New Therapies for Type 2 Diabetes

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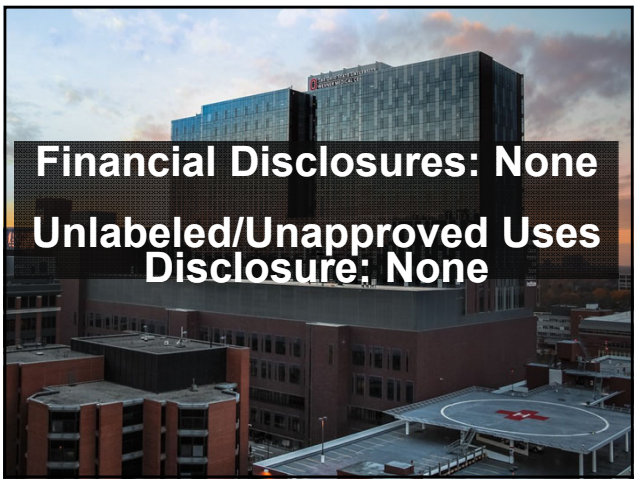
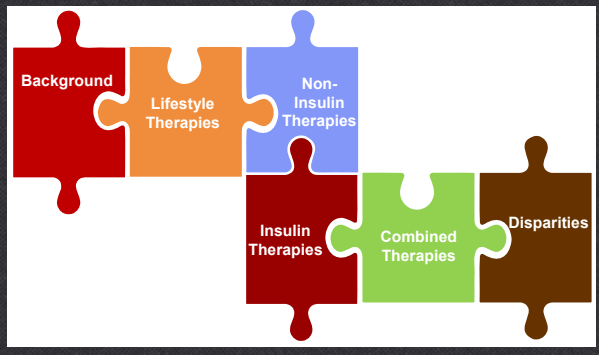


Objectives



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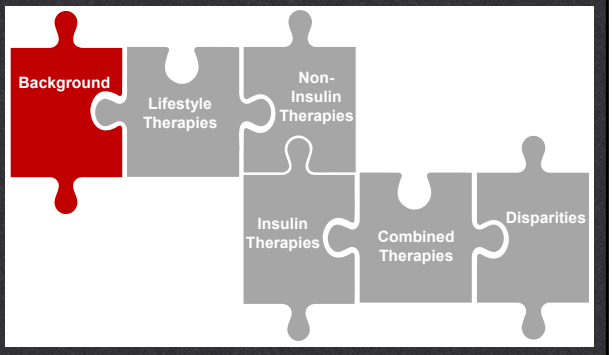

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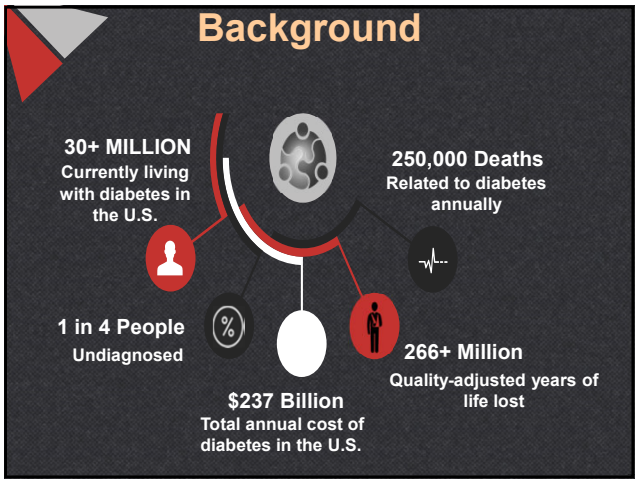
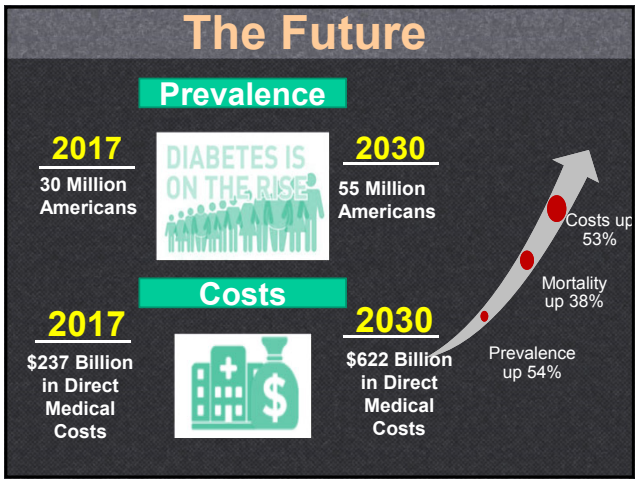
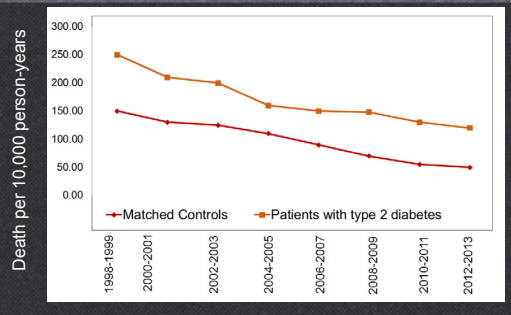


The Future



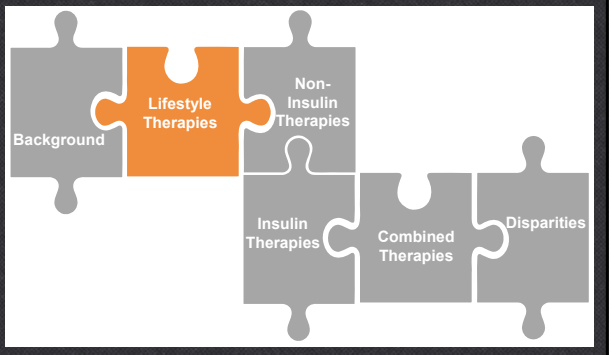
Death from Cardiovascular Disease in Patients with Type 2 Diabetes vs. Matched Controls



N=457,473

Rawshami A, NEJM, 2017

Lifestyle Therapies



Lifestyle Therapy: Weight Loss

Look AHEAD – Intensive lifestyle intervention focused on physical activity, diet and weight loss

- **4.7% weight loss at 8 years**
- **No CVD reduction**

Improvements:

- **HbA1C**
- **Sleep Apnea**
- **Liver Fat**
- **Kidney Disease**
- **Decreased Meds**
- **Lower Costs**
- **Quality of Life**

(Wing, NEJM, 2013)

