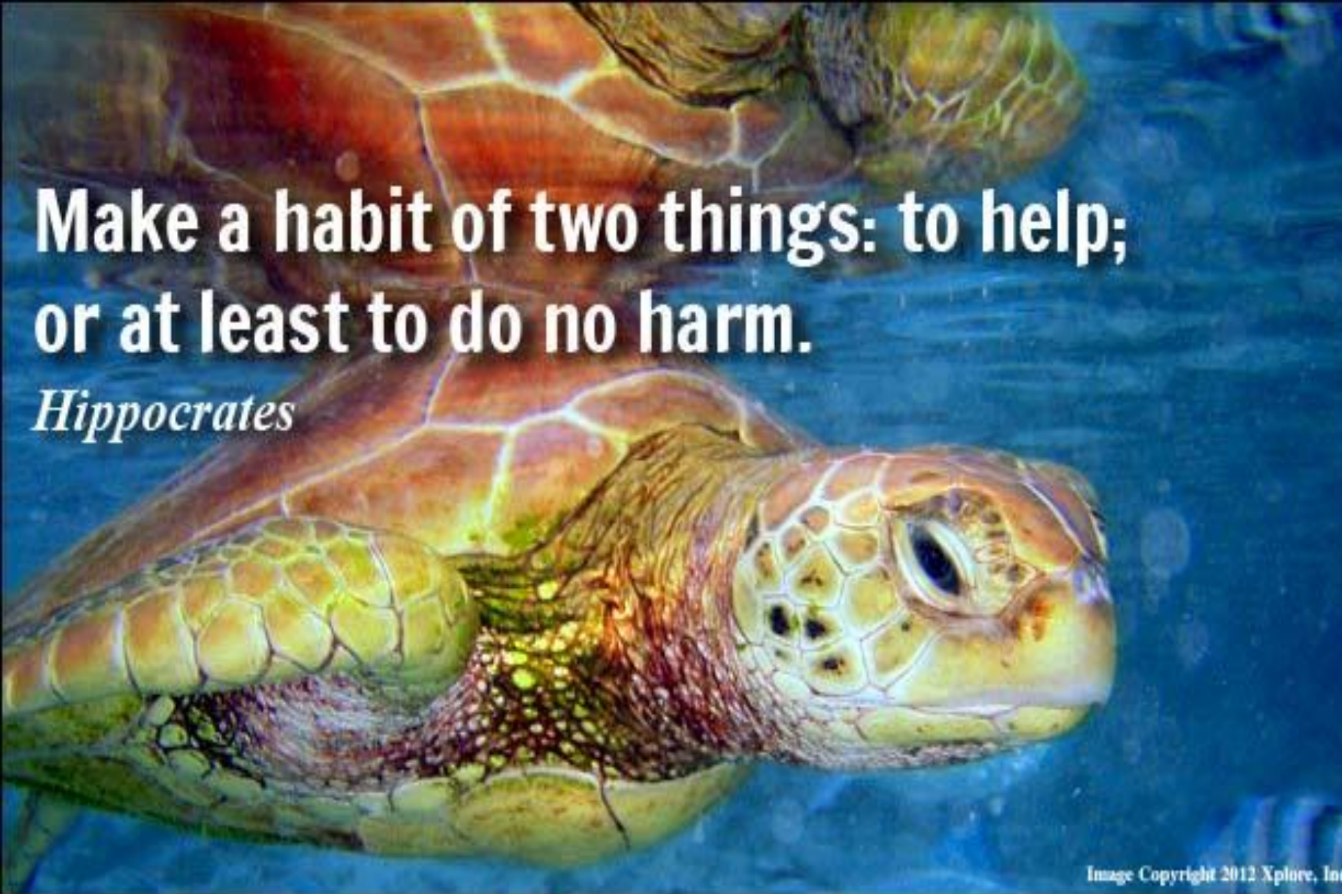

HIPPOCRATES

What's new in diabetes?

A medicine that does the wrong thing for the right reason

EMPA-REG OUTCOME

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7% vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no

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This article was published on September 17, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1504720

Zinman B, et al. *N Engl J Med*. 2015 Sep 17. [Epub ahead of print]

