Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Diabetes - The Place of New Therapies

Dr Ketan Dhatariya MBBS MSc MD MS FRCP PhD

Consultant in Diabetes and Endocrinology

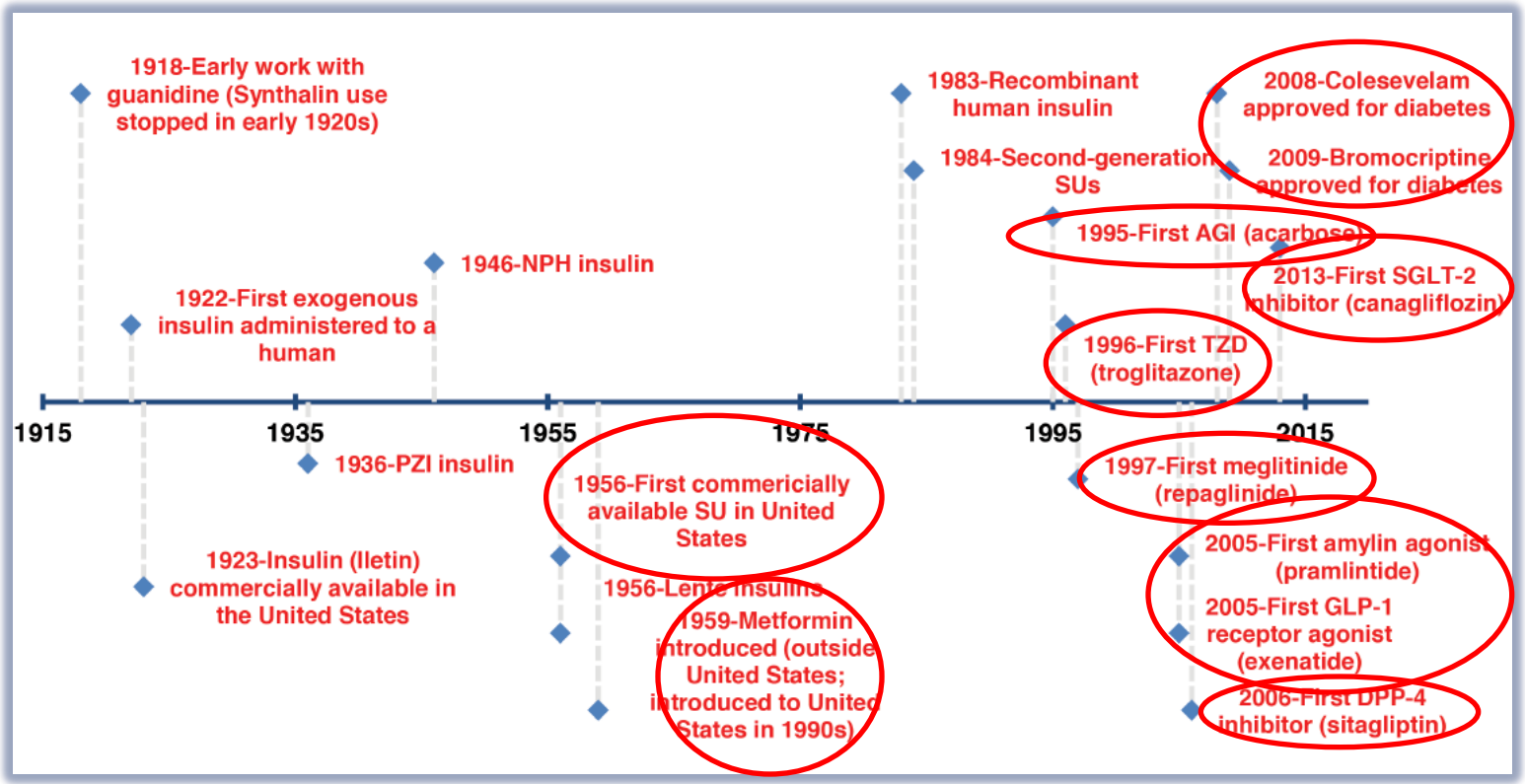
Norfolk and Norwich University Hospitals

Disclosures

- I am the lead author of the updated 2013 edition of the JBDS guidelines for the management of diabetic ketoacidosis
- I am the lead author of the JBDS guidelines on the management of the adult patient with diabetes undergoing surgery or procedures
- I am a co-author on almost all of the other JBDS national guidelines
- I am on the clinical endpoint adjudication committee for the sotagliflozin trials implemented by Lexicon Pharmaceuticals
- In the last 24 months, I have also received consulting fees and honoraria from Genentech, Sanofi Diabetes, and Novo Nordisk

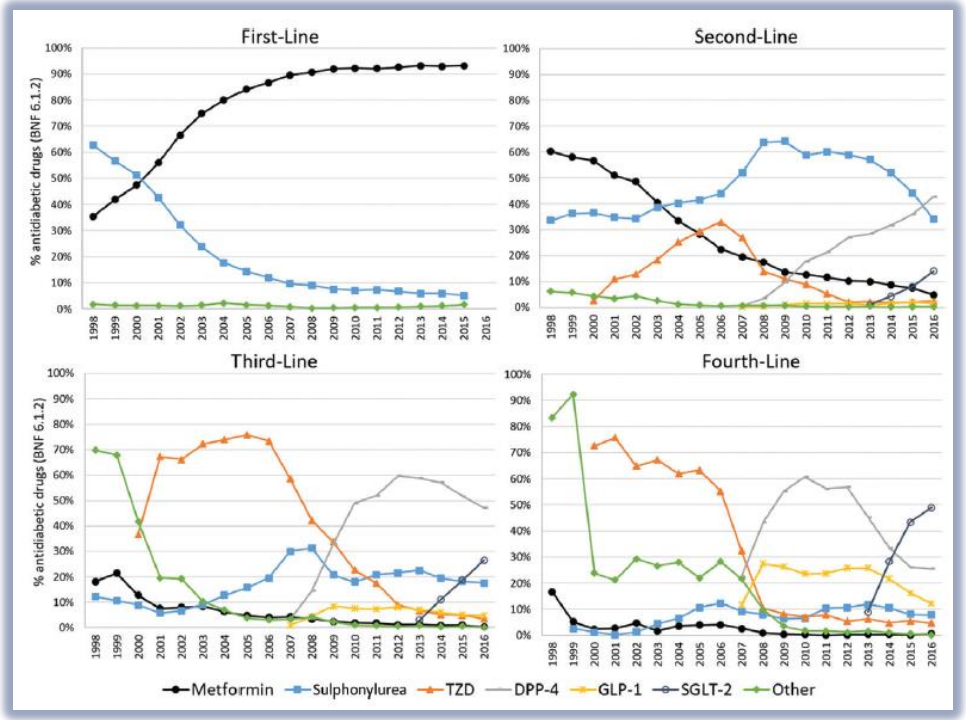
JBDS, Joint British Diabetes Societies.

