



BRIGHAM AND
WOMEN'S HOSPITAL

| Heart & Vascular Center |

Latest Clinical Trial Evidence for Reducing CVD Risk in Diabetes: EMPA- REG, LEADER, and SUSTAIN 6

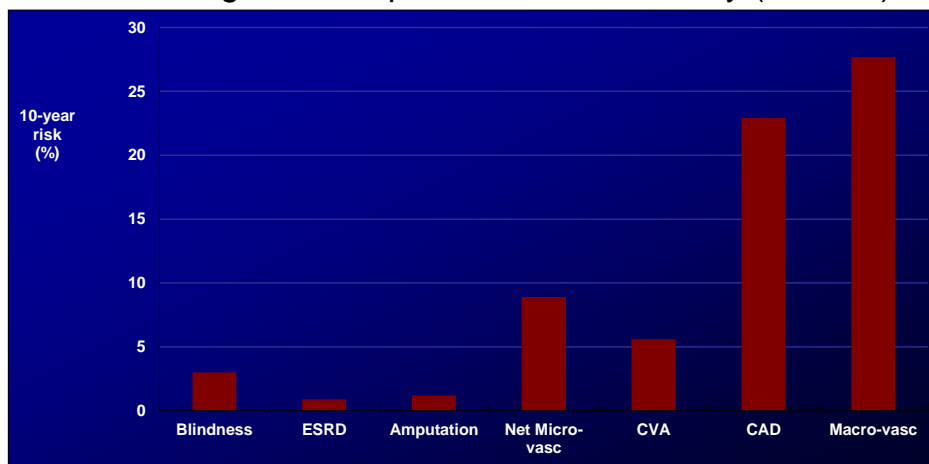
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Division of Cardiology



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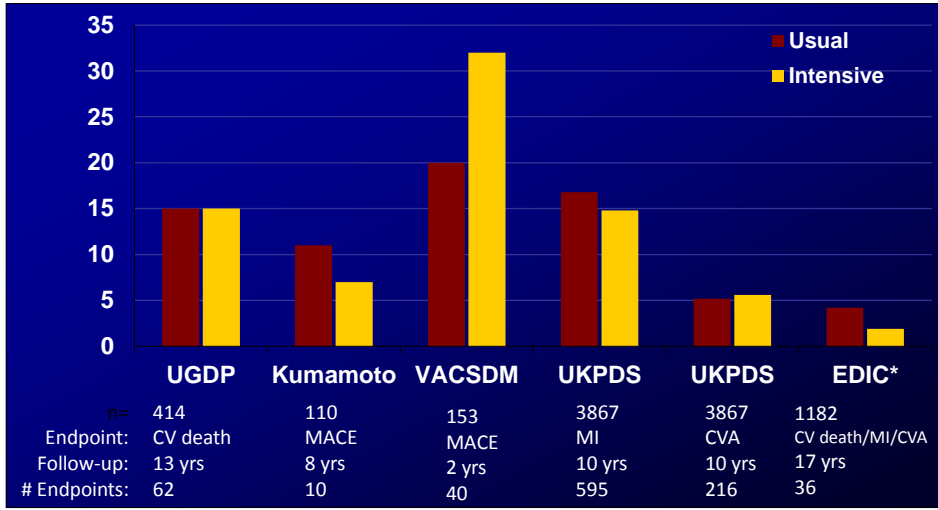
Diabetes Mellitus: A Cardiovascular Disease

United Kingdom Prospective Diabetes Study (n=3867)