Baseline Characteristics of Population in EMPA-REG OUTCOME

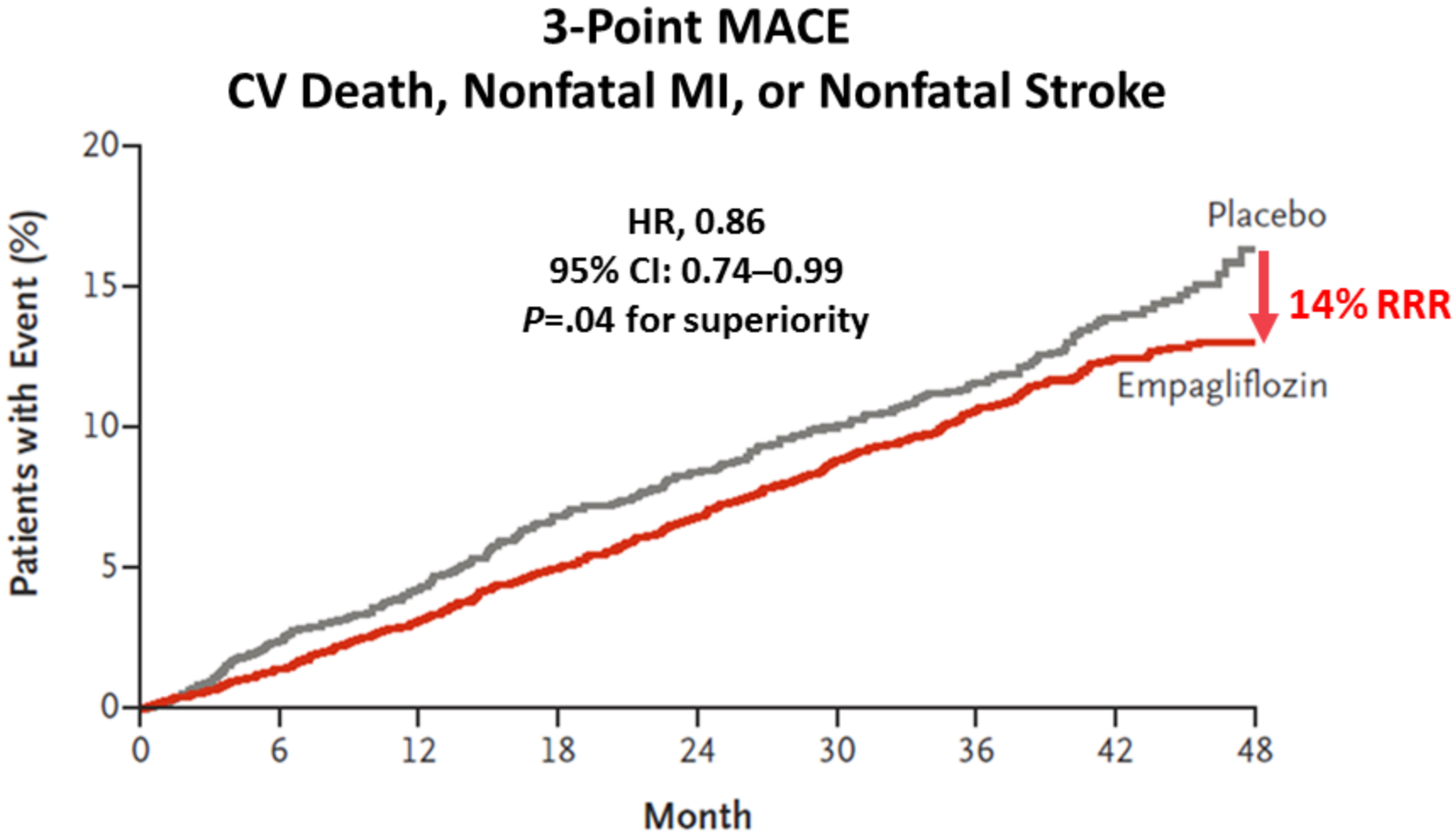
- Enrolled patients with established CVD (MI, CHD, CVD, PVD)
- All participants entering the trial had prevalent atherosclerotic vascular disease

	Empagliflozin (n = 7020)
Age, y	63
> 10 y since diagnosis of T2D, %	57
BMI, kg/m^2	30.6
HbA_{1c}, %	8.1
Prior CVD, %	99

Product label updated in December 2016 to indicate CV death reduction for empagliflozin in patients with T2D and established CVD[b]

a. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.
b. Jardiance (empagliflozin) PI. 2017.

EMPA-REG OUTCOME: Effect of Empagliflozin vs Placebo on the Primary Composite Outcome



From New England Journal of Medicine, Zinman et al, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes, 373(22):2117-28, Copyright© (2015) MMS. Reprinted with permission from Massachusetts Medical Society

