diabetics?

- Studies
  - DAPA-HF
  - DAPA-CKD (GFR > 25 cc/min)

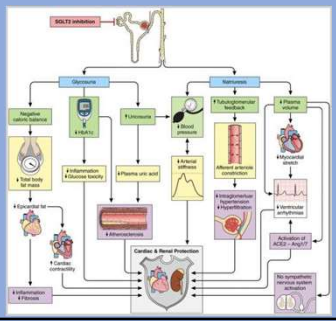
GLP-1 Physiology



SGLT-2 Protection Physiology

- Natriuresis
- Inhibition of tubuloglomerular feedback
- BP lowering – Arterial and heart changes
- Increased ketone production
- Hemoconcentration – Increased O2 delivery
- Inhibition of Na/H exchanger - Heart (NHE1), Kidney (NHE3)
- Cytokine production

Pathways involved in cardioprotective role of SGLT2's

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Have the Blockbuster Diabetes Drug Trials Been Biased?

Miriam E. Tucker
January 15, 2020

8 Read Comments | ADD TO EMAIL ALERTS

- **Imbalance of glycemic control**
- **Imbalance of BP**
- **Imbalance of diuretic use**

Imbalances in glycemic control, blood pressure, and diuretic use between treatment and placebo arms could have biased the cardiovascular and renal outcomes of recent large trials in favor of the study drugs for treating type 2 diabetes, some experts assert.

The cardiovascular outcomes trials (CVOTs) were mandated by the US Food and Drug Administration in 2008 to ensure the safety of newer agents being

Journal of Pharmaceutical Policy and Practice

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Imbalance in glycemic control between the treatment and placebo groups in cardiovascular outcome trials in type 2 diabetes

Rumiko Shimazawa & Masayuki Ikeda

Journal of Pharmaceutical Policy and Practice **12**, Article number: 30 (2019) | Cite this article

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Abstract

Background

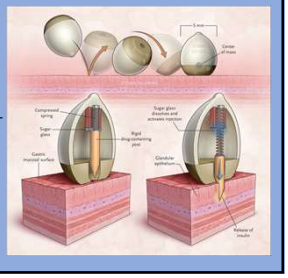
Glycated hemoglobin (HbA1c) is accepted as the most reliable marker for assessing chronic glycemia. The present study aimed to investigate glycemic control in cardiovascular outcome trials (CVOTs) performed by pharmaceutical sponsors, at the request of the United States Food and Drug Administration (FDA) to ensure that newer hypoglycemic agents do not

Trial	HbA1c imbalance[a]	Additional hypoglycemic agents	Primary endpoint	Cardiovascular death	Nonfatal MI	Nonfatal Stroke	Heart failure	Death from any cause	Increased adverse events[b]
EXAMINE	0.36 (mean)	NA	0.96 (0.8–1.16)	0.79 (0.60–1.04)	1.08 (0.88–1.33)	0.91 (0.55–1.50)	**1.76**[c] **(1.07–2.90)**	0.88 (0.71–1.13)	Heart failure
CARMELINA	0.36 (mean)	More in P group	1.02 (0.89–1.17)	0.96 (0.81–1.14)	1.15 (0.91–1.45)	0.88 (0.63–1.23)	0.90 (0.74–1.08)	0.98 (0.84–1.09)	
SAVOR-TIMI	0.3 (52[a])	More in P group	1.00 (0.95–1.12)	1.03 (0.87–1.22)	0.95 (0.80–1.12)	1.11 (0.88–1.39)	**1.27 (1.07–1.51)**	1.11 (0.96–1.27)	Heart failure
TECOS	0.29 (mean)	More in P group	0.98 (0.89–1.08)	1.03 (0.89–1.19)	0.96 (0.81–1.13)[d]	0.93 (0.75–1.16)[f]	1.00 (0.83–1.20)	1.01 (0.90–1.14)	
HARMONY	0.63 (8[a])	More in P group	0.78 (0.68–0.90)	0.93 (0.73–1.19)	0.73 (0.61–0.90)[e]	0.86 (0.66–1.14)[g]	0.85 (0.70–1.04)	0.95 (0.79–1.16)	
EXSCEL	0.53 (mean)	More in P group	0.91 (0.83–1.00)	0.88 (0.73–1.05)	0.95 (0.84–1.09)	0.86 (0.70–1.07)	0.94 (0.78–1.13)	*0.86 (0.77–0.97)*	
LEADER	0.4 (36[a])	More in P group	*0.87 (0.78–0.97)*	0.78 (0.66–0.92)	0.88 (0.75–1.03)	0.89 (0.72–1.11)	0.87 (0.73–1.05)	*0.85 (0.74–0.97)*	
ELIXA	0.27 (mean)	NA	1.02 (0.89–1.17)	0.98 (0.78–1.22)	1.03 (0.87–1.22)	1.12 (0.79–1.58)	0.96 (0.75–1.23)	0.94 (0.78–1.13)	
SUSTAIN-6	1.00 (104[a])	More in P group	*0.74 (0.58–0.95)*	0.98 (0.65–1.48)	*0.74 (0.51–1.08)*	*0.61 (0.38–0.99)*	1.11 (0.77–1.61)	1.05 (0.74–1.50)	
CANVAS	0.58 (mean)	More in P group	*0.86 (0.75–0.97)*	0.87 (0.72–1.06)	*0.85 (0.69–1.05)*	0.90 (0.71–1.15)	*0.67 (0.52–0.87)*	*0.87 (0.74–1.01)*	Amputation
DECLARE–TIMI	0.42 (mean)	More in P group	0.93 (0.84–1.03)	0.98 (0.82–1.17)	0.89 (0.77–1.01)	1.01 (0.84–1.21)	*0.73 (0.61–0.88)*	0.93 (0.82–1.04)	Ketoacidosis Genital infection
EMPA-REG OUTCOME	0.47 (94[a])	More in P group	*0.86 (0.74–0.99)*	*0.62 (0.49–0.77)*	*0.87 (0.70–1.09)*	1.24 (0.92–1.67)	*0.65 (0.50–0.85)*	*0.68 (0.57–0.82)*	

[a]HbA1c concentrations were significantly higher in the placebo group than in the treatment group, [b]Adverse events that had a significant increase in frequency in the treatment group. [c]In patients without a history of heart failure at baseline, [d]Week at which the data were obtained. [e]Fatal myocardial infarction included. [f]Fatal stroke included. Data are presented as the hazard ratio (95% confidence interval). Bold type represents a significant increase of the event in the treatment group compared with that in the placebo group. Italic type represents a significant reduction. *MI* Myocardial infarction, *NA* Data not available, *P* Placebo

New Ideas in DM management

- Absorption enhancers
  - Was injection, now PO
  - Rebelsys = Oral semaglutide
  - Oral insulin
  - Alternative insulin injection methods ---------
- CGM



Thank You