Clinical trials update

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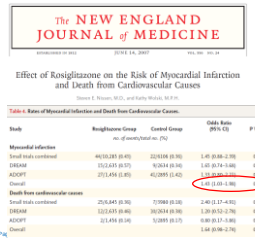
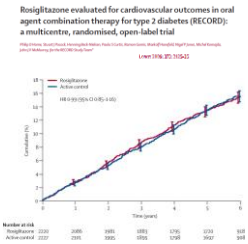
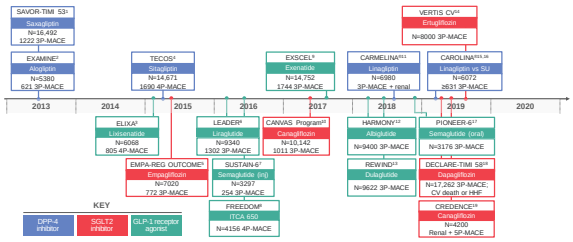
CV safety of hypoglycaemic agents


The NEW ENGLAND JOURNAL of MEDICINE

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


Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial

Timeline of CVOT of glucose-lowering agents

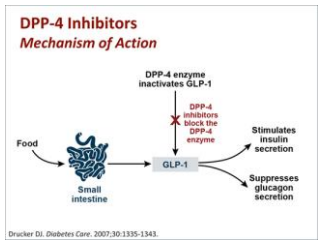


3P-MACE, 3-point major adverse CV events; 4P-MACE, 4-point major adverse CV events; 5P-MACE, 5-point major adverse CV events; CV, cardiovascular; CVOT, CV outcomes trial; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HHF, hospitalisation for heart failure; SGLT2, sodium-glucose co-transporter-2; SU, sulphonylurea
Trial disclosure dates for non-published trials from clinicaltrials.gov; Adapted from Johansen OE. World J Diabetes 2015;6:1092

Important points about CVOTs

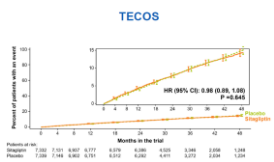
- These are now mandated by the FDA for registration of diabetes therapeutics
- They are primarily designed to asses CV safety of therapeutics
- They are designed for glucose equivalence so we can assess the effects of the drug, not the glucose levels
- Study design is important and they are not all the same

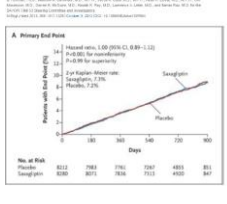
DPP 4 inhibitors



Drucker DJ. *Diabetes Care*. 2007;30:1335-1343.

DPP4 inhibitors and CV safety




Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

CARMELINA (linagliptin)

Time to first occurrence of 3P-MACE

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

Design and baseline characteristics of the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA®)

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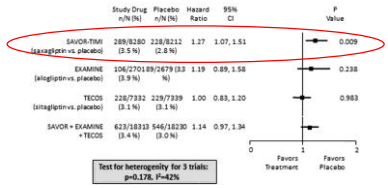
Heart failure signal?

SAVOR-TIMI 53, EXAMINE, and TECOS: Hospitalization for Heart Failure



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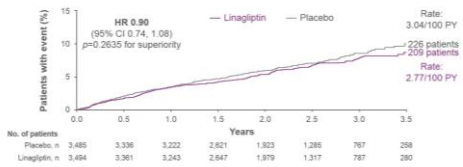
Time to first occurrence of adjudicated confirmed hospitalization for heart failure



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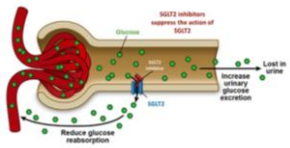
SGLT 2 inhibitors



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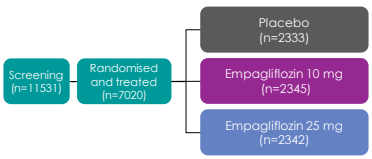
EMPA-REG



Study medication was given in addition to standard of care

Treatment assignment double masked

The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

EMPA-REG OUTCOME®

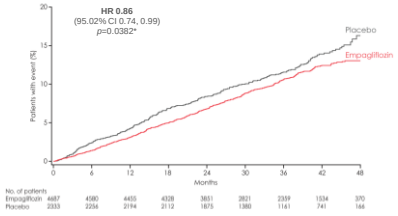
Key inclusion and exclusion criteria

- Key inclusion criteria
  - Adults with type 2 diabetes
  - BMI ≤45 kg/m²
  - 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/1.73m² (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