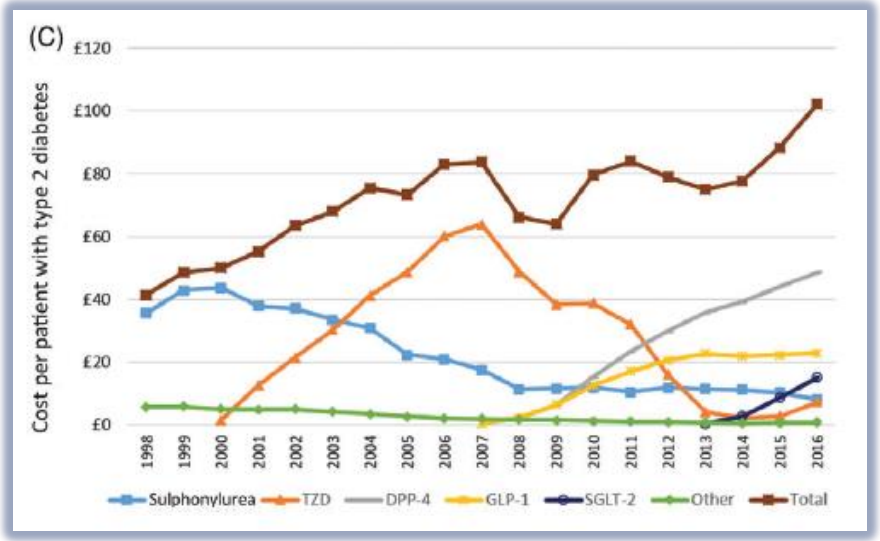
So, What is 'New'?