EMPA-REG OUTCOME: Potential Mechanism

Not related to

- Glycemic control
- Blood pressure reductions
- Weight loss

Possibly related to

- Volume depletion
- Diuretic effect
- Antiarrhythmic effect

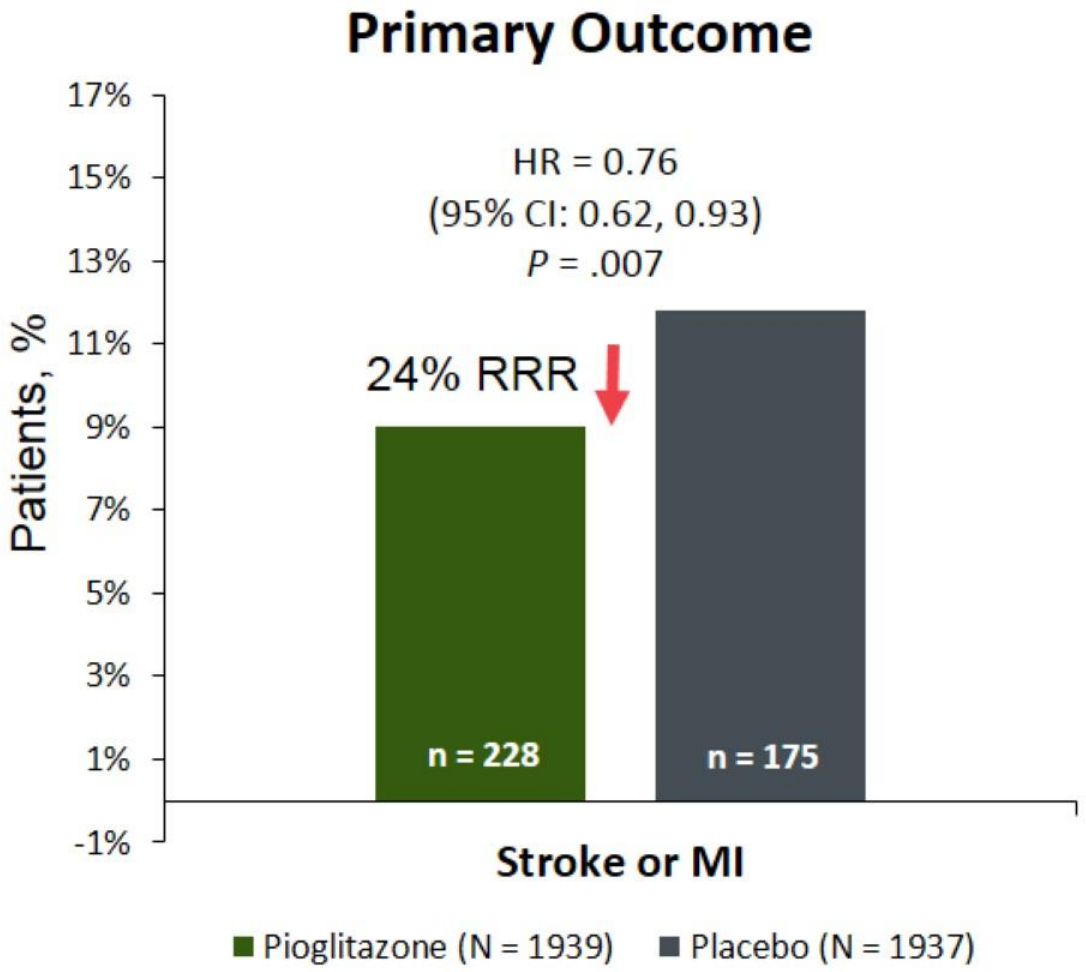
2-12-1206 FDA

The U.S. Food and Drug Administration approved a new indication for Empagliflozin to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease.

