Preventing CV disease & Heart Failure in patients with Type II Diabetes –

Getting to the HEART of the matter!

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Deakin University

Director Geelong Cardiology Research Centre

Director Barwon Health CHF Program

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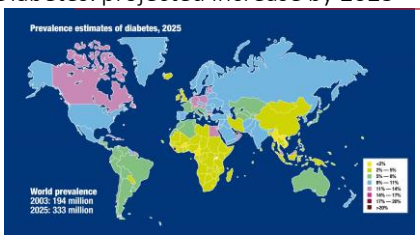
Disclosures

- Steering Committee
  - RELY trial (dabigatran)
  - PALLAS trial (dronederone)
  - SAVOR trial (saxagliptin)
  - ARISTOTLE trial (apixaban)
  - FOURIER study (AMG 249)
  - COMPLETE study
  - THEMIS study
- Consultant
  - Boehringer Ingelheim (Dabigatran)
  - Sanofi-aventis (Dronedarone)
  - Johnson & Johnson / Bayer (Rivaroxaban)
  - BMS / Pfizer (Apixaban)
  - Astra-Zeneca (Ticagrelor)
  - Novartis
- Honorarium for CME speaking:
  - Sanofi-aventis / BI / BMS / Pfizer / Bayer / Astra-Zeneca / Novartis

Diabetes: projected increase by 2025



Adapted from International Diabetes Federation. Diabetes Atlas 2nd ed. 2003

diabetes australia

Facts about diabetes

•280 Australians develop diabetes every day. That's one person every five minutes

•Around 1.7 million Australians have diabetes. This includes all types of diagnosed diabetes (1.2 million known and registered) as well as silent, undiagnosed type 2 diabetes (up to 500,000 estimated)

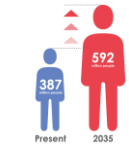
•More than 100,000 Australians have developed diabetes in the past year

•For every person diagnosed with diabetes there is usually a family member or carer who also 'lives with diabetes' every day in a support role. This means that an estimated 2.4 million Australians are affected by diabetes every day

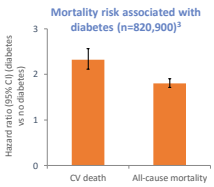
•Total annual cost impact of diabetes in Australia estimated at $14.6 billion

Type 2 diabetes is increasingly prevalent

- Globally, 387 million people are living with diabetes[1]
- At least 68% of people >65 years with diabetes die of heart disease[2]



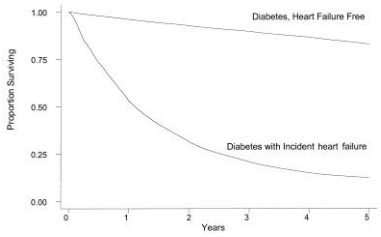
This will rise to 592 million by 2035[1]



1. IDF Diabetes Atlas 6th Edition 2014 http://www.idf.org/diabetesatlas; 2. Centers for Disease Control and Prevention 2011; 3. Seshasai et al. N Engl J Med

EMPA-REG OUTCOME

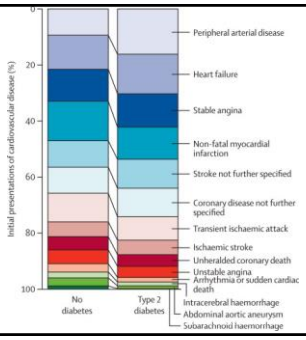
Five-year Kaplan-Meier survival estimates for 115,803 adults age ≥65 years in fee-for-service Medicare with diabetes by incident heart failure status.



Alain G. Bertoni et al. Dia Care 2004;27:699-703

©2004 by American Diabetes Association

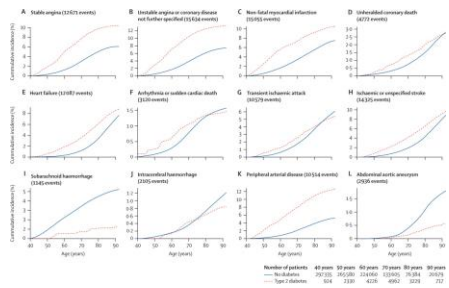
American Diabetes Association.