Lifestyle Therapy: Weight Loss

➢ **Primary Care Led Weight Management**

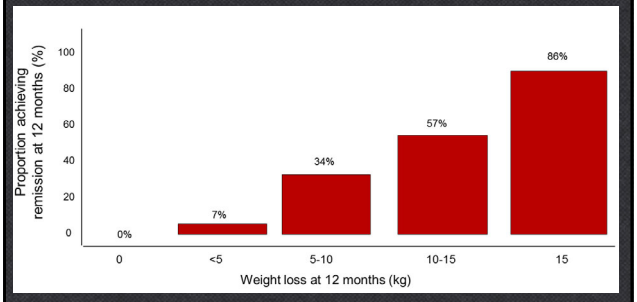
- **T2DM dx in past 6 years, 20–65 years, BMI 27–45 kg/m2, and were not receiving insulin**

➢ **Intervention**

- **Withdrawal of antidiabetic and antihypertensive drugs**
- **total diet replacement (825–853 kcal/day formula diet for 3–5 months)**
- **stepped food reintroduction (2–8 weeks)**
- **structured support for long-term weight loss maintenance**

Lean et al. *Lancet*, 2018

Proportion of Patients Achieving Diabetes Remission over 12-months



Adapted from Lean et al. *Lancet*, 2018

Bariatric Surgery is Superior to Medical Therapy for T2DM

➢ **Dixon et al. (JAMA 2008)**

- **73% of patients undergoing LAGB and 13% in lifestyle group achieved T2DM remission.**

➢ **Schauer et al. (NEJM 2012)**

- **42% after RYGB and 37% after LSG compared to 12% in intensive medical therapy and lifestyle group achieved T2DM remission (A1c<6% without diabetes medications)**

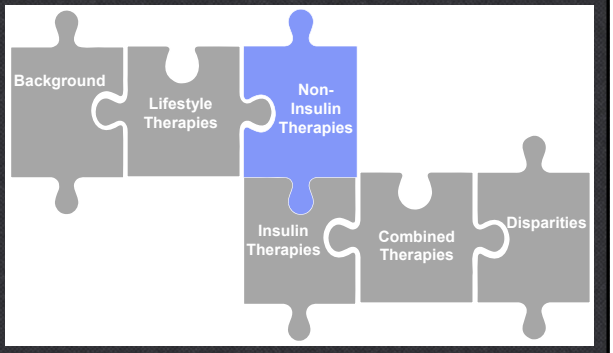
➢ **Mingrone et al. (NEJM 2012)**

- **95% after BPD and 75% after RYGB (with equivalent weight loss) compared to 0% with conventional medical therapy achieved T2DM remission (FPG <100, A1c <6.5% without diabetes medications).**

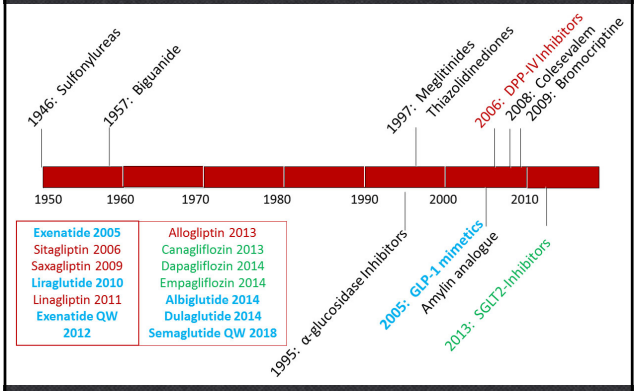
➢ **Fisher et al. (JAMA 2018)**

- **40% lower risk of incident Coronary Artery Disease**

Non-Insulin Therapies



Timeline of Currently Available Non-Insulin Medications



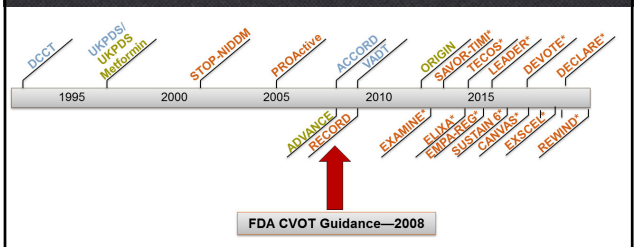
Tahrani et al. Lancet. 2011;378(9786):182-97

Cardiovascular Outcomes Trials

2008 FDA guidance mandating assessment of CV safety of all antihyperglycemic agents in RCTs

- **Designed as noninferiority studies to demonstrate study drug was not associated with more MACE than placebo**
- **Some study designs tested for superiority if noninferiority criteria were met**
- **Primary endpoint: composite of cardiovascular death, nonfatal MI, and nonfatal stroke**

Timeline of Major Diabetes Outcomes Trials



Blue = Intensive vs standard control using same set of glucose-lowering agent(s)
Purple = Intensive control with a specific agent vs standard care
Red = Placebo- or active-controlled study
* = FDA-mandated cardiovascular safety trial

Dipeptidyl peptidase IV (DPP-IV) Inhibitors

- Blocks the breakdown of GLP-1
- increase incretin levels (GLP-1 and GIP), increases insulin
- inhibit glucagon release, which in turn increases insulin secretion

- CVOT Trials Neutral

Glucagon-Like Peptide–1 (GLP-1) Agonists

- an incretin secreted normally from intestinal cells

- decreases blood sugar levels in a glucose-dependent manner by enhancing the secretion of insulin

- inhibits glucagon secretion at glucose levels above fasting levels

- in the stomach it inhibits gastric emptying, acid secretion and motility collectively decreasing appetite

Elixa

Evaluation of Lixisenatide in Acute Coronary Syndrome

ELIXA Trial

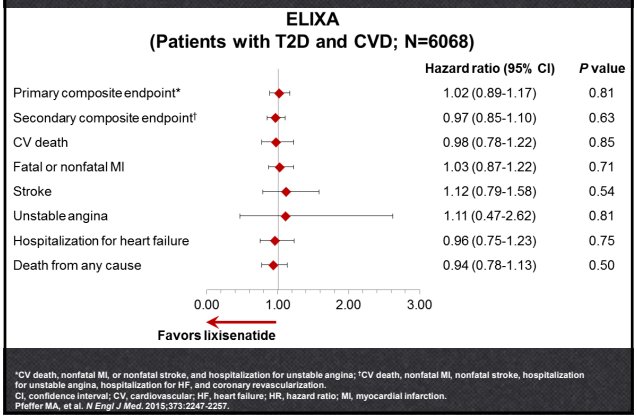
- Patients with T2D with an MI or hospitalized for unstable angina within 180 days
- 6068 patients randomized to Lixisenatide or Placebo
- Baseline A1c 7.7%, BMI 30.1, Duration of Diabetes 9.2 years
- Tested non-inferiority and superiority to placebo
- Composite primary endpoint: CV death, non fatal MI, non fatal stroke, or hospitalization for unstable angina
- Followed for a median of 25 months

Pfeffer et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Symptoms. NEJM. 2015. 373, 2247-2257.