IRIS: Pioglitazone in Patients With Insulin Resistance

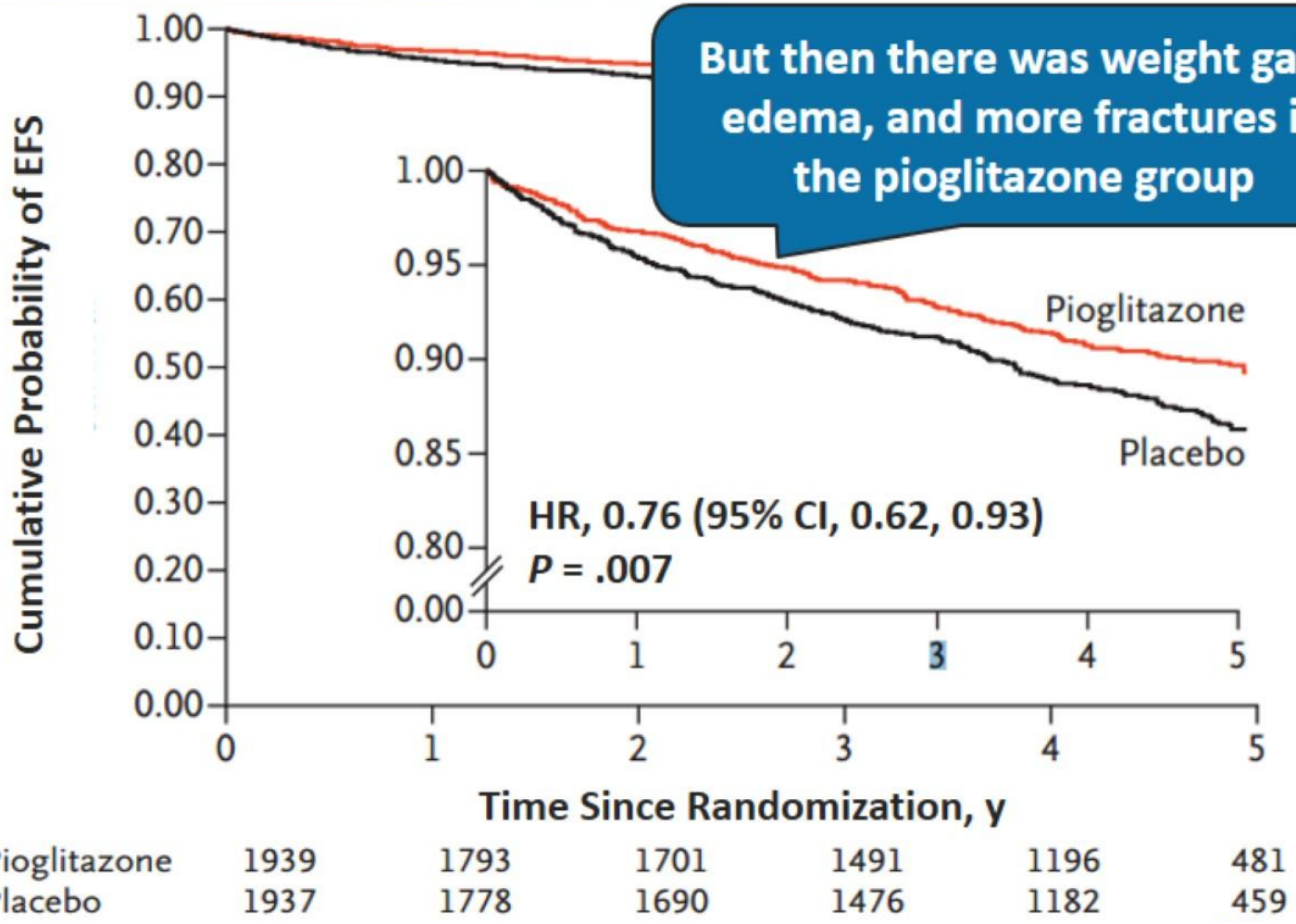
Inclusion Criteria

Ischemic stroke or TIA within 6 months
Age ≥ 40 years
Insulin resistance
No diabetes
No HF
No bladder cancer



Kernan WN, et al. *N Engl J Med*. 2016;374:1321-1331.

IRIS Trial: *Post-Stroke EFS of Pio in Patients With Insulin Resistance*



Kernan WN, et al. *N Engl J Med*. 2016;374:1321-1331.

Pioglitazone Use Not Linked to Bladder Cancer at 10 Years

The new 10-year findings, from three large database analyses,were published July 21 in the *Journal of the American Medical Association (JAMA)*

Pioglitazone is currently used by up to a quarter of diabetes patients in the United States.

In a large, 10-year study, we found no statistically significant association between the use of pioglitazone and the increased risk of bladder cancer, which should be reassuring to clinicians and patients,“

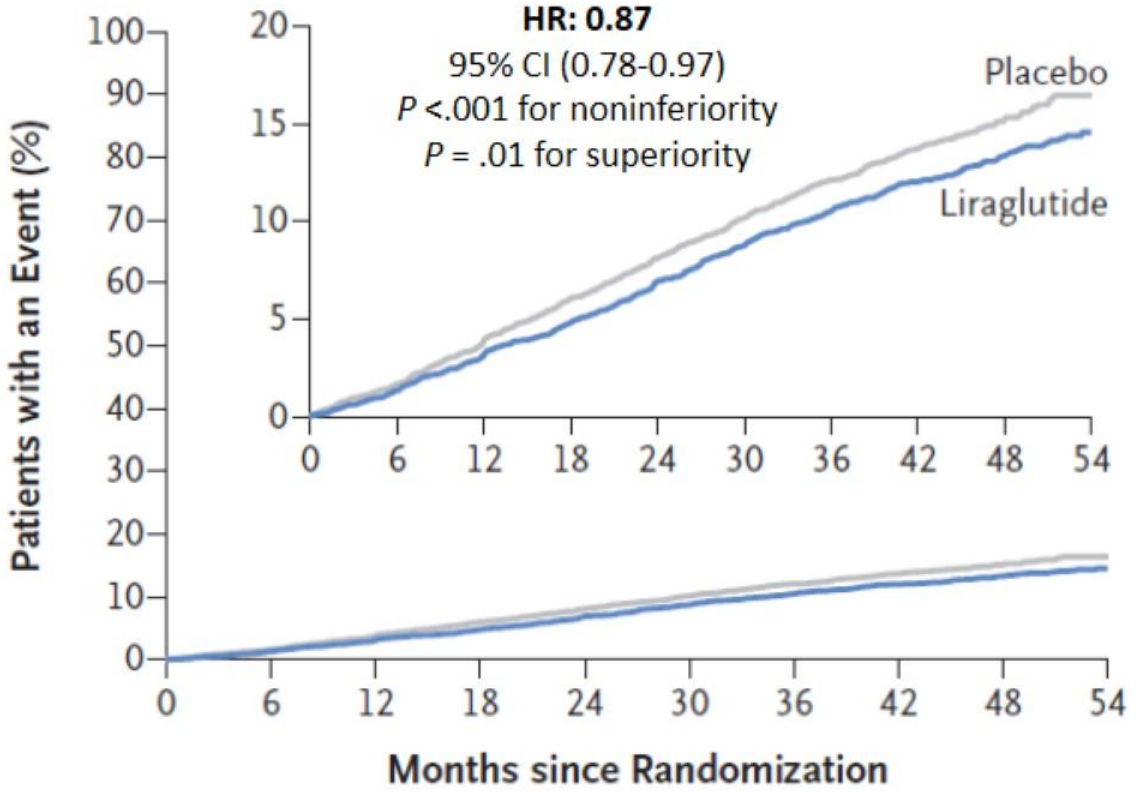
Assiamira Ferrara, MD, PhD, July 21, 2015

Pioglitazone.

.

At the moment, the most insulin-resistant patients—identifiable by an increased waist circumference, low HDL cholesterol level, and fatty liver—may be the best candidates for treatment with pioglitazone.