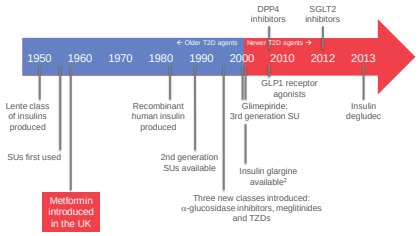
Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people

Dr Anoop Dinesh Shah, MRCP, Claudia Langenberg, PhD, Eleni Rapsomaniki, PhD, Spiros Denaxas, PhD, Mar Pujades-Rodriguez, PhD, Chris P Gale, FRCP, Prof John Deanfield, FRCP, Prof Liam Smeeth, FRCGP, Prof Adam Timmis, FRCP, Prof Harry Hemingway, FRCP

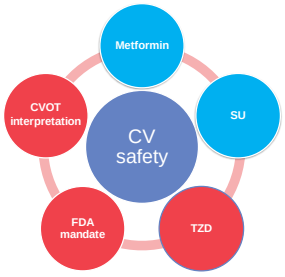
The Lancet Diabetes & Endocrinology
Volume 3, Issue 2, Pages 105-113 (February 2015)
DOI: 10.1016/S2213-8587(14)70219-0

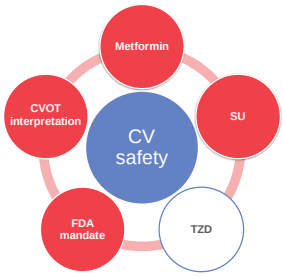


Evolution of T2D agents

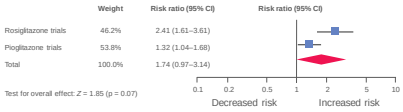


Adapted from 1. Kirby. Br J Diabetes Vasc Dis 2012;12:315–20 2. Lantus® SPC.





Meta-analysis showed increased risk for congestive heart failure (FLUID RETENTION) with both pioglitazone and rosiglitazone



- In a meta-analysis of 20,191 patients with pre-diabetes or T2D, the increased risk for congestive heart failure with TZDs did not differ between rosiglitazone and pioglitazone (p = 0.07)

Lago et al. Lancet 2007;370:1129–36.

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.

ABSTRACT

BACKGROUND
Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

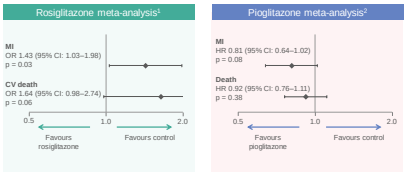
METHODS
We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissense@ccf.org.

This article (10.1056/NEJMoa072761) was published at www.nejm.org.

Nissen et al. N Engl J Med 2007

In 2007, separate meta-analyses suggested differing CV effects of drugs within the TZD class



No clinical trial directly compares the CV effects of pioglitazone and rosiglitazone

1. Nissen & Wolski. N Engl J Med 2007;356:2457–71. 2. Lincoff et al. JAMA 2007;298:1180–8.

BLACK BOX

- CHD
- CHF
- INSULIN

Real uncertainty about off-target effects

CNN
Can a dirt-cheap diabetes drug fight cancer?

THE WALL STREET JOURNAL.
FDA Urged to Test Diabetes Drugs' Heart Risk

THE WALL STREET JOURNAL.
Study: Sanofi's Lantus Insulin Has Possible Cancer Link

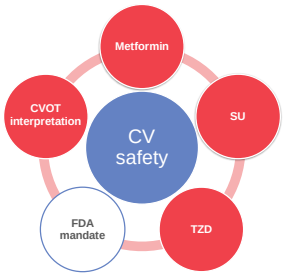
From The Times
May 11, 2007
GlaxoSmithKline defends Avandia as shares drop 13% in nine days

CBS NEWS
Judge sets first hearing for diabetes drug lawsuits

WebMD
Better information. Better health.
More Evidence Links Fractures to Diabetes Drugs
Avandia, Actos Boost Fracture Risk in Older Women, Study Finds

The New York Times
Diabetes drug tied to pancreatitis, deaths

s Care.
es Association



Regulatory Obligations for all New Diabetes Medications - 2008

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

"HbA1c remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication to treat hyperglycemia secondary to DM"

"…a post-marketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent CI for the estimated risk ratio is less than 1.3.