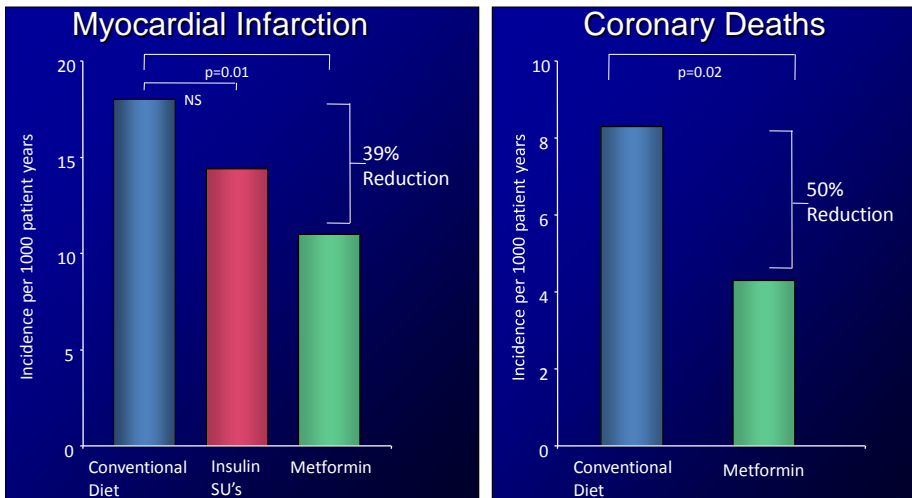
UKPDS Investigators. Lancet 1998; 352: 837

Impact of Glycemic Control on Cardiovascular Outcomes



Diabetes 1970;19 (Suppl 2):747; Diabetes Care 2000; 23 (Suppl 2):B21; Arch Intern Med 1997; 157:181; Lancet 1998; 352: 837; NEJM 2005; 353: 2643

UKPDS Metformin Sub-study: CHD Events

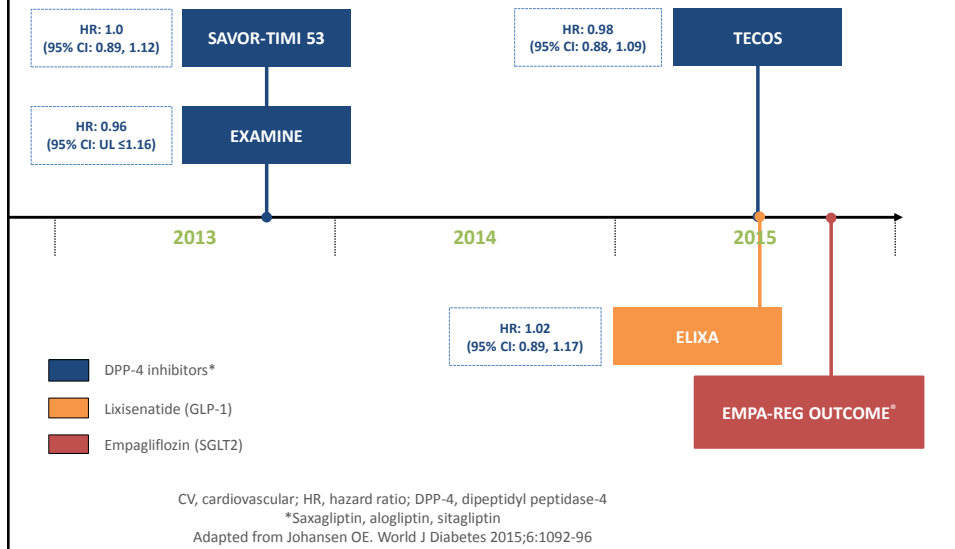


	Conventional Diet	Insulin SU's	Metformin
n=	411	951	342
#Events	73	139	39

	Conventional Diet	Metformin
n=	411	342
#Events	36	16

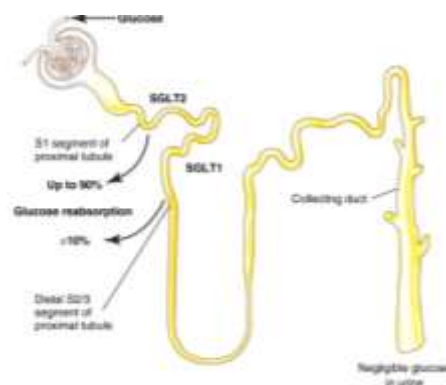
UKPDS 34, Lancet 352: 854, 1998

Recent trials of newer glucose-lowering agents have been neutral on the primary CV outcome