LEADER: Primary Outcome*



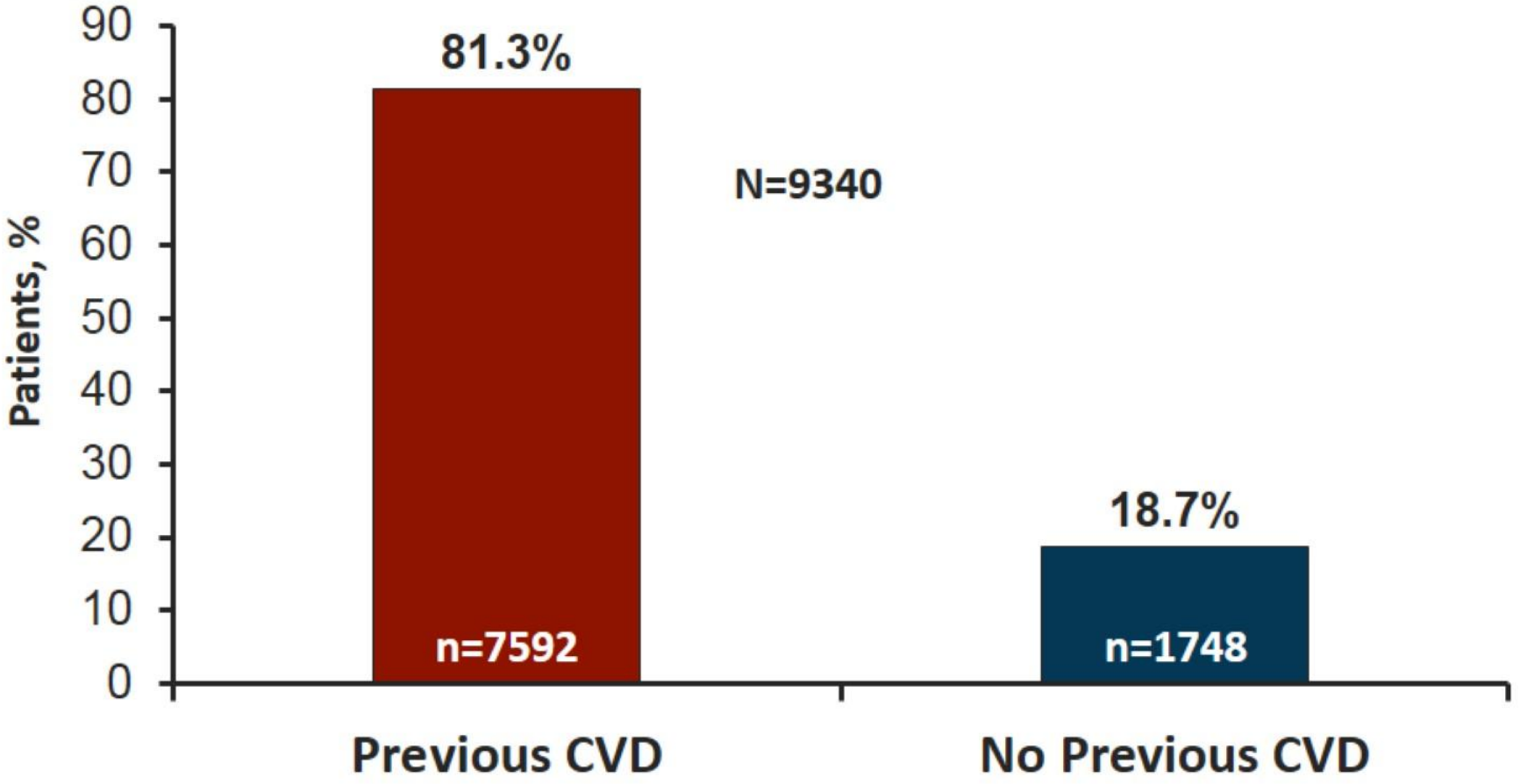
No. at Risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

*3-point MACE consisting of CV death, nonfatal MI, or nonfatal stroke

LEADER

Majority of Participants Had Previous CVD



Marso SP, et al. *N Engl J Med.* 2016. [Epub ahead of print]

What Explains the Macro- and Microvascular Improvements Observed in LEADER?

- 0.4% reduction in HBA1C[a]
- -2.3 kg reduction in body weight[a]
- -1.2 mm Hg reduction in systolic blood pressure[a]
  - Possible improvement in arterial stiffness
- Benefits observed preclinically on endothelial function, cardiac contractility, HF, etc[b-d]