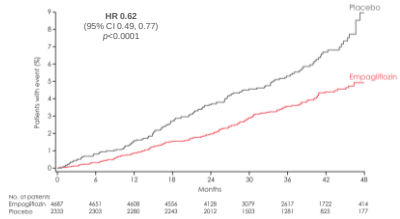
EMPA-REG OUTCOME®

Primary outcome: 3-point MACE



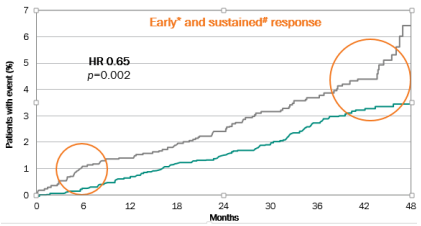
Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

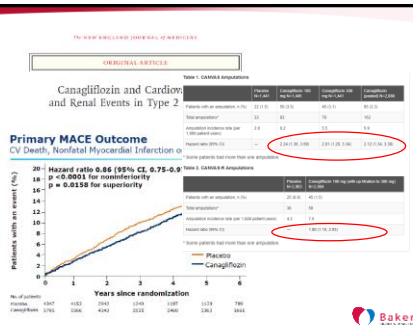
CV death



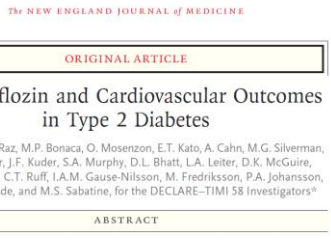
Cumulative incidence function. HR, hazard ratio

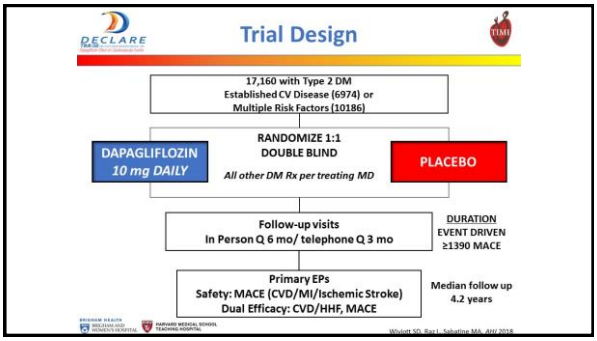
Hospitalisation for heart failure





DECLARE trial





Enrollment Criteria

Diagnosis of T2DM, HbA1c 6.5-12%, CrCl ≥60 ml/min

AND

Established ASCVD (Secondary prevention)

- Ischemic heart disease
- Cerebrovascular disease
- Peripheral Artery Disease

Or

Multiple risk factors for ASCVD (Primary prevention)

Men ≥ 55 yrs and women ≥ 60 yrs with at least one additional risk factor:

- Dyslipidemia
- Hypertension
- Current Tobacco use

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

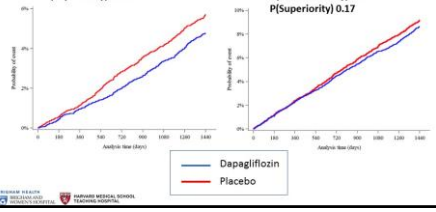
Primary Endpoints

CVD/HHF

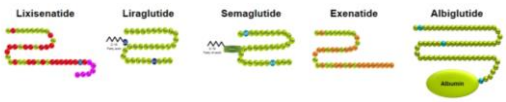
4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005

MACE

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



GLP 1 agonists



Drug	Lixisenatide od	Liraglutide od	Semaglutide qw	Exenatide XR qw	Albiglutide qw
Structure (sequence homology)	Exendin-4 (50%)	GLP-1 (97%)	GLP-1 (94%)	Exendin-4 (53%)	GLP-1 (97%)
In vivo EC_{10} nmol/kg)*	0.02	0.6	NA	0.01	1.4
t½	2–4 h	11.6–13 h	7 days	2 weeks	~ 5 days
Dose	20 µg	0.6–1.8 mg	0.5, 1 mg	2 mg	30, 50 mg

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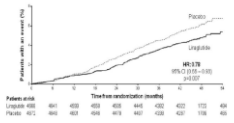
GLP 1 agonists

LEADER

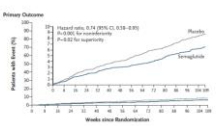
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

CV death



ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes



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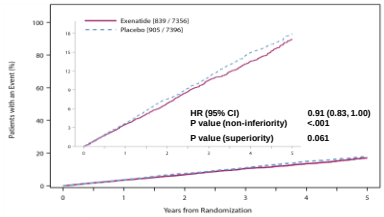
EXSCEL trial - MACE



No at Risk

Exenatide	7356	7101	6893	6580	5912	4475	3595	3053	2281	1417	727
Placebo	7396	7120	6897	6565	5908	4468	3565	2961	2209	1366	687