White JR Diabetes Spectrum 2014;27(2):82-86

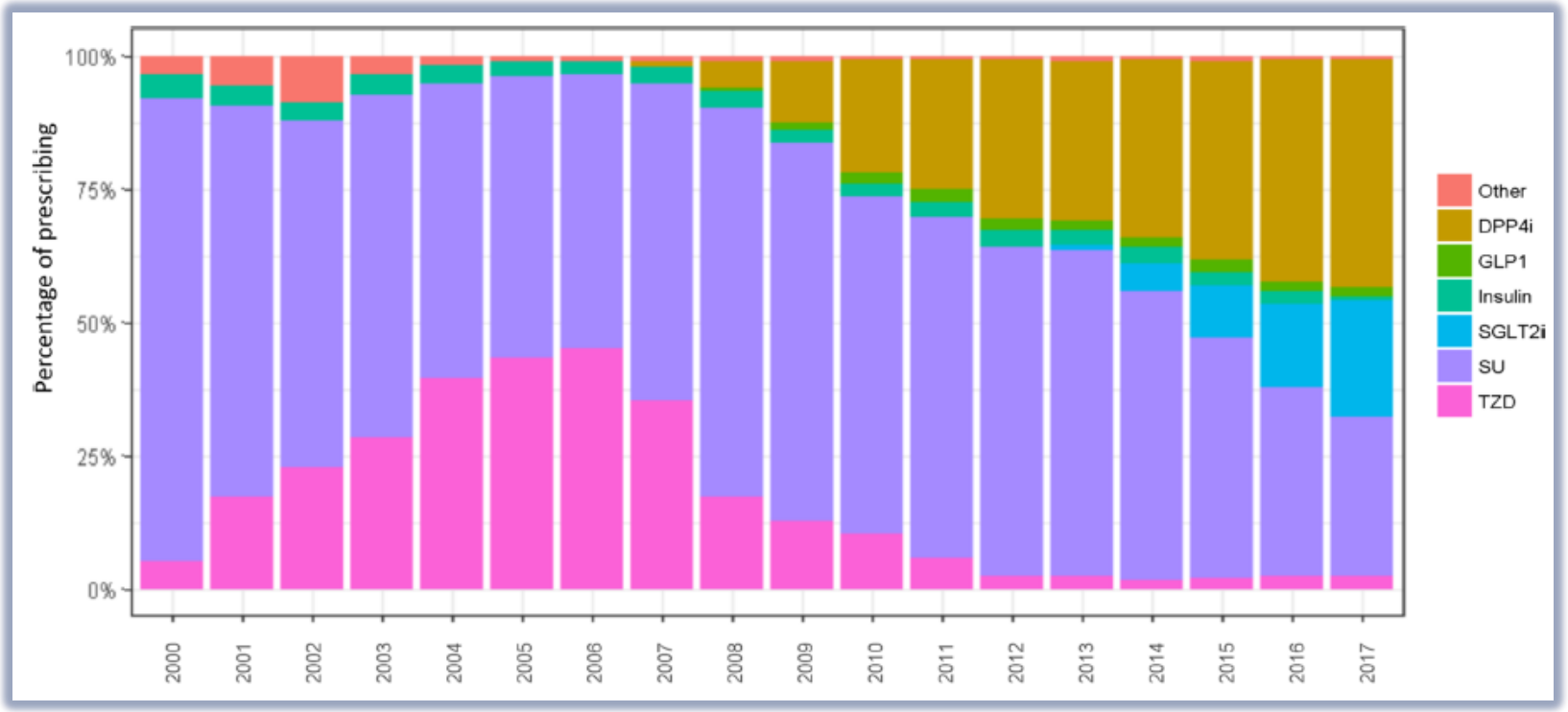
Changes in Prescribing Practices



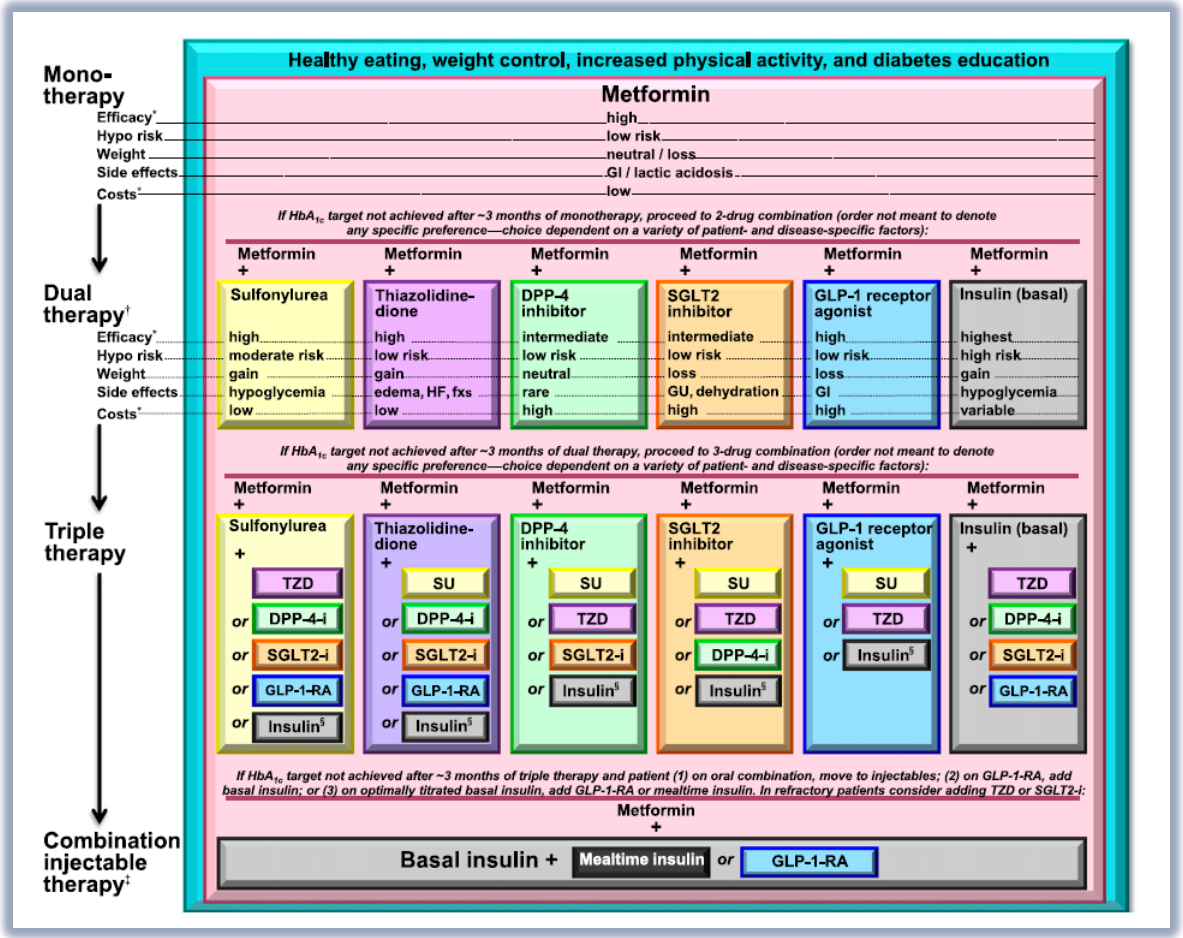


Curtis HJ et al Diab Obes Metabol 2018;20(9):2159-2168

Showing that Another Way….