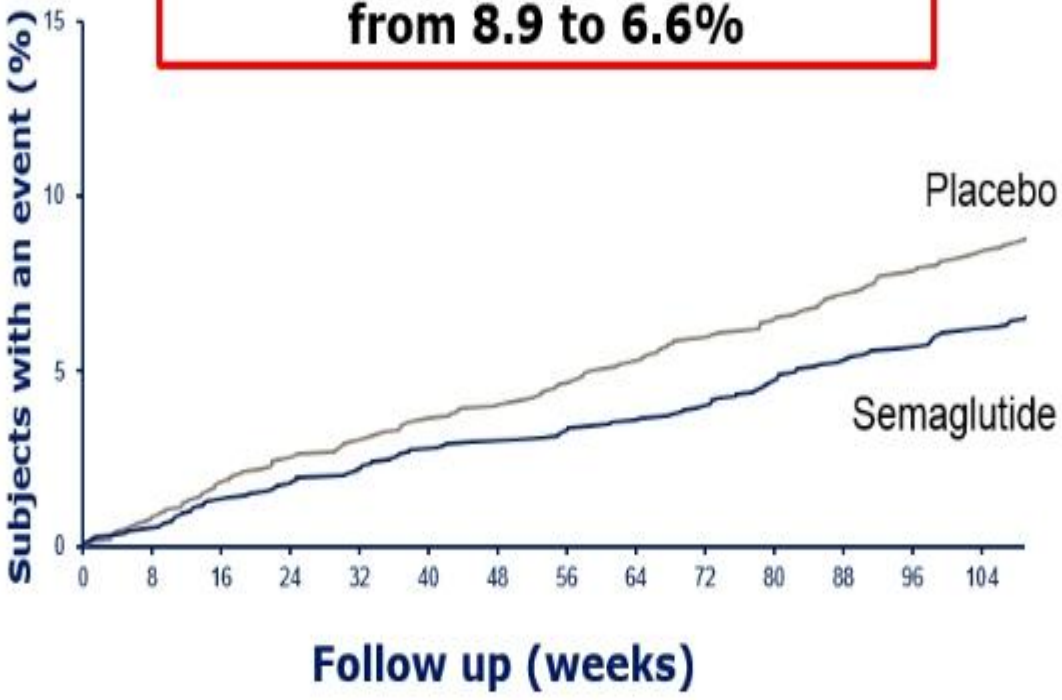
a. Marso SP, et al. LEADER Trial Investigators. *N Engl J Med.* 2016 Jun 13. [Epub ahead of print] b. Poornima I, et al. *Circ Heart Fail*. 2008;1:153-160. c. Cariou B. *Diabetes Metab*. 2012;38:298-308. d. Noyan-Ashraf MH, et al. *Diabetes. 2009;*58:975-983.

SUSTAIN 6

Primary endpoint

First of CV-death, nonfatal myocardial infarction or stroke

A meaningful reduction of 26 %
from 8.9 to 6.6%



EXSCEL: Meets Primary Safety Objective

EXSCEL is a phase 3/4, double-blind, placebo-controlled, trial that included more than 14,000 patients with T2DM from 35 countries[a,b]

- The trial compared the effect of once weekly exenatide vs placebo, when added to standard care, on the risk of MACE, in adults with T2DM at a wide range of CV risk

The EXSCEL trial met its primary safety objective of noninferiority for MACE[c]

Fewer CV events were observed in the exenatide once weekly arm, however, the efficacy objective of a superior reduction in MACE did not reach statistical significance[c]

a. Holman RR, et al. *Am Heart J*. 2016;174:103-110.
b. Mentz RJ, et al. *Am Heart J*. 2017;187:1-9.
c. AstraZeneca website, 2017. Primary safety objective.

Nice to Know

ITCA 650 (Intarcia Therapeutic, Inc)

- Continuous subcutaneous exenatide delivery
- Phase III trials
- **Once or twice yearly** administration !!!

FREEDOM: Global Phase 3 Program

Global Phase 3—Studying 5000+ Patients

Complete	FREEDOM	• Placebo-controlled trial • HbA_{1c} ≥7.5% to ≤10% • 460 patients • PE: Δ in HbA_{1c} @ 9 mo	Presented at EASD 2015[a]
Complete	FREEDOM HBL	• Open-label substudy • HbA_{1c} >10% and ≤12% • 60 patients • PE: Δ in HbA_{1c} @ 9 mo	Presented at EASD 2015[b]
Complete	FREEDOM	• Cardiovascular outcomes study • 4156 patients • Event-driven, noninferiority trial to support cardiovascular safety	Press release May 6, 2016[c]

a. Baron M, et al. EASD 2015. Oral presentation 112; b. Henry RR, et al. EASD 2015. Oral presentation 786; c. Intarcia [press release]. May 6, 2016.

Intarcia loses some of its sparkle with FDA rejection

FDA rejects Intarcia's drug pump

Sept. 28, 2017

The FDA sent bad news to Intarcia Therapeutics Inc., rejecting aspects of its manufacturing plan for a matchstick-sized drug pump for the treatment of Type 2 diabetes.

CANVAS Program Included CANVAS and CANVAS-R

- N = 10,142 participants with T2D and high CV risk
- Enrolled both a primary prevention population and a secondary prevention population
- Overall objective: to show noninferiority for the composite of death from CV causes, nonfatal MI, or nonfatal stroke

	Canagliflozin (n = 5795)	Placebo (n = 4347)
Mean age, y	63	63
Female, %	35	37
Mean duration of diabetes, y	14	14
CVD, %	65	67

Neal B, et al. *N Engl J Med*. 2017. [Epub ahead of print]

Higher Risk for Amputations in Patients Taking Canagliflozin

- 2-fold excess risk for amputations in patients who take canagliflozin compared with placebo
- ~ 180 amputations, 71% of those amputations were toes and metatarsal bones
- 3 independent risk factors for amputation identified across CANVAS program, whether the participant received canagliflozin or placebo

Exert caution in people who have 1) a prior amputation, 2) neuropathy, or 3) PVD; canagliflozin may not be the best antihyperglycemic agent in these situations

Neal B, et al. *N Engl J Med*. 2017. [Epub ahead of print]

FDA Drug Safety Communication

[5-15-2015] "The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization."