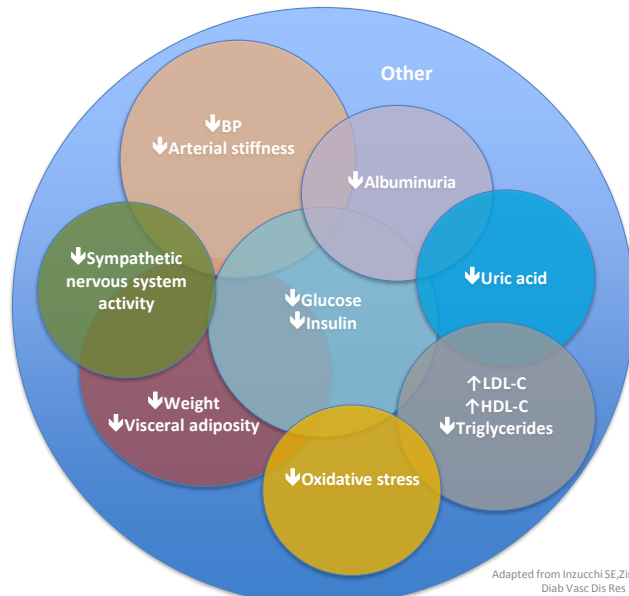
Empagliflozin

- Empagliflozin is a highly selective inhibitor of the sodium glucose cotransporter 2 (SGLT2) in the kidney
- Glucose reduction occurs by reducing renal glucose reabsorption (90%) and thus increasing urinary glucose excretion
- In patients with type 2 diabetes, empagliflozin leads to:
 - Significant reductions in HbA1c
 - Weight loss
 - Reductions in blood pressure without increases in heart rate



Liakos A et al. Diabetes Obes Metab 2014;16:984-93. Bailey, CJ Volume 32, Issue 2, 2011, 63-71

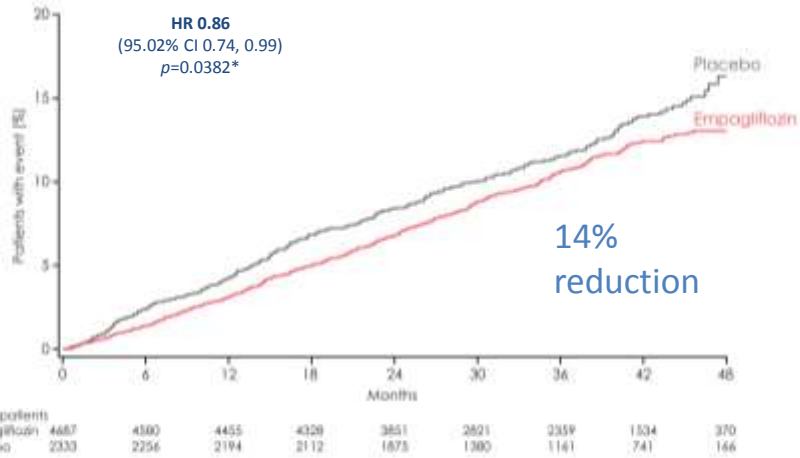
Empagliflozin modulates several factors related to CV risk