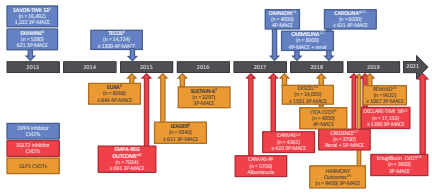
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

Trials are growing in number, size & complexity

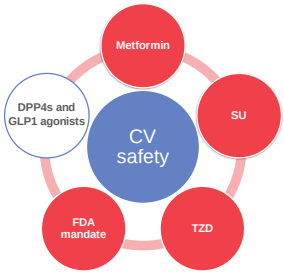
	Pre-FDA guidance (n=8)	Post-FDA guidance (n=16)
Size, median (IQR)	1116 (300-4447)	6000 (4082-9313)
<1000, n(%)	3	2
1000 - 5000, n(%)	3	3
>5000, n(%)	1	11
Countries participating, median (IQR)	17 (1-20)	27 (6-35)
Sites participating, median IQR	160 (3-332)	501 (183-635)

AND COST!!!

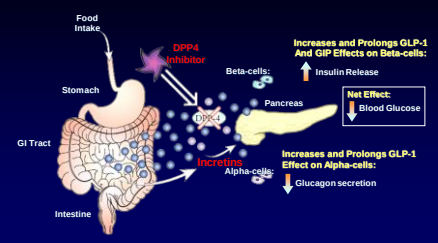
Overview of CVOTs of glucose-lowering drugs



Timings represent estimated completion dates as per ClinicalTrials.gov.
Adapted from Johansen, World J Diabetes 2015;6:1092–96.(references 1–19 expanded in slide notes)

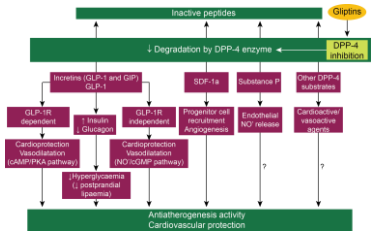


How DPP4 / Incretin mimetics Inhibitors Work



Adapted from Drucker and Nauck, 2006; Idris and Donnelly, 2007; Barnett, 2006

DPP inhibition / Incretin activation and beneficial effects on CV system



1. Scheen A. Cardiovascular effects of gliptins. *Nature Reviews Cardiology* **10**, 73-84 (February 2013)

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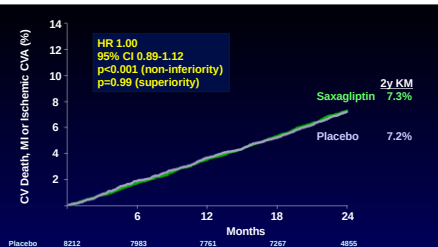
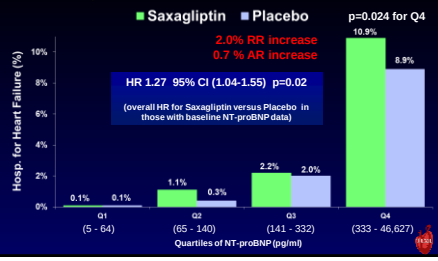
Primary Endpoint: CV Death, MI, Ischemic Stroke



Scirica BM, Bhatt DL, Braunwald E, et al.…. Raz I. *NEJM* 2013 at www.NEJM.org.