- FAERS database: 20 cases reported from March 2013 to June 6, 2014
- Indication: type 2 diabetes in most cases, type 1 diabetes in a few cases, and none in some cases
- DKA not typically observed in patients with type 2 diabetes

FDA website.[4]

CVDREAL

Lower Rates of Hospitalization for Heart Failure and All-Cause Death in New Users of SGLT-2 Inhibitors: The CVD-REAL Study

Mikhail Kosiborod, MD[1]; Matthew Cavender, MD, MPH[2]; Anna Norhammar, MD[3]; John Wilding, DM FRCP[4]; Kamlesh Khunti, MD, PhD[5]; Alex Z. Fu, PhD[6]; Reinhard W Holl, MD, PhD[7]; Kåre I Birkeland, MD, PhD[8,9]; Marit Eika Jørgensen MD, PhD[10,11]; Niklas Hammar, PhD[3,12]; Johan Bodegård, MD, PhD[13]; Betina Blak, MSc, PhD[14]; Eric T Wittbrodt, PharmD, MPH[15]; Sara Dempster, PhD[16]; Markus Scheerer, MSc, PhD[17]; Niki Arya, MSc[18]; Marcus Thuresson, PhD[19]; Peter Fenici[20]

on behalf of the CVD-REAL Investigators and Study Group

[1]Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, USA; [2]University of North Carolina, North Carolina, USA; [3]Karolinska Institutet, Stockhom, Sweden; [4]Institute of Ageing & Chronic Disease, Liverpool, UK; [5]Diabetes Research Centre, Leicester, UK; [6]Georgestown University Medical Center, Washington DC, USA; [7]Institute for Epidemiology and Medical Biometry, University Ulm, Ulm, Germany; [8]University of Oslo, Oslo, Norway; [9]Oslo University Hospital, Oslo, Norway; [10]Steno Diabetes Center, Copenhagen, Gentofte, Denmark; [11]National institute of Public Health, Southern Denmark University, Denmark; [12]AstraZeneca Gothenburg, Mölndal, Sweden; [13]AstraZeneca, Oslo, Norway; [14]AstraZeneca, Luton, UK; [15]AstraZeneca, Wilmington, Delaware, USA; [16]AstraZeneca, Waltham, Massachusetts, USA; [17]AstraZeneca, Wedel, Germany; [18]AstraZeneca, Gaithersburg, Maryland, USA; [19]Statisticon AB, Uppsala, Sweden; [20]AstraZeneca, Cambridge, UK

FDA Approves SGLT2 Inhibitor Ertugliflozin for Type 2 Diabetes 12/2017

(co developed by Merck and Pfizer)

Two fixed-dose combinations: with sitagliptin), and with metformin.

Supported by studies from the VERTIS clinical development program for ertugliflozin, which consists of nine phase 3 trials in approximately 12,600 adults with type 2 diabetes.

The drug class **has also been associated with some rare side effects**, including diabetic ketoacidosis, fracture risk, acute renal failure. and increased risk of toe amputation, although it's not clear whether these are class effects or not.

Similar Outcomes With Flexible and Fixed Once-Daily Degludec* Dosing

- Patients with T2D, 26 weeks†
- FLEX – dosed every 8 to 40 hours
- FIXED QD, dosed daily with evening meal

Outcome	FLEX 8-40 h (n = 229)	FIXED QD (n = 228)
ΔHbA_{1c}, %	–1.28	–1.07
Overall hypoglycemia, EPY	3.6	3.6
Nocturnal hypoglycemia, EPY	0.6	0.6
Severe hypoglycemia, episodes	2	2

*Insulin degludec is not FDA approved for clinical use.
†N = 457; DEG ± OADs (not specified).
EPY = events/patient year.
Meneghini L, et al. *Diabetes Care*. 2013;36:858-864.[28]