EMPA-REG

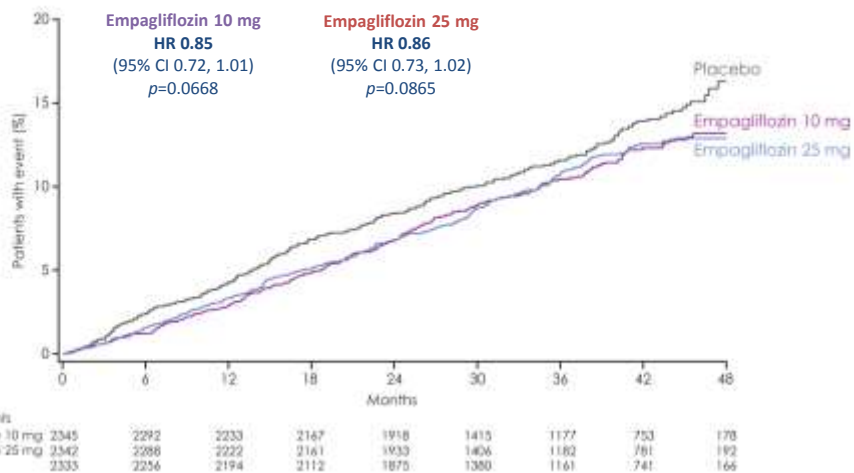
- Randomized, double-blind, placebo-controlled CV outcomes trial
- High Risk CV risk population
 - All with known cardiovascular disease
- Two doses of empagliflozin (10 mg and 25 mg) studied
- Endpoint:
 - Composite of death from cardiovascular causes, nonfatal myocardial infarction, or non fatal stroke.

Primary outcome: Death from CVD, Non fatal MI, Non fatal Stroke



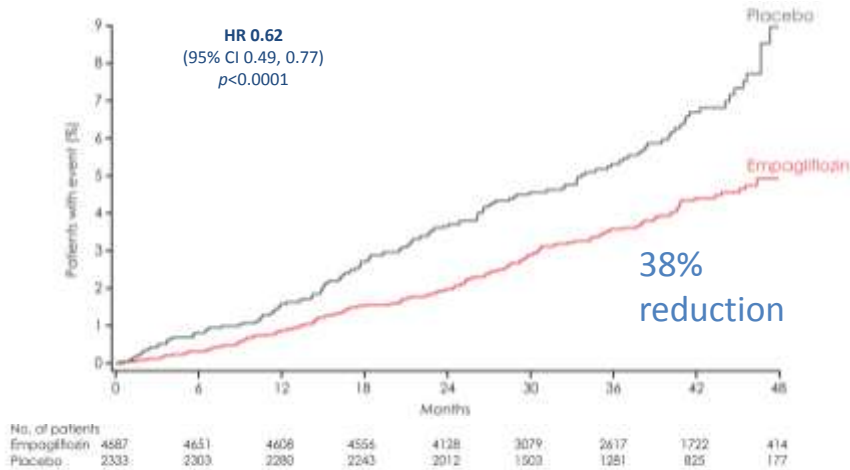
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Outcomes