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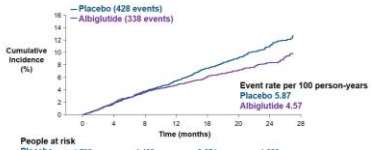
HARMONY – albiglutide

Primary Outcome:
Time to CV Death, MI or Stroke (MACE)



People at risk

Placebo	4,732	4,460	3,074	1,030
Albiglutide	4,731	4,503	3,148	1,064

Harmony Outcomes

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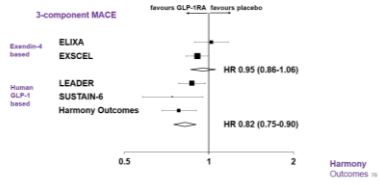
GLP 1 summary

Findings in Context with Other GLP-1R Agonist CV Outcome Trials



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Dulaglutide

Trulicity® (dulaglutide) demonstrates superiority in reduction of cardiovascular events for broad range of people with type 2 diabetes

Only 31 percent of REWIND trial participants had established CV disease

INDIANAPOLIS, November 5, 2018 – Trulicity® (dulaglutide) significantly reduced major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (heart attack) or non-fatal stroke, meeting the primary efficacy objective in the precedent-setting REWIND trial. Eli Lilly and Company's (NYSE: LLY) once-weekly Trulicity is the first type 2 diabetes medicine to demonstrate superiority in the reduction of MACE events in a clinical trial that included a majority of participants who did not have established CV disease.

The study included a majority of patients without established CV disease at baseline, a first for the GLP-1 receptor agonist class. REWIND assessed the risk of MACE in adults with type 2 diabetes with a wide range of CV risk. The study compared the effect of once-weekly Trulicity 1.5 mg to

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Mechanisms ?

- SGLT 2 inhibitors
  - Weight loss
  - BP lowering
  - Diuresis
  - Ketone formation
  - Renal protection
- GLP 1 agonists
  - Direct cardiac effects
  - Weight loss
  - Reduction in insulin resistance

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Other classes of glucose lowering agents

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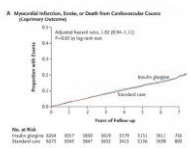
Insulin

ORIGIN trial



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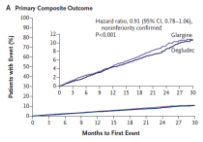
ORIGINAL ARTICLE

Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes



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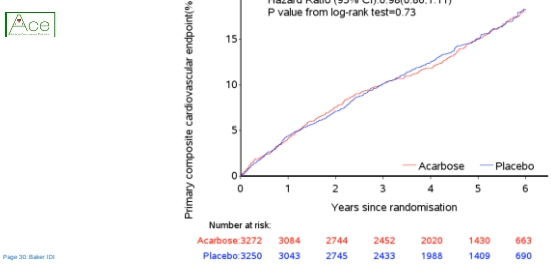
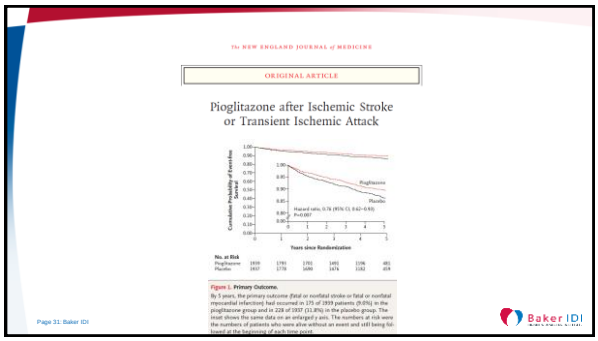
Acarbose





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ORIGINAL ARTICLE

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

Figure 1. Primary Outcome.

By 5 years, the primary outcome (fatal or nonfatal stroke or fatal or nonfatal myocardial infarction) had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group. The inset shows the same data on an enlarged y axis. The numbers at risk were the numbers of patients who were alive without an event and still being followed at the beginning of each time point.

Future?

- CAROLINA – potentially answering the DPP 4 inhibitor vs. sulphonylurea question
- VERTIS (ertugliflozin CVOT)
- PIONEER (oral semaglutide CVOT)
- SGLT 2 trials in heart failure, renal impairment
- Combined GLP 1 /GIP /glucagon dual, or triple agonists

Conclusions

- Large outcome trials have given us important perspectives in therapeutics, safety, efficacy and adverse effects
- Most glucose lowering agents have established CV safety
- SGLT 2 inhibitors and GLP 1 agonists appear to have CV benefits over and above glucose lowering effects through mechanisms that are not established
- These important studies have shaped the current guidelines and shifted the focus away from just glucose lowering to cardiovascular protection