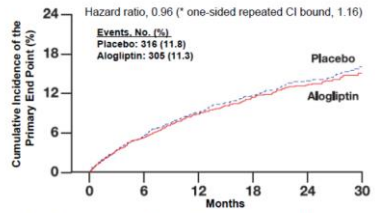
Baseline NT-pro BNP and Hospitalization for Heart Failure

Preliminary data (N=12,397 patients; 387 HF events)



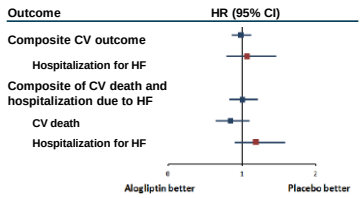
Time to Primary End Point (CV Death, Nonfatal MI, Nonfatal Stroke)

EXAMINE



* Using alpha=0.01

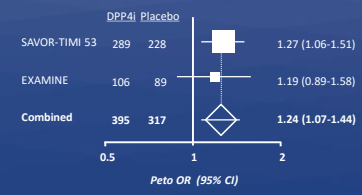
EXAMINE
Heart Failure Outcomes



- Composite CV outcome: first occurrence of all-cause mortality, nonfatal MI and stroke, urgent revascularization due to unstable angina, and hospitalization for HF

Zannad F, et al. *J Am Coll Cardiol*. 2014;63(12S).

Meta-Analysis of Hospitalization for HF in the SAVOR-TIMI 53 and EXAMINE Trials



OR: odds ratio

Scirica BM, et al. *American Heart Association Scientific Sessions*. November 2013.

Bristol-Myers Squibb
Confidential – For Internal Training Use. Not approved for promotional use. Could be used for reactive scientific exchange, provided back approval is obtained.
AstraZeneca

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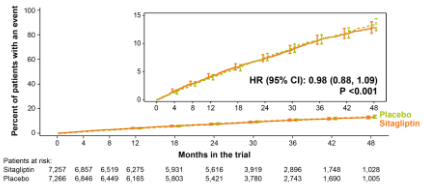
Postulated mechanisms for excess CHF hospitalisations with DPP4s

1. More use of glitazones in treatment cohort
2. Better glycemic control, less glycosuria, more fluid retention in active group?
3. More hypo's, more activation of sympathetic nervous system in treatment group?
4. Class effect – increased CHF admissions with saxagliptin, alogliptin and vildaglitin

Primary Composite Cardiovascular Outcome*
PP Analysis for Non-inferiority

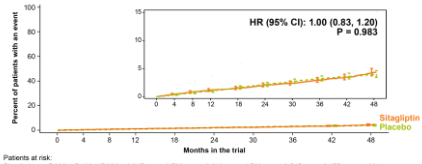


** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

TECOS

Hospitalization for Heart Failure*
ITT Analysis



Patients at risk:

Sitagliptin	7,332	7,189	7,036	6,917	6,780	6,619	4,728	3,515	2,175	1,324
Placebo	7,339	7,204	7,025	6,903	6,712	6,549	4,599	3,443	2,131	1,315

** Adjusted for history of heart failure at baseline*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

TECOS

DPP4s

Modest hypoglycemic effect

No overall CV benefit or harm

DPP4s should be avoided in pts with HF (or history of) but sitagliptin could be used if necessary

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

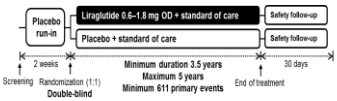
Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

June 13, 2016 | DOI: 10.1056/NEJMoa1603827

Comments open through June 20, 2016

LEADER

LEADER: Study design



Key inclusion criteria
- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure
  or
- Age ≥60 years and risk factors for CV disease

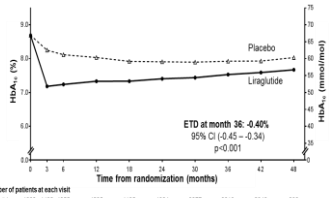
Key exclusion criteria
- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

LEADER

CV: cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; HbA_{1c}: glycated hemoglobin; MEN-2: multiple endocrine neoplasia type 2; MTC: medullary thyroid cancer; OAD: oral antidiabetic drug; OD: once daily; T2DM: type 2 diabetes mellitus.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SYO9, June 13 2016, New Orleans, LA, USA.