10

CV death

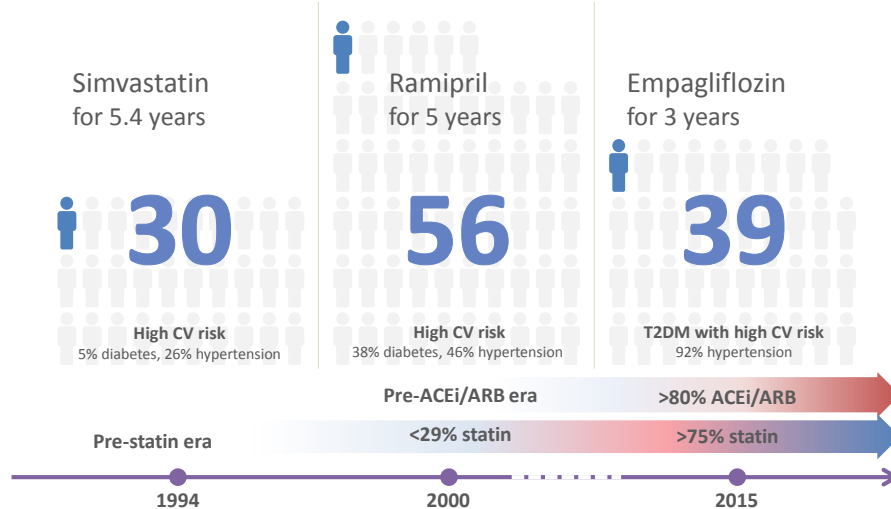


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EMPA-REG

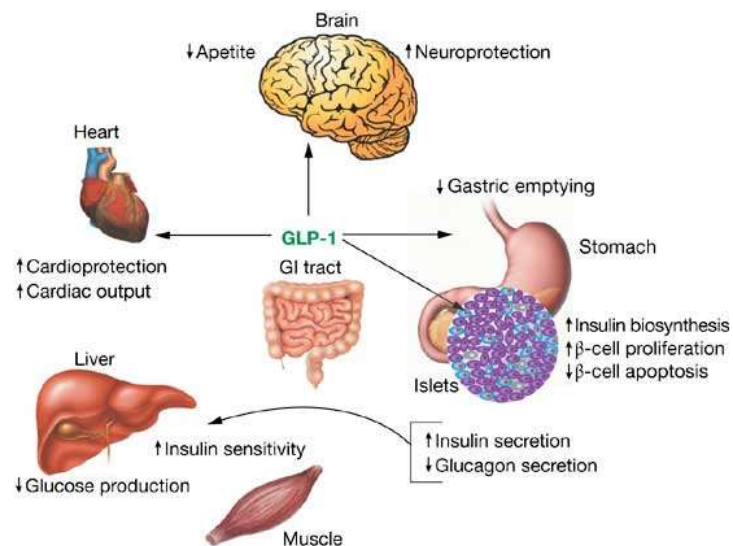
- 14% reduction in MACE
- 38% reduction in CV Death
- 32% reduction in all-cause mortality
- 35% reduction in hospitalizations for heart failure
- Small reductions in HgA1c, weight, blood pressure.
- Small increases in HDL and LDL and genital infections

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



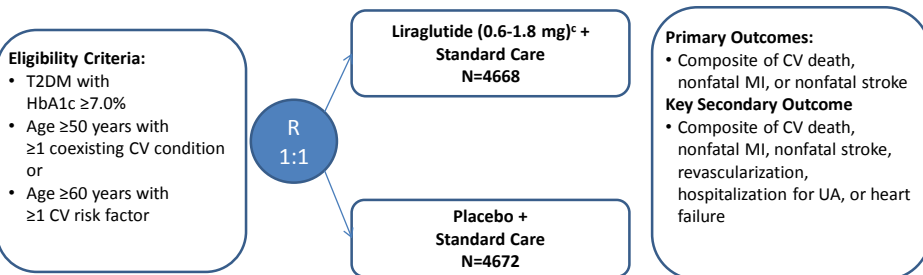
1. 4S investigator. Lancet 1994; 344: 1383-89, <http://www.trialresultscenter.org/study2590-4S.htm>;
2. HOPE investigator N Engl J Med 2000;342:145-53, <http://www.trialresultscenter.org/study2606-HOPE.htm>

Actions of glucagon-like peptide 1 on multiple target tissues



Drucker DJ *Nat Clin Pract Endocrinol Metabol* 1: 22-31

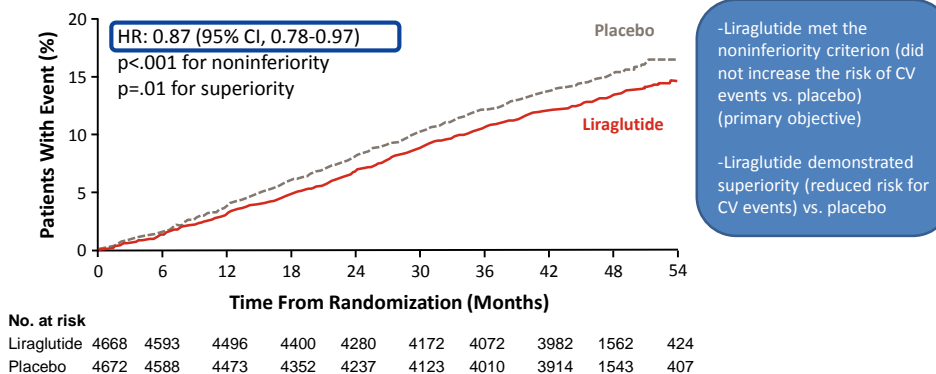
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER)