ELIXA Trial

- **Statistically significant reductions at study end:**
  - Hemoglobin A1C (0.3%),
  - Systolic blood pressure (0.8 mmHg), and
  - Weight (0.7 kg)
- **Slightly increased heart rate (0.4 bpm)**

ELIXA Trial



*CV death, nonfatal MI, or nonfatal stroke, and hospitalization for unstable angina; †CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, hospitalization for HF, and coronary revascularization.
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.
Pfeffer MA, et al. *N Engl J Med.* 2015;373:2247-2257.

ELIXA Trial

Confirmed non-inferiority of lixisenatide to placebo in respect to primary outcome, but no superiority on any CV outcome

LEADER
LIRAGLUTIDE EFFECT AND ACTION IN DIABETES: EVALUATION OF CARDIOVASCULAR OUTCOME RESULTS

LEADER Trial

- Patients with T2D and high CV risk:
  - Age >50 yo with at least 1 of the following: CAD, cerebrovascular disease, PVD, Stage III or IV CKD, Class II or III heart failure
  - Age >60 you with at least 1 of the following: microalbuminuria, hypertension and LVH, systolic or diastolic dysfunction, or ABI <0.9
- 9340 patients randomized to liraglutide 1.8 mg daily (or highest tolerated dose) or placebo

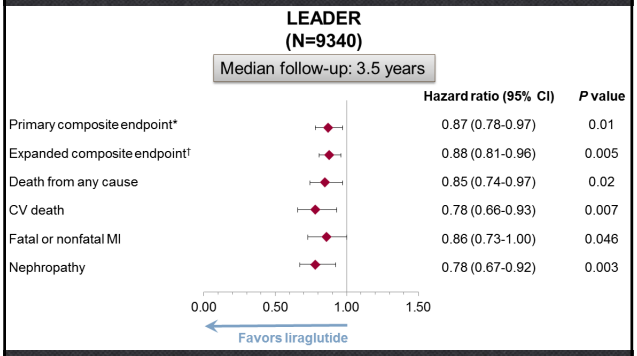
Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. NEJM. 2016.

LEADER Trial

- Baseline A1c 8.7%, BMI 32.5, Duration of Diabetes 12.8 years
- Primary composite endpoint: First occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke
- Median follow up 3.8 years

Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. NEJM. 2016.

LEADER Trial



*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.

Marso SP, et al. *N Engl J Med.* 2016:375:311-322.

LEADER Trial

- Liraglutide Had Greater Benefit In:
  - < 60 yo
  - Males
  - Obesity
  - Absence of Congestive Heart Failure
  - GFR < 60
  - A1c > 8.3%
  - Presence of known Cardiovascular Disease
- NNT to prevent one death: 66

SUSTAIN 6

TRIAL TO EVALUATE CARDIOVASCULAR AND OTHER LONG-TERM OUTCOMES WITH SEMAGLUTIDE IN SUBJECTS WITH TYPE 2 DIABETES

SUSTAIN 6

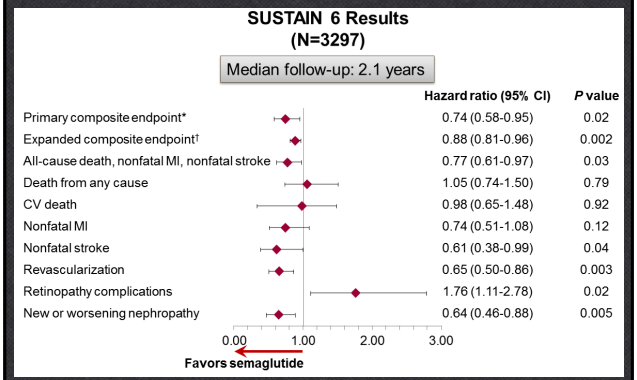
- N=3297 patients with T2D with CVD, CHF, CKD, or age ≥60 with ≥1 CV risk factor
- 2 year duration
- Semaglutide 0.5 mg or 1.0 mg vs. Placebo
- Baseline A1c 8.7%, Duration of Diabetes 14.3 years
- 83% had established CVD and/or CKD
- Primary Outcome: 3 point MACE

Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834-1844. Epub 2016 Sep 15.

SUSTAIN 6

- **Statistically significant reductions in:**
  - HbA1C (0.7 and 1.0%, respectively),
  - Systolic blood pressure (1.3 and 2.6 mmHg, respectively)
  - Weight (2.9 and 4.3 kg)
- **Increase in heart rate (2.0 and 2.5 bpm, respectively)**

SUSTAIN 6



*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI, nonfatal stroke, coronary or peripheral revascularization, and hospitalization for unstable angina or HF.
CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction. Marso SP, et al. *N Engl J Med*. 2016:375:1834-1844.

SUSTAIN 6

- Achieved statistical superiority for the 3-point MACE
- Significant decrease in nonfatal stroke and a non-significant decrease in nonfatal MI (P = 0.12)
- No trend for reduction in CV death or all-cause mortality
- Significant increase in complications from retinopathy

EXSCEL
(EXENATIDE STUDY OF CARDIOVASCULAR EVENT LOWERING)

EXSCEL

Study Design

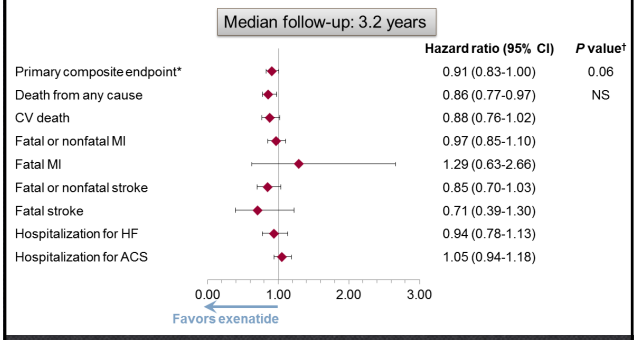
- N=14,752 patients with T2D with or without CVD
  - By design, ≥70% had CVD
  - Baseline A1c 8.0%, BMI 31.8, Duration of Diabetes 12.0 years
  - Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke

Key Results

- Median follow-up: 3.2 years
- Difference from placebo at trial end
  - A1C: −0.53%
  - Weight: −1.3 kg (P<0.001)
  - SBP: −1.6 mm Hg
- CV outcomes
  - Primary endpoint: HR 0.91 (95% CI 0.83 to 1.00); P<0.001 for noninferiority, P=0.06 for superiority

Holman RR, et al. *N Engl J Med.* 2017 Sept 14 [Epub before print].

EXSCEL



*CV death, nonfatal MI, or nonfatal stroke. †For superiority.
NS, not statistically significant based on hierarchical testing plan.
Holman RR, et al. *N Engl J Med.* 2017 Sept 14 [Epub before print].