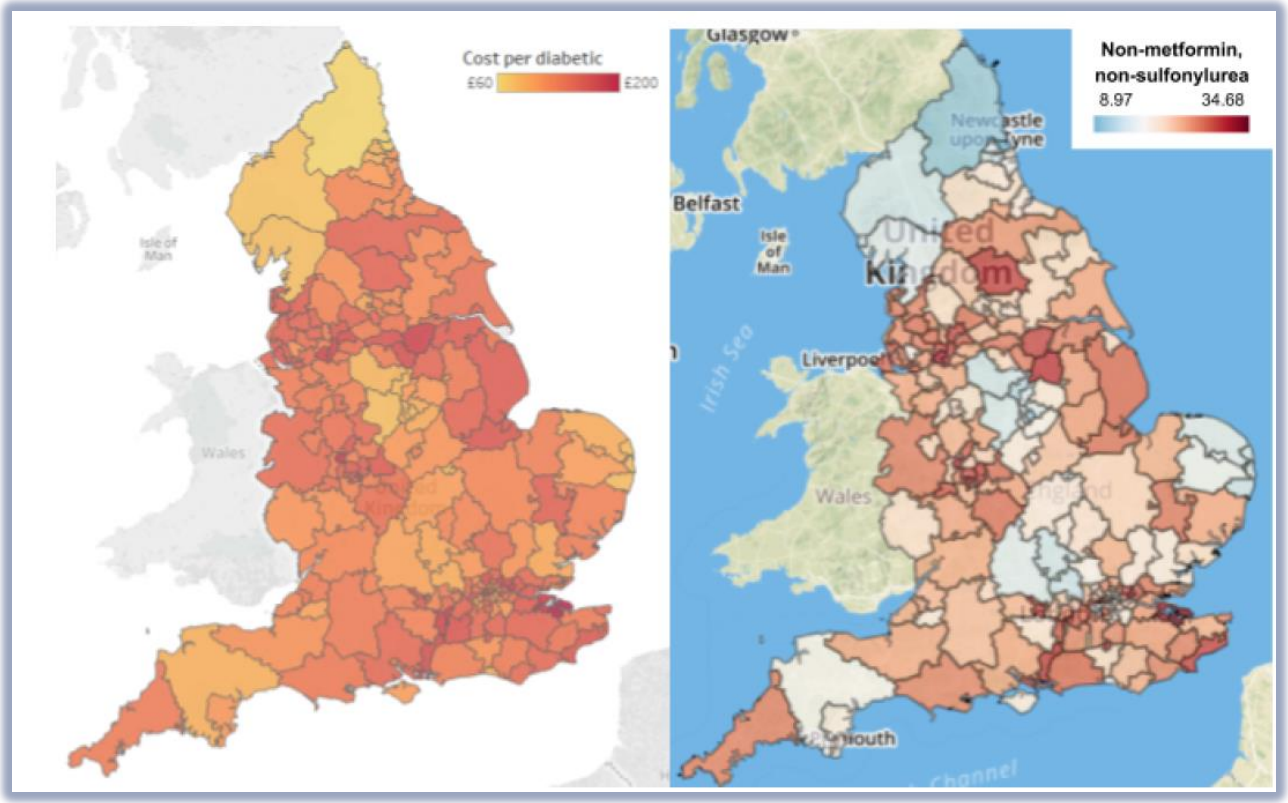


Wilkinson S et al BMJ Open 2018;8(7):e022768



Inzucchi SE et al Diabetes Care 2015;38(1):140-149

Variations in Practice and Spending



Curtis HJ et al Diab Obes Metabol 2018;20(9):2159-2168

Back to 2007

The NEW ENGLAND JOURNAL of MEDICINE

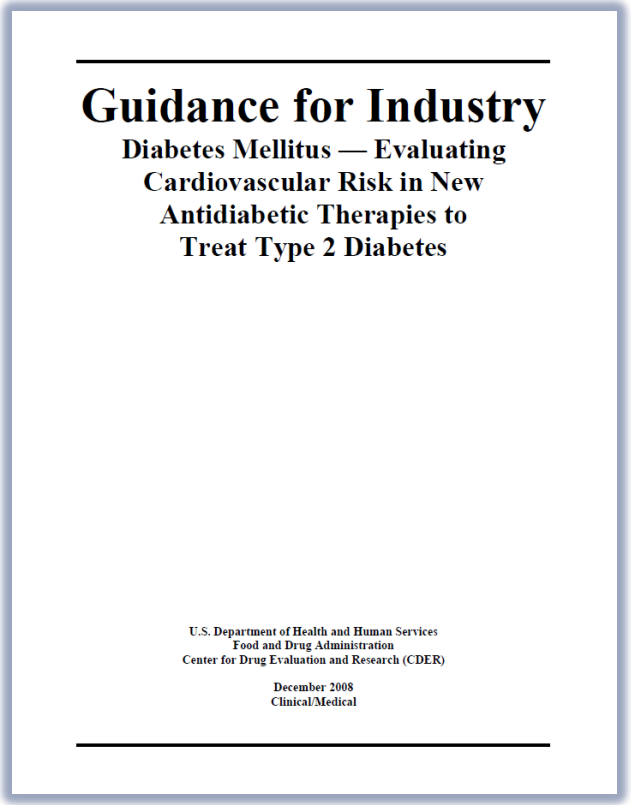
ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Some More Bad Press

The Result



Guidance for Industry

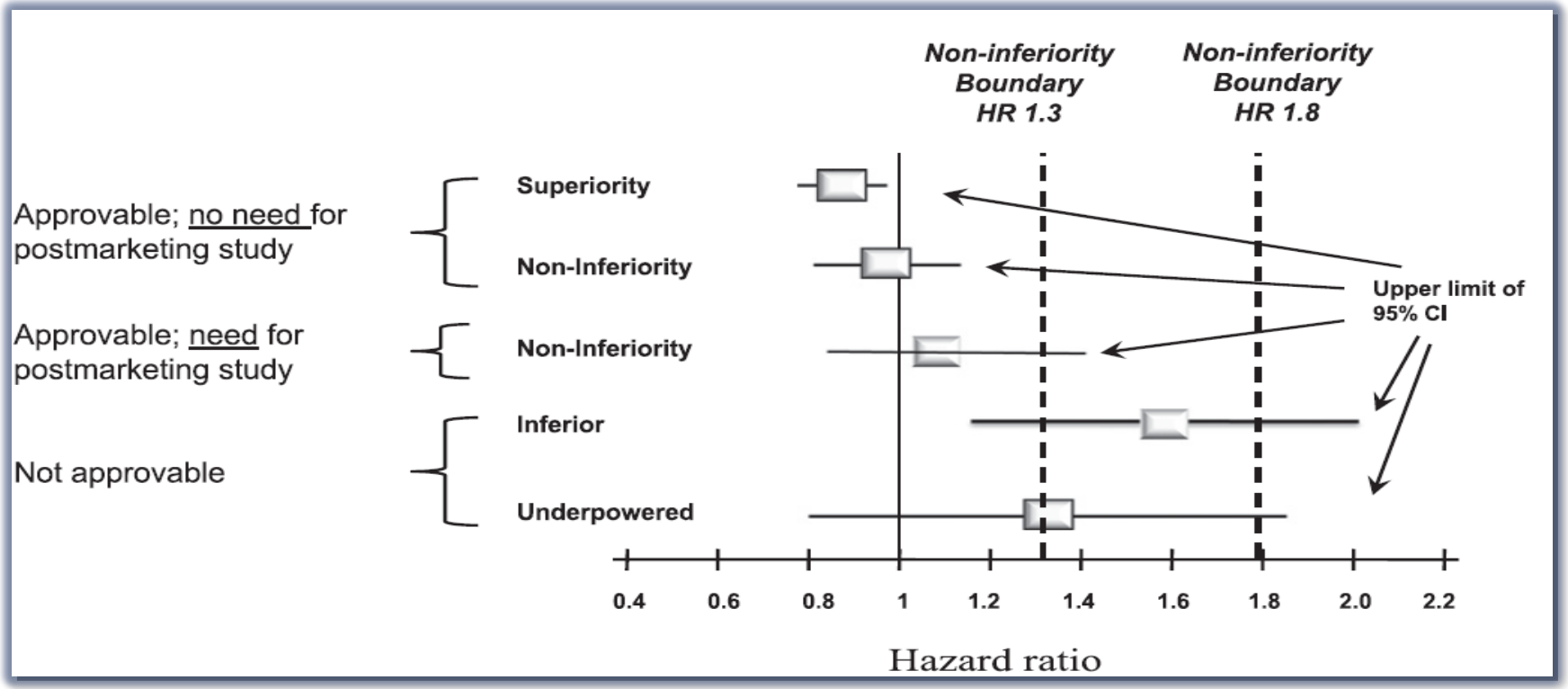
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