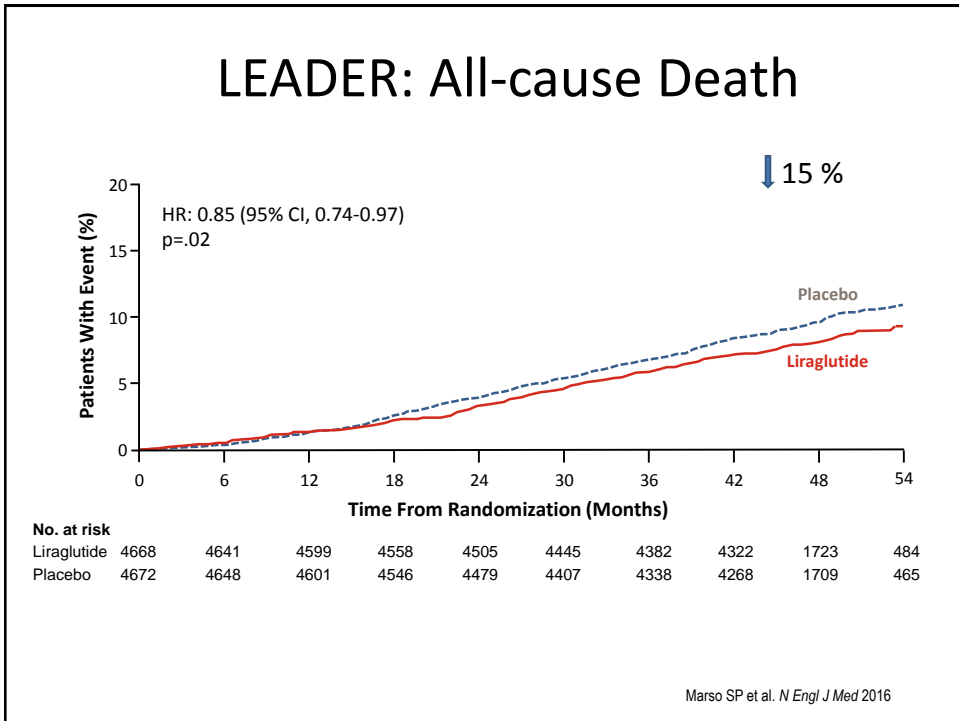
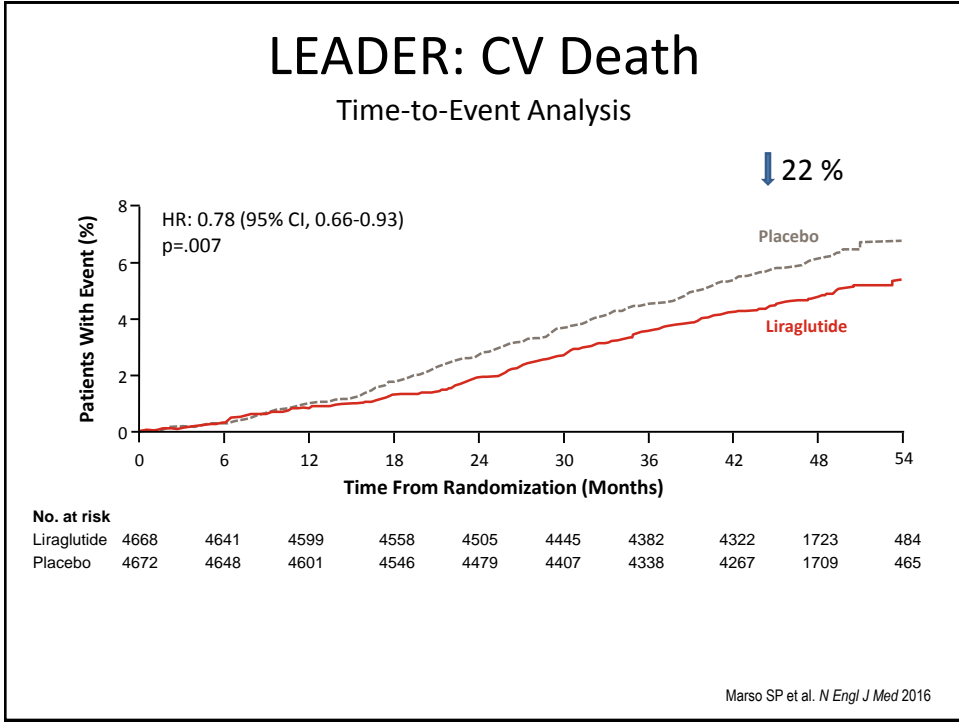
- **Study design:** International, randomized, placebo-controlled study
- **Primary objective:** To evaluate the effect of liraglutide compared to placebo on the incidence of CV events in adults with type 2 diabetes