EXSCEL

- Confirmed the noninferiority, but not superiority, of once-weekly treatment with 2 mg of the long-acting extended-release exenatide (HR 0.91 [95% CI 0.83–1.00], P = 0.06).
- The rates of CV death, fatal or nonfatal MI, fatal or nonfatal stroke, HF hospitalization, and ACS hospitalization did not differ significantly between the two treatment groups.
- Treatment adherence with weekly exenatide was low, with 43% drug discontinuation.
- Despite this limited drug exposure and a heterogeneous population of whom 27% had no history of CVD, the 3-point MACE reduction of 9% came close to reaching statistical significance, with HRs of almost all measured parameters in the direction of benefit.

HARMONY

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial
Lancet 2018

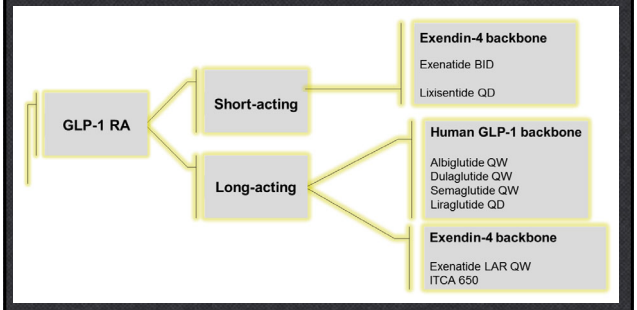
CVD 3-Point MACE Significant (Hazard ratio 0.78, 95% CI 0.68–0.90)

*Currently not on the market

Summarizing GLP-1 Trials

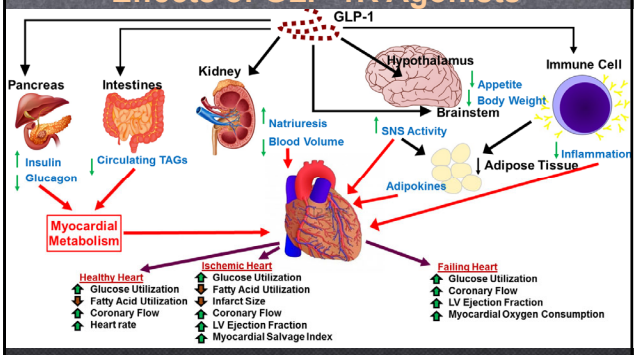
- ↓ HbA1c, Weight and Blood Pressure
- ↓ CV Risk (Liraglutide, Semaglutide & Albiglutide), Trend with Exenatide ER in Participants with Established CVD
- ■ Side Effects: Mainly Gastrointestinal, Small Increase Risk of Pancreatitis
- ■ REWIND, American Diabetes Association, 2019 (Primary Prevention?)

GLP-1 RAs Differ in Chemical Structure

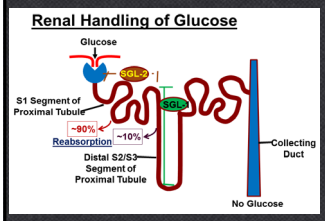


Classification of glucagon-like peptide-1 receptor agonists Data from: Meier JJ. Nat Rev Endocrinol 2012;8:728-42; Madsbad S, et al. Diabetes Obes Metab 2011;13:394-407

Potential Indirect Cardiovascular Effects of GLP-1R Agonists

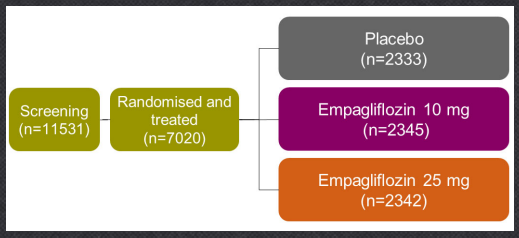


Sodium/Glucose Cotransporter 2 (SGLT2 Inhibitors)



- SGLT2 is responsible for 90% of the glucose reabsorption in the kidney
- Inhibition causes 50-80 grams of glucose to be eliminated in the urine per day with some water loss due to osmotic diuresis

EMPA-REG Trial design



- Primary outcome: 3-point MACE: Time to first occurrence of CV death, non-fatal MI or non-fatal stroke
- Key secondary outcome: 4-point MACE: Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina

EMPA-REG Trial

Key inclusion criteria

- Adults with type 2 diabetes
- BMI ≤45 kg/m^2
- HbA1c 7–10%
- ***Established cardiovascular disease***
  Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease

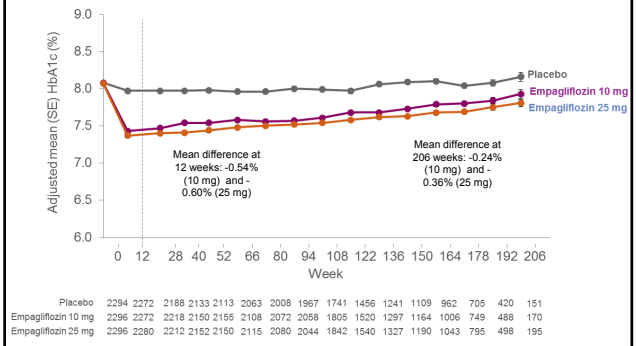
No glucose-lowering therapy for ≥12 weeks prior to randomization or no change in dose for ≥12 weeks prior to randomization or, in the case of insulin, unchanged by >10% compared to the dose at randomization

Key exclusion criteria

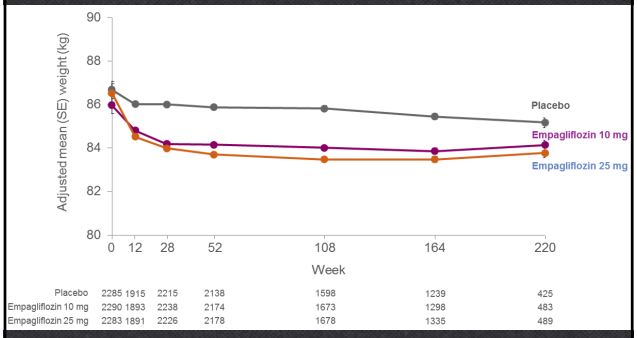
- eGFR <30 mL/min/1.73m^2

Zinman, NEJM, 2015

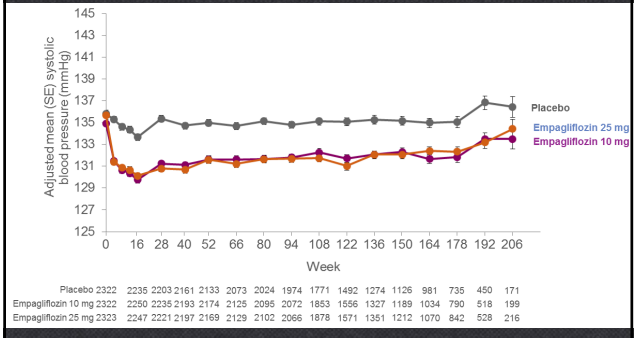
Change in HbA1c greater with Empagliflozin