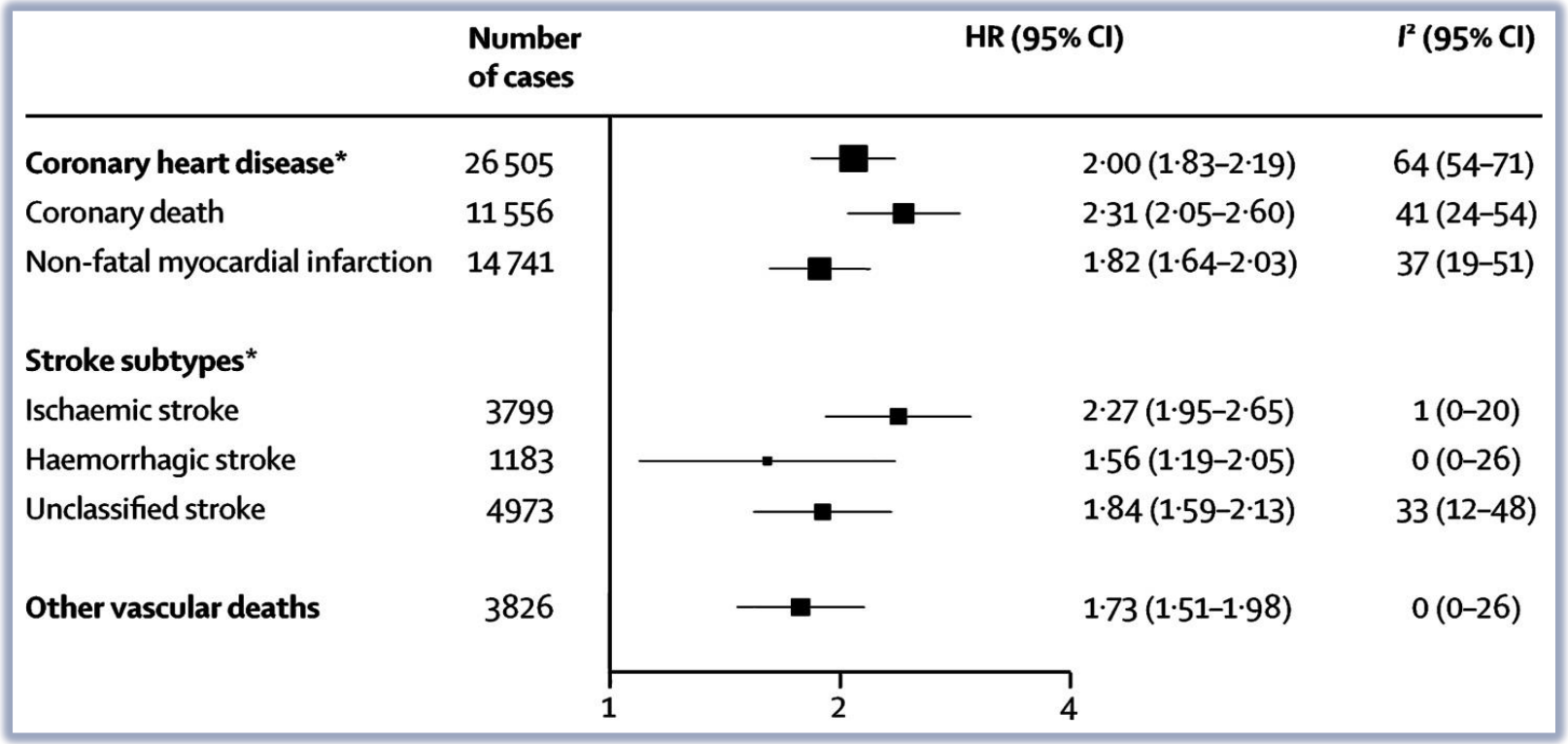
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