HbA_{1c}



Number of patients at each visit

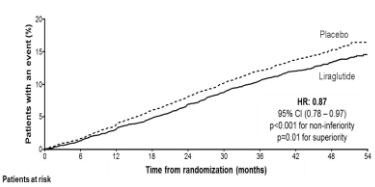
Liraglutide	4668	4402	4355	4296	4135	4034	3877	3810	2349	809
Placebo	4672	4413	4356	4235	4030	3905	3742	3640	2303	796

LEADER

Data are estimated mean values from randomization to month 48.
CI: confidence interval; ETD: estimated treatment difference; HbA_{1c}: glycated hemoglobin.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SYO9, June 13 2016, New Orleans, LA, USA.

Primary outcome
CV death, non-fatal myocardial infarction, or non-fatal stroke



Patients at risk

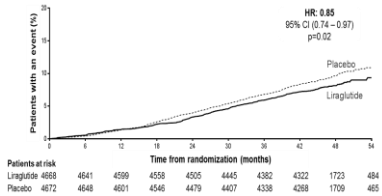
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

LEADER

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard rates with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SYO9, June 13 2016, New Orleans, LA, USA.

All-cause death

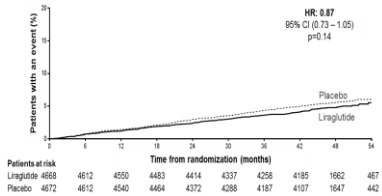


LEADER

The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 2-CT-SY29, June 10 2016, New Orleans, LA, USA.

Hospitalization for heart failure



LEADER

The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; HR: hazard ratio.

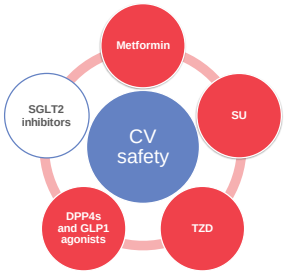
Presented at the American Diabetes Association 76th Scientific Sessions, Session 2-CT-SY29, June 10 2016, New Orleans, LA, USA.

Incretin mimetics - Liraglutide

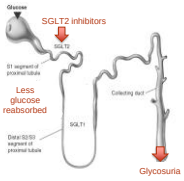
Modest hypoglycemic effect

CV benefit – MACE and ACM

Reasonable choice but injectable and not on PBS yet



Inhibition of Renal Glucose Reabsorption



- SGLT2 inhibitors are potent, selective inhibitors of SGLT2.
  - SGLT2
    - Expressed only in the kidney
    - Responsible for majority of renal glucose reabsorption
  - SGLT1
    - Expressed in bowel and kidney
    - Responsible for small portion of renal glucose reabsorption
    - Prominent role in intestinal glucose absorption
- Resulting in Urinary Glucose Excretion ~ 80-100 grams/day, thereby reducing plasma glucose.
- Mechanism of action is independent of pancreatic beta cell function and insulin.

Adapted from Bakris H. Diabetes Ther 2013;4:195-200.

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The Consequences of SGLT2 Inhibition

- ~80-100 g of glucose (~50% of glomerular filtered glucose) is excreted in the urine.[1,2]
- ~320-400 calories eliminated each day.[1]
  - ~ 2 cans of soft drink per day
- ~107 to 470 ml of additional urine is excreted each day.[3]
  - ~1 extra void per day

1.Bakris H. Diabetes Ther 2013;4:195-200. 2. DeFronzo RA et al. Diabetes Obes Metab. 2012 Jan;14(1):5-14. 3. Kim Y and Babu AR. Diabetes Metab Syndr Obes. 2012;5:15-27.

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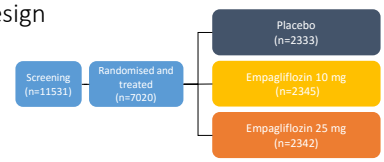
Trial design



- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

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Key inclusion and exclusion criteria

- 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
- Key exclusion criteria
  - eGFR <30 mL/min/1.73m^2 (MDRD)

BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease
*No glucose-lowering therapy for ≥12 weeks prior to randomisation or no change in dose for ≥12 weeks prior to randomisation or, in the case of insulin, unchanged by >10% compared to the dose at randomisation

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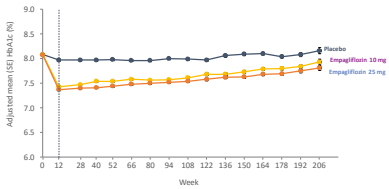
HbA1c



Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2054	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)

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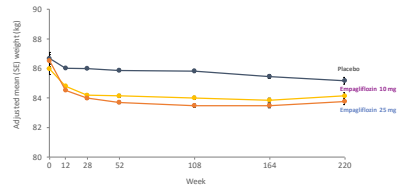
Weight



Placebo	2285	1915	2215	2138	1598	1239	425
Empagliflozin 10 mg	2290	1893	2228	2174	1673	1298	483
Empagliflozin 25 mg	2283	1891	2226	2178	1678	1335	489

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)

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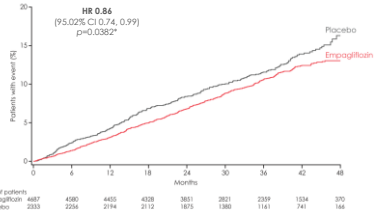
Primary outcome: 3-point MACE



No. of patients									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	144

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

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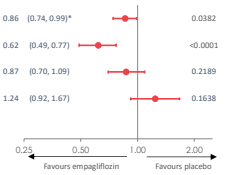
CV death, MI and stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	p-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



Cox regression analysis. MACE, Major Adverse Cardiovascular Event;
HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction

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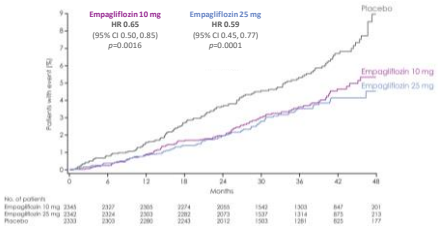
CV death



Cumulative incidence function. HR, hazard ratio

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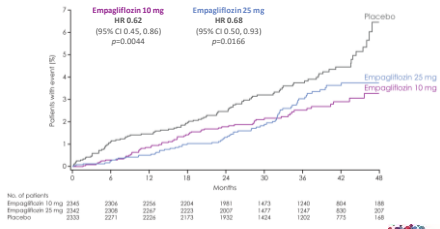
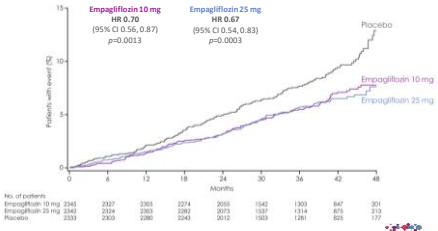
Hospitalisation for heart failure



Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

All-cause mortality



Kaplan-Meier estimate. HR, hazard ratio

EMPA-REG OUTCOME®

EMPA-REG OUTCOME®: Therapeutic considerations

- Empagliflozin, as used in this trial, for 3 years in 1,000 patients with type 2 diabetes at high CV risk:
  - 25 lives saved (82 vs 57 deaths)
    - 22 fewer CV deaths (59 vs 37)
  - 14 fewer hospitalisations for heart failure (42 vs 28)
  - **53 additional genital infections (22 vs 75)**

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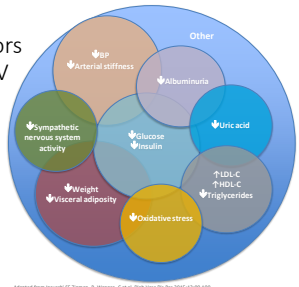
Empagliflozin modulates several factors related to CV risk



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

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Mechanism of benefit?

- **Excess events in the placebo group –**
  - difference in background therapy early in the study?
- **Cumulative effect of reduction in BP, weight and HBA1c with increase in HDL?**
  - BUT benefit was early
- **Antiatherosclerotic effect –**
  - possibly for ACM as benefit after 2 yrs
- **Antiarrythmic effect –**
- BUT no SGLT2 recetors in heart or blood vessels
- **Play of chance?**
  - BUT everything except NF stroke went in the right direction?