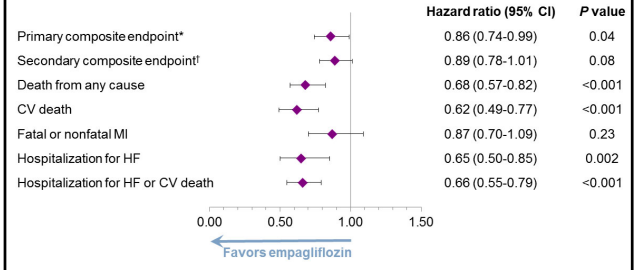
Change in Weight greater with Empagliflozin



Systolic blood pressure lower with Empagliflozin



EMPA-REG Trial



*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

EMPA-REG OUTCOME: Summary

- Empagliflozin reduced risk for 3-point MACE by 14% (superior to control)

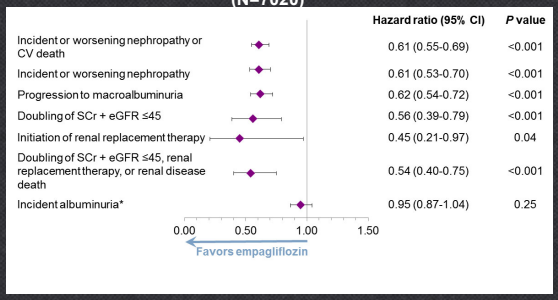
Most benefits were seen only in Age >65 years old (65 was average age), Males, Caucasians and Asians, A1c <8.5%, BMI <30, GFR 60-90

- reduced hospitalization for heart failure by 35%
- reduced CV death by 38%: Biggest contributor was death due to heart failure
- did not reduce the risk of MI or stroke (trend for ↑ risk)
- was associated with an increase in genital infections but was otherwise well tolerated, 97% of subjects completed the trial.

FDA: JARDIANCE is indicated 1) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, 2) to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.

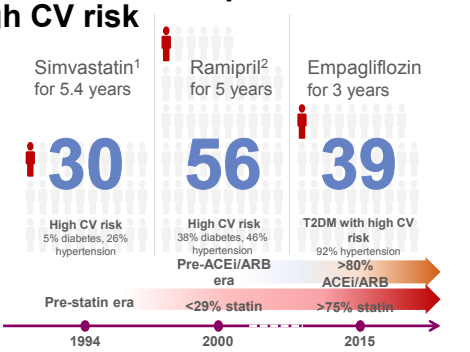
Renal Outcomes with Empagliflozin Over 3.2 Yrs

EMPA-REG RENAL (N=7020)



*In patients with normal albuminuria at baseline.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; HR, hazard ratio; SCr, serum creatinine.
Wanner C, et al. *N Engl J Med*. 2016 Jun 14.

NNT to prevent one death across landmark trials in patients with high CV risk



1. 4S investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm;2. HOPE investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

CANVAS PROGRAM

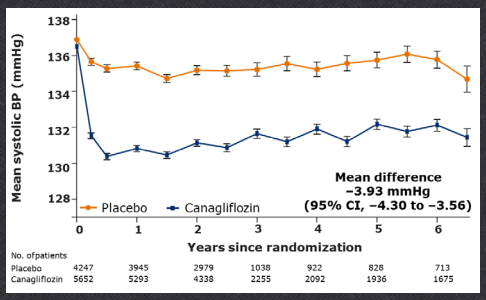
- Patients with type 2 diabetes
  - HbA1c ≥7.0% to ≤10.5%
  - eGFR ≥30 mL/min/1.73 m²
  - Age ≥30 years and history of prior CV event
    - *OR*
    - Age ≥50 years with ≥2 CV risk factors*

*Diabetes duration ≥10 years, SBP >140 mmHg on ≥1 medication, current smoker, micro- or macroalbuminuria, or HDL cholesterol <1 mmol/L.

CANVAS PROGRAM

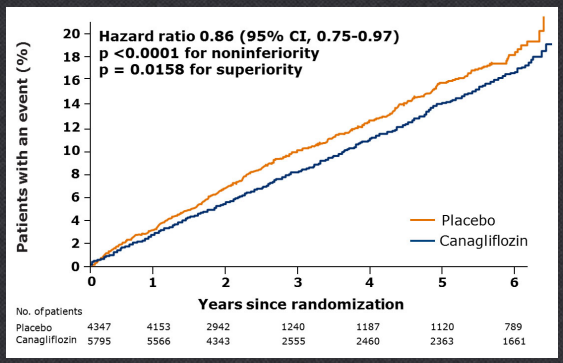
- **Statistically significant reductions at study end:**
  - Hemoglobin A1C (0.58%),
  - Weight (1.6 kg)

Effects on Systolic BP

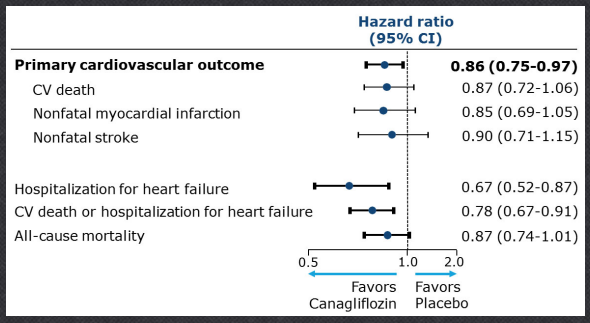


Primary MACE Outcome

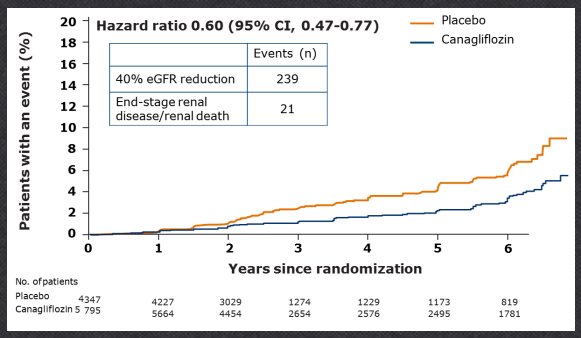
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