What The FDA Want



Hirshberg B et al Diabetes Care 2011;34(Suppl 2):S101-106

Diabetes and CV Risk

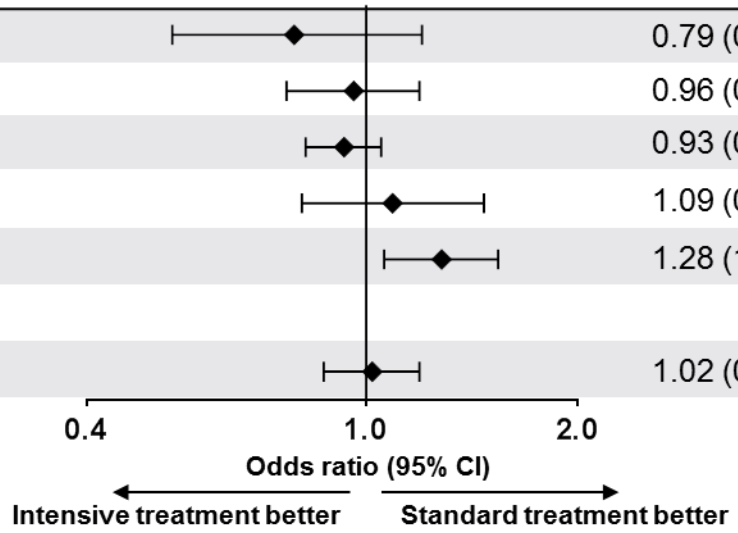


Emerging Risk Factors Collaboration Lancet 2010;375(9733):2215-2222

All Cause Mortality

Intensive vs Standard Glucose Lowering

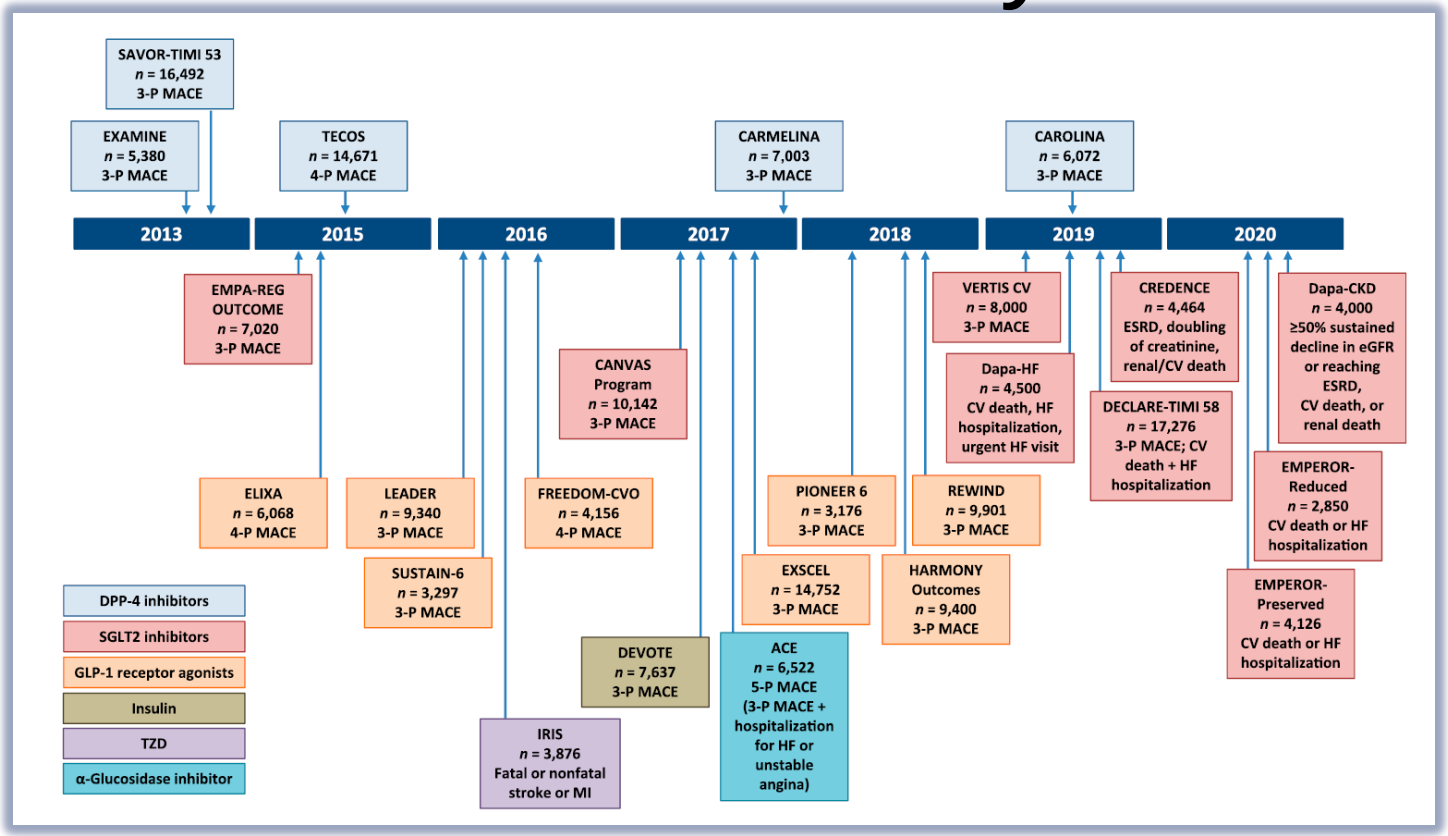
Trial	Odds ratio (95% CI)	Intensive treatment/ standard treatment: Participants	Intensive treatment/ standard treatment: Events	Weight of study size
UKPDS	0.79 (0.53 – 1.20)	3071/1549	539/302	10.1%
PROactive	0.96 (0.77 – 1.19)	2605/2633	177/186	21.5%
ADVANCE	0.93 (0.82 – 1.05)	5571/5569	498/533	29.4%
VADT	1.09 (0.81 – 1.47)	892/899	102/95	15.5%
ACCORD	1.28 (1.06 – 1.54)	5128/5123	257/203	23.6%
Overall	1.02 (0.87 – 1.19)	17267/15773	1573/1319	100%



CI: confidence interval; HR: hazard ratio.