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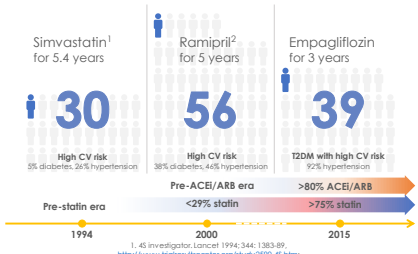
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk



1. 4S investigator. Lancet 1994; 344: 1383-89.
http://www.trialresultscenter.org/study/2590-4S.htm;
2. HOPE investigator N Engl J Med 2000;342:145-53.
http://www.trialresultscenter.org/study/2606-

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SGLT2 (empaglifozin)

Modest hypoglycemic effect

Decrease in CV and All Cause death

Decrease in Heart Failure

Effects independent of glycemic control

Increased risk of mycotic infection and UTI

What effect will these results have on clinical practice guidelines?

EASD European Association for the Study of Diabetes
American Diabetes Association
Canadian Diabetes Association
International Diabetes Federation
AACE
ENDOCRINE SOCIETY
AMERICAN COLLEGE of CARDIOLOGY
American Heart Association
EUROPEAN SOCIETY OF CARDIOLOGY
ESH
Wonca
AMERICAN ACADEMY OF FAMILY PHYSICIANS
STRONG MEDICINE FOR AMERICA

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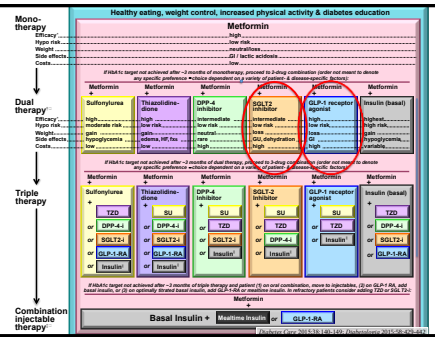


Recent guideline updates following the EMPA-REG OUTCOME® results

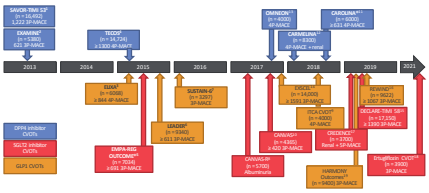
Cardiology guidelines	Diabetes guidelines
European Society of Cardiology 2016 guidelines on cardiovascular disease prevention in clinical practice[1] 'Empagliflozin demonstrated substantial reductions in CVD death (by 38%) and all-cause mortality (by 32%), as well as in hospitalisation for HF (by 35%)'	American Diabetes Association standards of medical care in diabetes 2017[1] 'Empagliflozin is the first of the recently approved diabetes treatments associated with lower risk of cardiovascular disease.'
European Society of Cardiology 2016 guidelines for diagnosis and treatment of acute and chronic heart failure[2] 'Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.' JARDIANCE® is not indicated for heart failure.[1]	Canadian Diabetes Association pharmacologic management of type 2 diabetes: 2016 interim update[4] 'Empagliflozin should be utilised in patients with T2D and clinical CVD already taking antihyperglycaemic therapy.'

"Results obtained with empagliflozin cannot be considered as a proof of a class effect"[2]

The Heart of Diabetes

Where to from Here?

Overview of CVOTs of glucose-lowering drugs



Timings represent estimated completion dates as per ClinicalTrials.gov.
Adapted from Johansen. World J Diabetes 2015;6:1092–96.(references 1–19 expanded in slide notes)

Future Studies with SGLT2s

Empaglifozin (BI/Lilly) and Dapaglifozin (AZ) are both starting studies in NON DIABETIC patients with Heart Failure

(reduced and preserved systolic function)

Comparative Efficacy and Safety of Oral Hypoglycemic Drugs (not head to head comparison)

	Decrease glucose	Hypos	Weight	CV risk	All Cause Mortality	Heart Failure
Metformin	↓	↔	↔	↔	↔	↔
SUs	↓	↑	↑	↔	↔	↔
Insulin	↓↓	↑↑	↑↑	↔	↔	↔
DPP4s	↓	↔	↔	↔	↔	↑
Incretins	↓	↔	↓	↓	↓	↔
SGLT2s	↓	↔	↓	↓	↓	↓