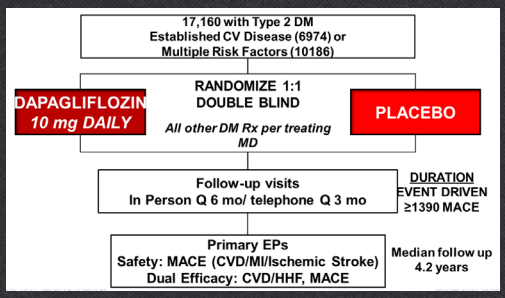
Summary



Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death



DECLARE-TIMI 58



Wiviott SD, Raz I...Sabatine MA, *AHJ* 2018

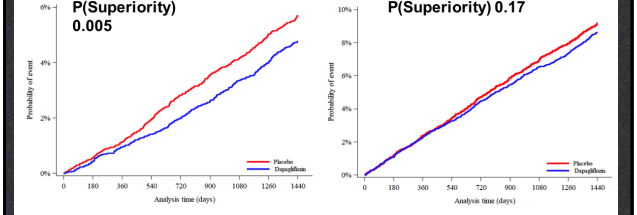
Primary Endpoints

CVD/HHF

4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005

MACE

8.8% vs 9.4%
HR 0.93 (0.84-1.03)
P(Noninferiority) <0.001
P(Superiority) 0.17



Secondary Endpoints

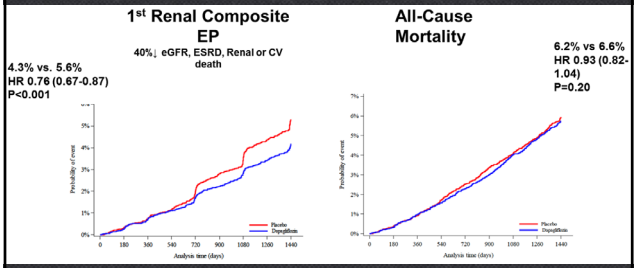
1st Renal Composite EP

40%↓ eGFR, ESRD, Renal or CV death

4.3% vs. 5.6%
HR 0.76 (0.67-0.87)
P<0.001

All-Cause Mortality

6.2% vs 6.6%
HR 0.93 (0.82-1.04)
P=0.20



Summarizing SGLT2-Inhibitor Trials

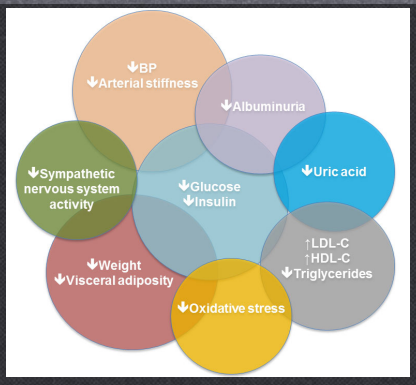
- SGLT2 Inhibitors: canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance), ertugliflozin (Steglatro)
- Meta-analyses (Zelnicker, Lancet, 2018): Moderate benefits on CVD in patients with established coronary artery disease.
- Robust effects on reducing hospitalizations for heart failure and progression of renal disease.

Less effective and dose reduction in moderate CKD (GFR 45-60) and contraindicated with severe CKD (GFR <45); Has not been studied with hepatic impairment

- Side effects are UTI's, acute kidney injury, yeast infections, increased thirst, dehydration, polyuria
- nterim clinical trial results find increased risk of leg and foot amputations. CANVAS Study of canagliflozin - mostly toe amputations
- Also possible increased risk of bone fractures and reduced BMD

New Inhibitors: ertuglifoxin (Steglatro) FDA approved for type 2 sotagliflozin (SGLT1 *and* SGLT2 inhibition), Type 1 indication.

SGLT2 inhibitors modulate several CV risk factors, but mechanism of cardioprotection unknown



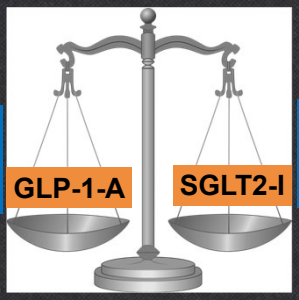
Adapted from Inzucchi SE,Zinman, B, Wanner, C et al. Diab Vasc Dis Res 2015;12:90-100

Clinical Practice

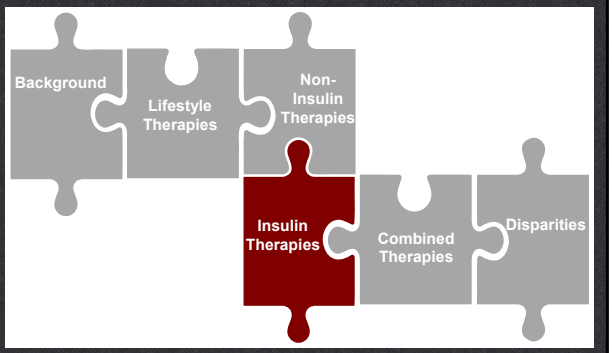
Clinical Practice

Obese
CKD
Atherosclerosis
? Class effect

Clinical Practice

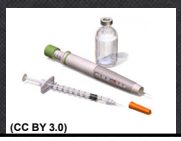


Insulin Therapies

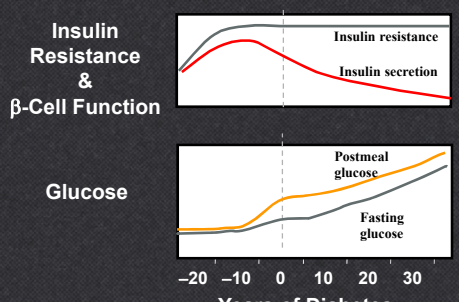


History of Insulin

- 1910 - Sir Edward Albert Sharpey-Schafer's study of the pancreas leads him to the discovery of insulin.
- 1921 - Frederick G. Banting and student Charles Best, advised by John MacCleod at Toronto University, extract insulin from animal pancreases. James Collip purified the extract
- 1922 - Leonard Thompson, 1st successful injection and insulin commercially available in England
- 1923 - Eli Lilly and Company begins commercial production of insulin.



Natural History of T2DM



- Loss of β-Cell function begins before diagnosis and progresses
- Insulin resistance doesn't change over time (unless weight loss)

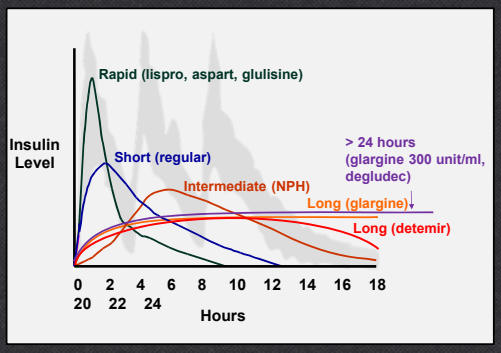
Adapted from International Diabetes Center (IDC). Minneapolis, Minnesota.

American Diabetes Association

- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic and/or have **A1C >10% and/or glucose levels > 300 mg/dL**
- If **noninsulin monotherapy at maximum tolerated dose** does not achieve or maintain the **A1C target < 7% after 3 months**, add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin
-
- For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed

ADA Standards of Medical Care, Diabetes Care, 2018

Pharmacokinetics of Insulin Products



Adapted from Hirsch I. *N Engl J Med.* 2005;352:174-183.