Ray KK et al Lancet 2009;373:1765–1772

Cardiovascular Safety Studies

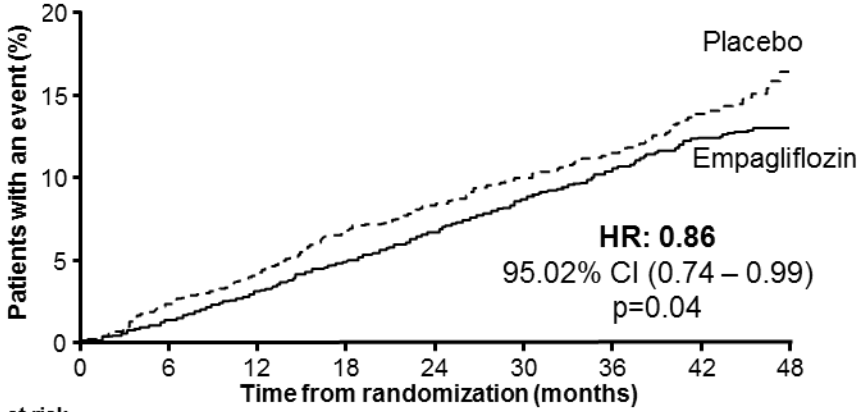


Cefalu WT et al Diabetes Care 2018;41(1):14-31

Empagliflozin and Liraglutide

EMPA-REG OUTCOME

CV death, non-fatal MI, or non-fatal stroke

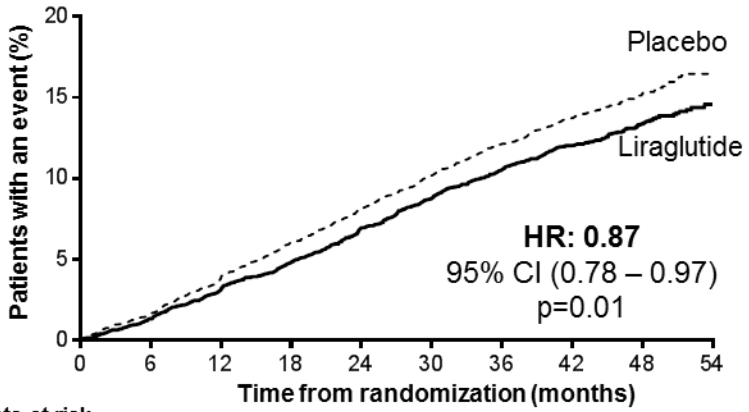


Patients at risk

Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

LEADER

CV death, non-fatal MI, or non-fatal stroke



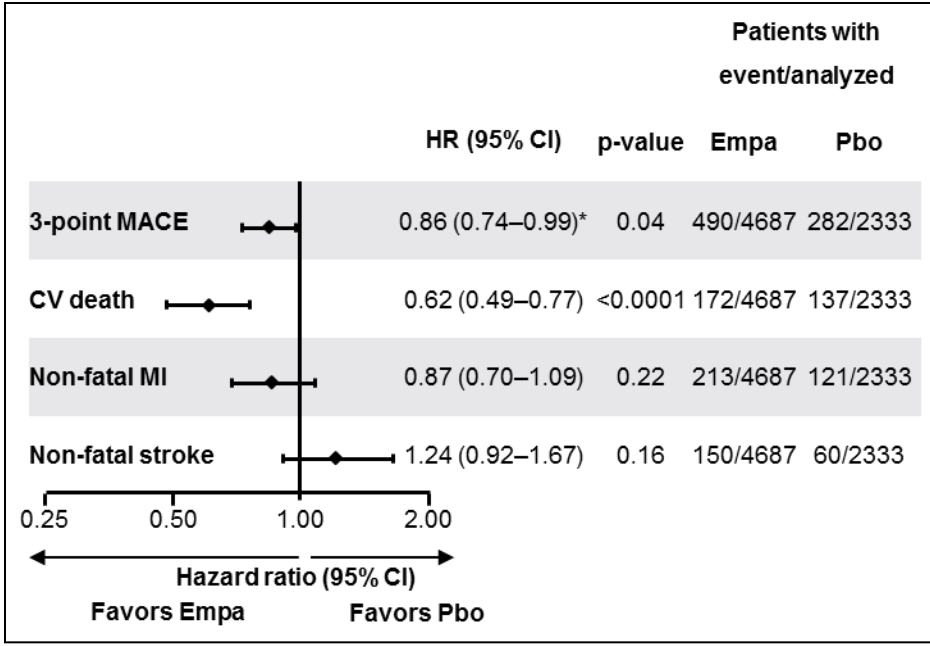
Patients at risk

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

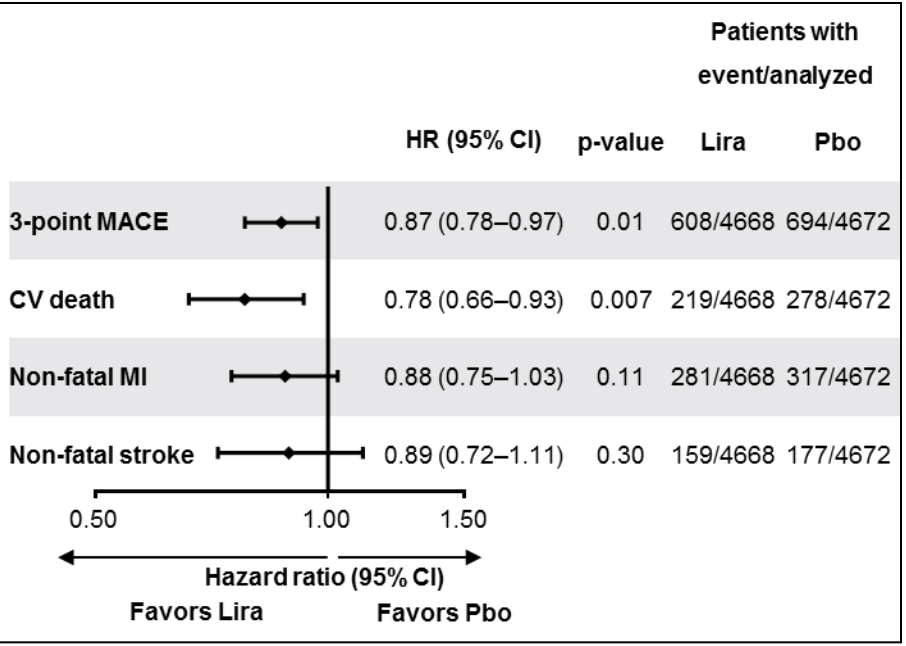
Zinman B et al. N Engl J Med 2015;373:2117-2128

Individual Components of the Primary Endpoint

EMPA-REG OUTCOME



LEADER



Lower Extremity Amputations

- Canagliflozin use was associated with a significant increase in the risk of LEA
- Empagliflozin had neutral effect on LEA
- Liraglutide use significantly reduces the risk of major amputation
- SGLT2s have a numerically higher risk of amputations than DPP-IVs and GLP-1 RA but it is not statistically significant

Neal B et al. N Engl J Med 2017;377(7):644-657; Verma S et al. Circulation 2018:137(4):405-407; Chang H-Y et al JAMA Int Med 2018 (in press)
Dhatariya K et al. Diabetes Care (in press); Adimadhyam S et al Diabetes, Obesity and Metabolism (in press);

DKA

Why is This Important?

Table 3. Summary of patients with treatment-emergent serious adverse events of DKA and related events in the canagliflozin development programme for type 2 diabetes

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Treatment group	C 300 mg	Placebo	C 100 mg	C 100 mg	C 300 mg	C 300 mg	C 300 mg	C 100 mg	C 100 mg	C 300 mg	S 100 mg	C 300 mg
Adverse event	Acidosis DKA (non-TEAE)	Metabolic acidosis	DKA	DKA	Metabolic acidosis	DKA	Ketoacidosis	DKA	DKA	DKA	DKA	Ketoacidosis
Blood glucose, mg/dL (mmol/L)*	Acidosis: 369 (20.5) DKA: 533 (29.6)	N/A	400 (22.2)	347 (19.3)	>500 (>27.8)	>500 (>27.8)	148–320 (8.2–17.8)†	481 (26.7)	400 (22.2)	470 (26.1)	481 (26.7)‡	571 (31.7)
pH	Acidosis: 7.24 DKA: N/A	N/A	7.14	N/A	6.82	N/A	N/A	7.23	7.022	N/A	7.22‡	N/A
Bicarbonate, mEg/L	Acidosis: 15 DKA: 15	N/A	15	N/A	3.4	N/A	13.6‡	11.7	1.8	N/A	11.4‡	N/A
Anion gap, mmol/L	Acidosis: 6 DKA: 17	N/A	25	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ketones (blood or urine)	Acidosis: +blood DKA: +blood, +urine	N/A	+Blood	N/A	+Blood	N/A	N/A	+Blood	N/A	N/A	N/A	+Urine

*Blood glucose value at presentation of the adverse event; †Range of all values reported; specific days and times not reported; ‡Specific date not reported.

17,956 randomised to canagliflozin or placebo

C, canagliflozin; S, sitagliptin; TEAE, treatment-emergent adverse event.

Erondu N, *et al. Diabetes Care* 2015;38:1680–1686.

How about Dapagliflozin?

Occurrence of diabetic ketoacidosis among type 2 diabetes patients in Humedica/Optum observational data and from the dapagliflozin clinical trial development program

- 5936 patients on dapagliflozin out of the ~1.5 million people on the database between 2011 and 2013
- Mean age 56.9 years
- M=F
- 77% Caucasian, 13% black/African, 2% Asian

Andersson Sundell K, *et al.* CODHy 2015; poster 28. http://www.codhy.com/2015/Uploads/Editor/PDF/POSTER1/28.pdf.

How about Dapagliflozin?

	2011 (N=257)	2012 (N=263)	2013 (N=398)
Venous pH measure	108 (42.0)	89 (33.8)	127 (31.9)
Arterial blood gases.HCO_3	62 (24.1)	64 (24.3)	116 (29.1)
Arterial blood gases.O_2 content	4 (1.6)	5 (1.9)	8 (2.0)
Arterial blood gases.O_2 saturation	100 (38.9)	86 (32.7)	127 (31.9)
Arterial blood gases.PaO_2	100 (38.9)	83 (31.6)	103 (25.9)
Arterial blood gases.total CO_2	43 (16.7)	40 (15.2)	79 (19.8)
Serum bicarbonate	67 (26.1)	62 (23.6)	55 (13.8)
Base excess in blood	71 (27.6)	61 (23.2)	50 (12.6)
Lactic acid	60 (23.3)	55 (20.9)	140 (35.2)
Blood glucose	54 (21.0)	42 (16.0)	43 (10.8)
Urine ketones	88 (34.2)	49 (18.6)	81 (20.4)

All data are presented as n (%).