DEVOTE CVOT of Insulin Degludec

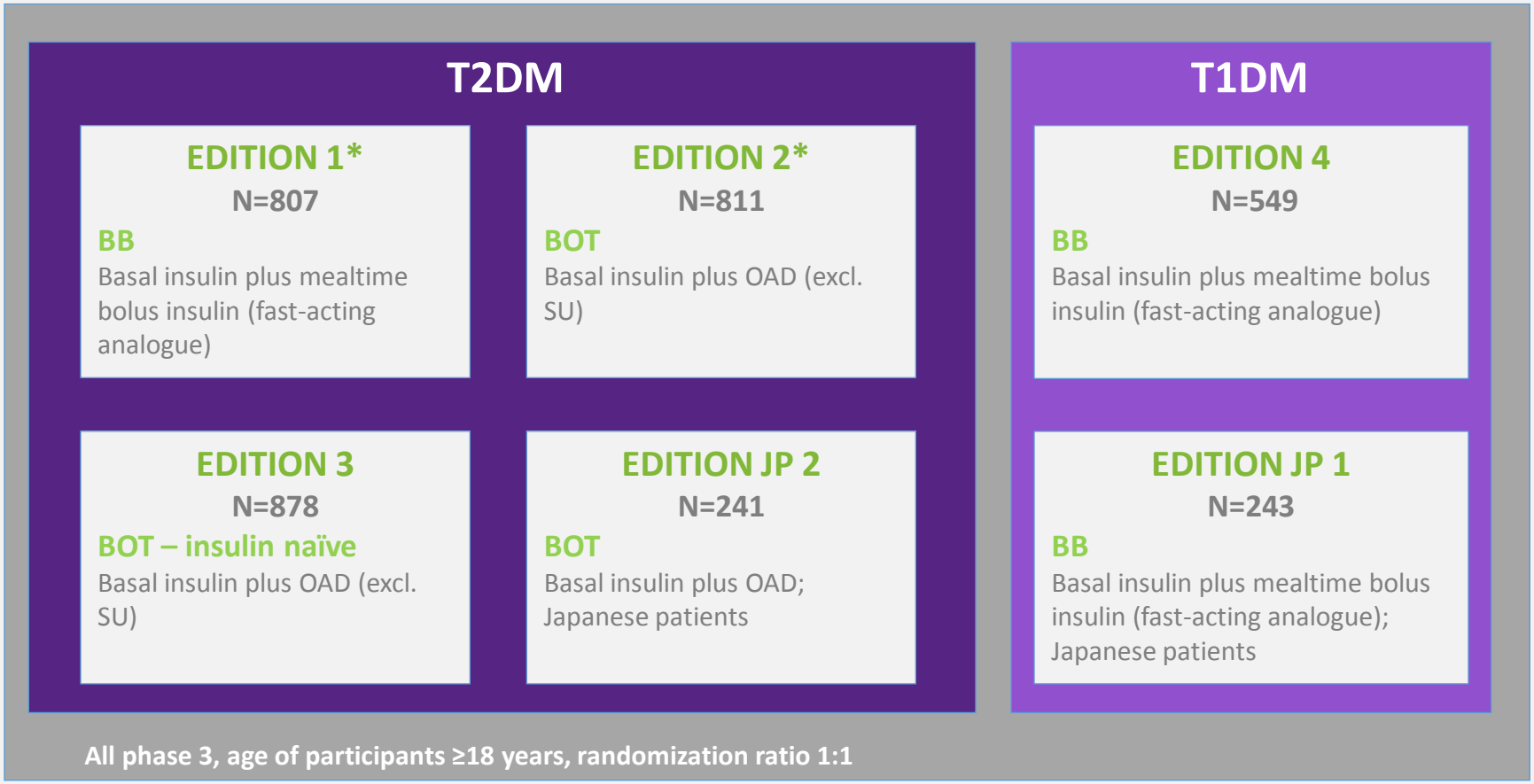
- The DEVOTE trial was an active comparator trial that tested 2 basal insulins head to head
  - Insulin degludec vs insulin glargine U100
- Marked reduction (40%) in severe hypoglycemia and 53% reduction in severe nocturnal hypoglycemia with degludec
- Demonstrates degludec is safe from a CV perspective with improvements in major hypoglycemia

End Point, n (%)	Degludec (n = 3818)	Glargine (n = 3819)	HR (95% CI)
CV death, nonfatal MI, or nonfatal stroke	325 (8.5)	356 (9.3)	0.91 (0.78, 1.06) *P* < .001 for noninferiority

Marso SP, et al. *N Engl J Med*. 2017. [Epub ahead of print]

EDITION program

Testing Gla-300 vs Gla-100 in several populations

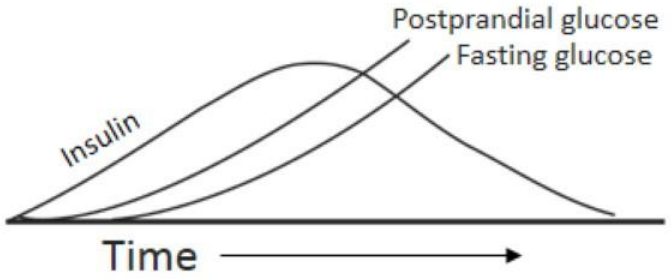


*In EDITION 1 and EDITION 2, people being treated with basal insulin ≥42 U/day were recruited

BB, basal-bolus therapy; BOT, basal only therapy; OAD, oral antihyperglycemic drug; SU, sulfonylurea; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Riddle MC et al. Diabetes Care. 2014;37:2755-62; Yki-Järvinen H et al. Diabetes Care. 2014;37:3235-43;
Bolli GB et al. Diabetes Obes Metab. 2015;17:386-94; Terauchi Y et al. Oral presentation at ADA 2015; Abstract 98-OR;
Home PD et al. Diabetes Care. 2015 Jun 17. pii: dc150249. [Epub ahead of print]; Matsuhisa M et al. Poster presentation at ADA 2015; Abstract 987-P

Progressive Nature of T2D



- Progressive rise and decline of insulin secretion over time
- Emergence of fasting and postprandial hyperglycemia
- Insulin regimens must evolve over time to meet patients' changing glycemic needs

Prandial options include
- **Rapid-acting insulin**
- **SGLT2 inhibitors**
- **DPP-4 inhibitors**
- **GLP-1 receptor agonists**

Chehade JM, et al. *Drugs*. 2000;60:95-113.
Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.

Novo Nordisk Receives FDA Approval for Fiasp®, a New Fast-Acting Mealtime Insulin

Sept. 29, 2017

No Fingerstick Necessary: FDA Approves Novel Continuous Glucose Monitoring System for Diabetes, September 28, 2017No

The US Food and Drug Administration has approved the FreeStyle® Libre Flash Glucose Monitoring System (Abbott Diabetes Care, Inc.) for use in adults with diabetes.

The FreeStyle Libre system can be worn continuously for up to 10 days.

The FreeStyle Libre is factory calibrated, eliminating the need for daily calibration.