Type Company	Concentration Duration	Notes	Start Dose naïve	Convert dose
Glargine Toujeo Sanofi 2015	U300 36 hour duration 1.5 ml per pen	Longer lasting basal compared to Lantus Same units less volume/ 1dy dose adjust 3u q3dy -steady state 5dy	T1 50%TDD .4 u/k/d T2 10 U – 0.2 u/k/d Max dose 80 units Once day steadier profile	Same as basal dose (may 10-15% more) 80% NPH dose If bid basal combine dose give once day
Glargine Basaglar Lilly 2016	U100 24 hour duration 3 ml per pen	Newest on market Bioidentical glargine inexpensive alternative	T1 50% TDD T2 10 U – 0.2 u/k/d Max dose 80 units per injection	Same as basal dose 80% NPH dose 80% of Toujeo
Tresiba Degludec Novo 2016	U100 U-200 42 hour duration 3ml pen	-use for flexibility in admin time -Less hypo -adjust q 3-4 days -can give more	T1 50%TDD .4 u/k/d T2 10 U – 0.2 u/k/d Max dose 80 U100 Max dose 160 U200 Once daily	Same as basal dose Decrease 20% if ESRD adjust q 3-4 days

Complications of Hypoglycemia

- **Seizures**
- **Ventricular Arrhythmias**
- **Hypokalemia**
- **Cardiovascular Events & Mortality**
  - **ADVANCE Trial: 2.9-fold increased risk of a CV event and 2.7-fold increased risk of CV Death**
- **Decreased Cognition and Dementia**
  - **2-Fold Increased Risk of Dementia**

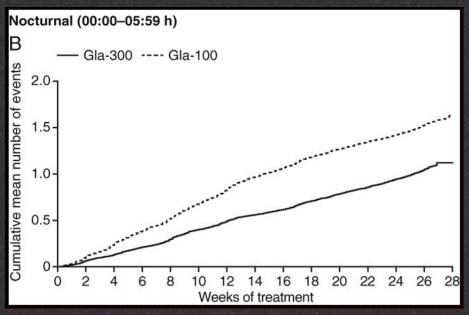
Joseph et al. Long-term insulin glargine therapy in type 2 diabetes mellitus: a focus on cardiovascular outcomes. Vascular Health & Risk Management, 2015; Yaffe, Association Between Hypoglycemia and Dementia in a Biracial Cohort of Older Adults With Diabetes Mellitus, JAMA IM, 2013.

Glargine U300 (Toujeo) vs. Glargine U100 (Lantus, Basaglar)

EDITION Studies	Months	DM Type	Baseline Rx	N	HbA1c	Hypoglycemia (overall)	Hypoglycemia (nocturnal)
1	12	2	Basal bolus	807	~	0.94 (0.89-0.99)	0.84 (0.75-0.94)
2	12	2	Basal	811	~	0.96 (0.89-1.02)	0.84 (0.71-0.99)
3	6	2	Naïve	873	~	0.88 (0.77-1.01)	0.76 (0.59-0.99)
4	6	1	Basal bolus	559	~	1.00 (0.95-1.04)	0.98 (0.88-1.09)

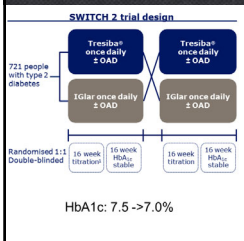
Ritzel et al. Diabetes Obes Metab. 2015 Sep; 17(9): 859–867

Nocturnal Hypoglycemia EDITION Trials Combined: U300 vs U100 glargine



Ritzel et al. Diabetes Obes Metab. 2015 Sep; 17(9): 859–867

Severe Hypoglycemia SWITCH-2: Degludec vs U100 glargine



Results

Event rate per 100 patient years exposed in maintenance period	Tresiba®	IGlar	Tresiba® reduction vs IGlar
Severe or BG confirmed symptomatic hypoglycaemia	186	265	30%*
Severe or BG confirmed symptomatic nocturnal hypoglycaemia	55	94	42%*
Severe hypoglycaemia	5	9	46%
Severe hypoglycaemia (Full treatment period)	4	9	51%*

*** severe - an episode requiring third-party assistance

Wysham, Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial: JAMA, 2017

Cardiovascular Safety of Insulin Degludec: DEVOTE Study

7637 people with T2DM at high CV risk were randomized to standard care plus

- Insulin degludec or
- Insulin glargine U-100
- Target: FPG 71 to 90 mg/dL

Follow-up ~2 years

At baseline

- Age (mean): 65.0 y
- HbA1c (mean): 8.4%
- Duration of T2DM (mean): 16.4 y
- 85.2% established CVD or moderate CKD
- 83.9% receiving insulin
  - 54.8% basal-bolus

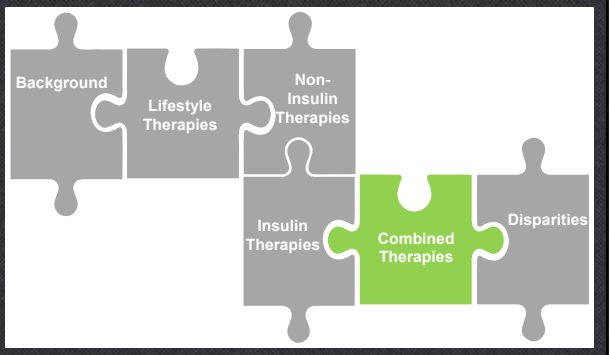
Marso SP, et al. *N Engl J Med*. 2017;doi:10.1056/NEJMoa1615692.

DEVOTE Study

Outcome	Hazard Ratio	95% CI
Primary composite[1]	0.91	0.78-1.06
Expanded composite[2]	0.92	0.80-1.05
All-cause death	0.91	0.76-1.11
Non-CV death	0.84	0.60-1.16
CV death	0.96	0.76-1.21
Nonfatal MI	0.85	0.68-1.06
Nonfatal stroke	0.90	0.65-1.23
UA → hospitalization	0.95	0.68-1.31
Severe hypoglycemia	0.60	0.48-0.76
Nocturnal severe hypoglycemia	0.47	0.31-0.73

→ Degludec non-Inferior to glargine for major CV events

Combined Therapies



Insulin Degludec + Liraglutide Combination

Inclusion criteria

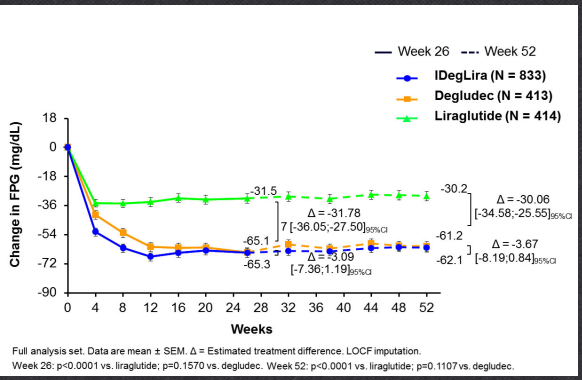
- T2DM
- Insulin-naïve, treated with metformin ± pioglitazone
- A1C 7.0%-10.0%
- BMI ≤40 kg/m^2
- Age ≥18 years**