These are the patients they presented as having DKA

Most had:
No pH
No HCO_3
No glucose
No ketones

Andersson Sundell K, *et al.* CODHy 2015; poster 28. http://www.codhy.com/2015/Uploads/Editor/PDF/POSTER1/28.pdf.

Euglycemic Diabetic Ketoacidosis: A Potential Complication of Tre... Cot...

Anne L. Peters,[1] Elizabeth O. Buschur,[2] John B. Buse,[3] Pejman Cohan,[4] Jamie C. Diner,[3] and Irl B. Hirsch[5]

Diabete...

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF SGLT-2 INHIBITORS AND DIABETIC KETOACIDOSIS

Association of British Clinical Diabetologists (ABCD) position statement on the risk of diabetic ketoacidosis associated with the use of sodium-glucose cotransporter-2 inhibitors

UMESH DASHORA,[1] ALISON GALLAGHER,[2] KETAN DHATARIYA,[3] PETER WINOCOUR[4] AND ROB GREGORY[2] ON BEHALF OF THE ABCD COMMITTEE

Br J Diabetes 2016;16:206-209

What About Type 1?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type Diabetes (the DEPICT-2 Study 24-Week Results From a Randomized Controlled Trial

Diabetes Care 2018;41:1938–1946 | https://doi.org/10.2337/dc18-0623

NIH U.S. National Library of Medicine
ClinicalTrials.gov

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾

Home > Search Results > Study Record Detail ☐ Save this study

A Study of Effects of Canagliflozin as Add-on Therapy to Insulin in the Treatment of Participants With Type 1 Diabetes Mellitus (T1DM)

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02139943

Recruitment Status ℹ: Completed
First Posted ℹ: May 16, 2014
Results First Posted ℹ: July 18, 2016
Last Update Posted ℹ: July 18, 2016

Garg SK et al N Engl J Med 2017;377(24):2337-2348
Mathieu C et al Diabetes Care 2018;41(9):1938-1946

Sota / Dapa in Type 1 - Hypos and DKA

- Rates of severe hypos were much the same between sota and placebo - 3.0% vs 2.4%; 6.3%, 8.5% vs 7.7% for dapa 5mg, 10mg and placebo

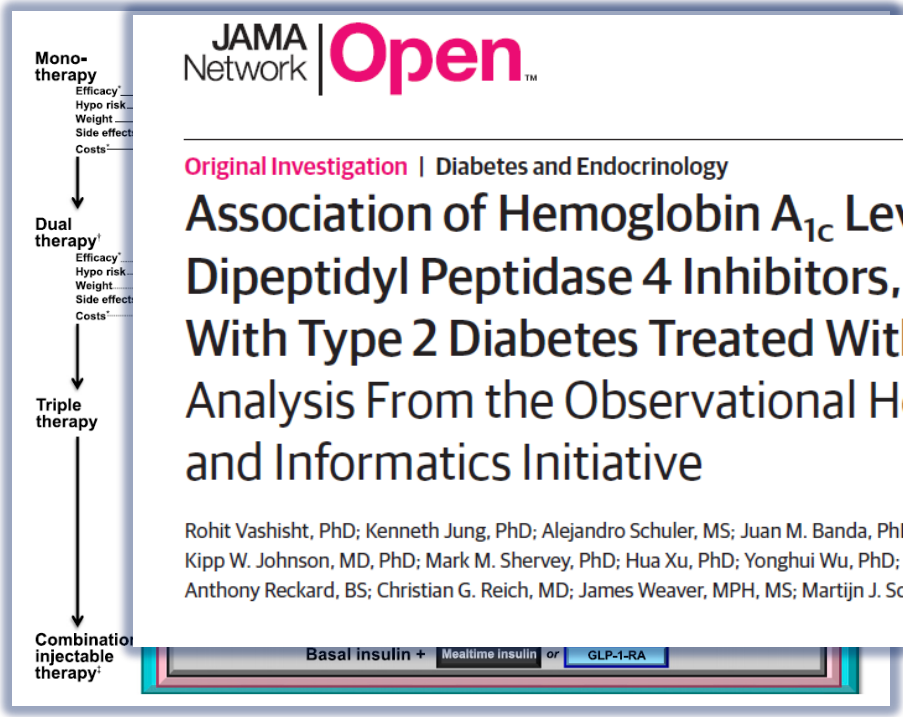
- Rates of DKA were higher - 3.0% vs 0.6% for sota; 2.6%, 2.2% vs 0% for dapa 5mg, 10mg and placebo)

Garg SK et al N Engl J Med 2017;377(24):2337-2348
Mathieu C et al Diabetes Care 2018;41(9):1938-1946

New Paradigms?

Type 2

Type 1



JAMA Network Open

Original Investigation | Diabetes and Endocrinology

Association of Hemoglobin A_{1c} Levels With Use of Sulfonylureas, Dipeptidyl Peptidase 4 Inhibitors, and Thiazolidinediones in Patients With Type 2 Diabetes Treated With Metformin

Analysis From the Observational Health Data Sciences and Informatics Initiative

Rohit Vashisht, PhD; Kenneth Jung, PhD; Alejandro Schuler, MS; Juan M. Banda, PhD; Rae Woong Park, MD, PhD; Sanghyung Jin, MS; Li Li, MS, MD; Joel T. Dudley, PhD; Kipp W. Johnson, MD, PhD; Mark M. Shervey, PhD; Hua Xu, PhD; Yonghui Wu, PhD; Karthik Natrajan, PhD; George Hripcsak, MD, MS; Peng Jin, MS; Mui Van Zandt, BS; Anthony Reckard, BS; Christian G. Reich, MD; James Weaver, MPH, MS; Martijn J. Schuemie, PhD; Patrick B. Ryan, PhD; Alison Callahan, PhD; Nigam H. Shah, MBBS, PhD

Vashisht R et al JAMA Open 2018;1(4):e181755

Inzucchi SE et al Diabetes Care 2015;38(1):140-149

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Diabetes - The Place of New Therapies

www.norfolkdiabetes.com

ketan.dhatariya@nnuh.nhs.uk

@ketandhatariya