Titration for IDeg + LIRA and IDeg

Mean Fasting PG		Dose Change
mg/dL	mmol/L	Dose steps or U
<72	<4.0	-2
≥72-≤90	≥4.0-≤5.0	0
>90	>5.0	+2

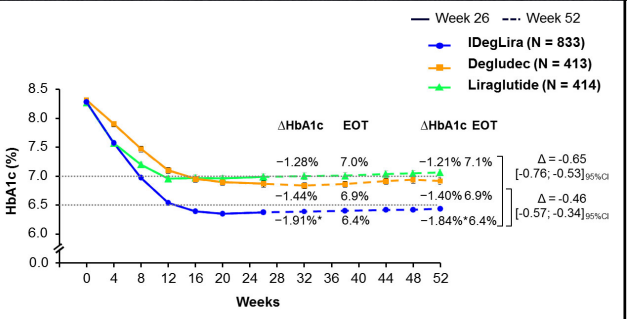
Gough SC, et al. *Lancet Diabetes Endocrinol*. 2014.

Fasting Glucose with IDegLira



Full analysis set. Data are mean ± SEM. Δ = Estimated treatment difference. LOCF imputation.
Week 26: p<0.0001 vs. liraglutide; p=0.1570 vs. degludec. Week 52: p<0.0001 vs. liraglutide; p=0.1107 vs. degludec.

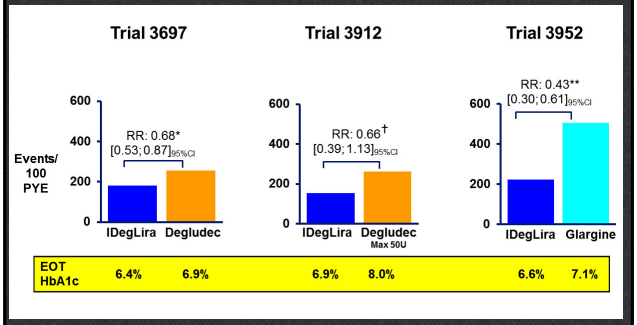
Significant Reduction in HbA1c



Full analysis set. Data are mean ± SEM. Δ= Observed change from baseline. LOCF imputation. EOT = End of treatment.

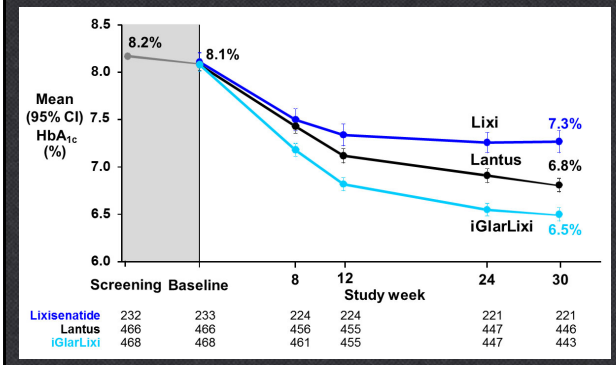
*p<0.0001 vs. degludec and vs. liraglutide.

Lower Rate of Confirmed Hypoglycemia With IDegLira vs. Basal Insulin

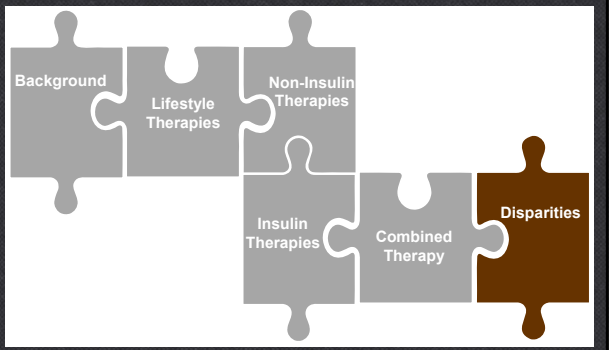


Safety analysis set. RR, Rate Ratio. PYE, patient-years of exposure. HbA1c and statistical analysis based on full analysis set. EOT, End of Treatment. 26 week data for 3697. *p<0.0023, †p-value is not significant, **p<0.0001.

iGlarLixi Demonstrated Superior HbA_{1c} Reduction



Disparities



Significant Causes of Death with the Highest Black to White Disparities

Cause of Death	Total # of Deaths	Death Rates per 100,000		Black-White Ratio
		Black	White	
HIV	6,000	8.3	1.1	7.5
Homicide	16,000	17.2	3.0	5.7
HTN & HTN Renal Disease	30,000	15.6	7.4	2.1
Kidney Disease	6,000	24.6	12.1	2.0
Diabetes	**76,000**	**37.3**	**19.3**	**1.9**
Stroke	133,000	49.7	35.2	1.4
Heart Disease	614,000	206.3	165.9	1.2

Fuchs, JAMA, 2016

SGLT-2: Ethnic Variation in MACE Effect Size

Racial/ Ethnic	EMPA-REG (Jardiance)			CANVAS (Invokana)		
	n	HR	CI	n	HR	CI
White	5081	0.88	0.74–1.04	7944	0.84	0.73–0.96
Asian	1517	0.68	0.48–0.95	1284	1.08	0.72–1.64
Black	**357**	**1.48**	**0.80–2.02**	**336**	**0.45**	**0.19–1.03**

**EMPA-REG & CANVAS – CV Death, nonfatal MI, or nonfatal stroke

Zinman, NEJM, 2015; Neal, NEJM, 2017

SGLT-2: Ethnic Variation in MACE Effect Size

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**EMPA-REG & CANVAS – CV Death, nonfatal MI, or nonfatal stroke

Zinman, NEJM, 2015; Neal, NEJM, 2017

GLP-1: Ethnic Variation in MACE Effect Size

Racial/ Ethnic	LEADER (Victoza)			EXSCEL (Bydureon)			SUSTAIN-6 (Ozempic)		
	n	HR	CI	n	HR	CI	n	HR	CI
White	7238	0.90	0.80–1.02	11,175	0.95	0.85-1.05	2736	0.76	0.58-1.00
Asian	936	0.70	0.46–1.04	1,452	0.81	0.57-1.14	273	0.58	0.25-1.34
Black	777	0.87	0.59-1.27	878	0.67	0.45-0.99	221	0.72	0.23-2.28

**LEADER,EXSCEL, SUSTAIN-6 MACE– CV Death, nonfatal MI, or nonfatal stroke; ELIXA ns

Marso, NEJM, 2016; Holman, NEJM, 2017
Marso, NEJM, 2016;Pfeffer, NEJM, 2015

Thank You!

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