Marso SP et al. *Am Heart J* 2013;166:823-30.e5

LEADER: Primary Outcome CV Death, Nonfatal MI, or Nonfatal Stroke



Marso SP et al. *N Engl J Med* 2016

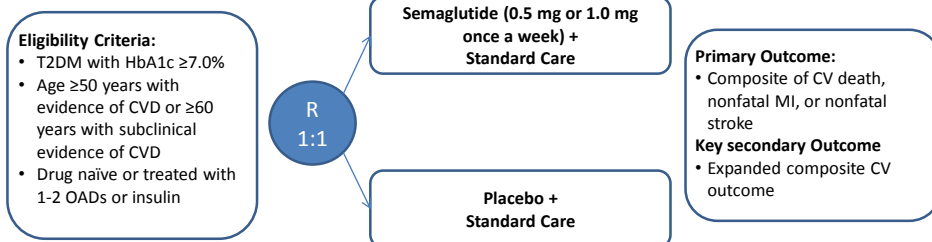


LEADER: Summary

- Liraglutide added to standard of care demonstrated noninferiority, as well as superiority, vs. placebo + standard of care for the primary endpoint
- 13% reduction in MACE (CV death, non fatal MI, non fatal stroke)
- 22% reduction in CV death
- 15% reduction in all-cause mortality

Marso SP et al. *N Engl J Med* 2016

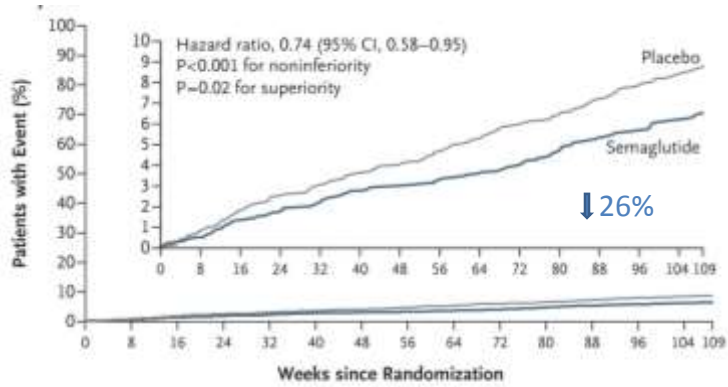
SUSTAIN 6: Study Design and Objectives



- **Study design:** Multicenter, randomized, placebo-controlled, double-blind study
- **Primary objective:** To evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes

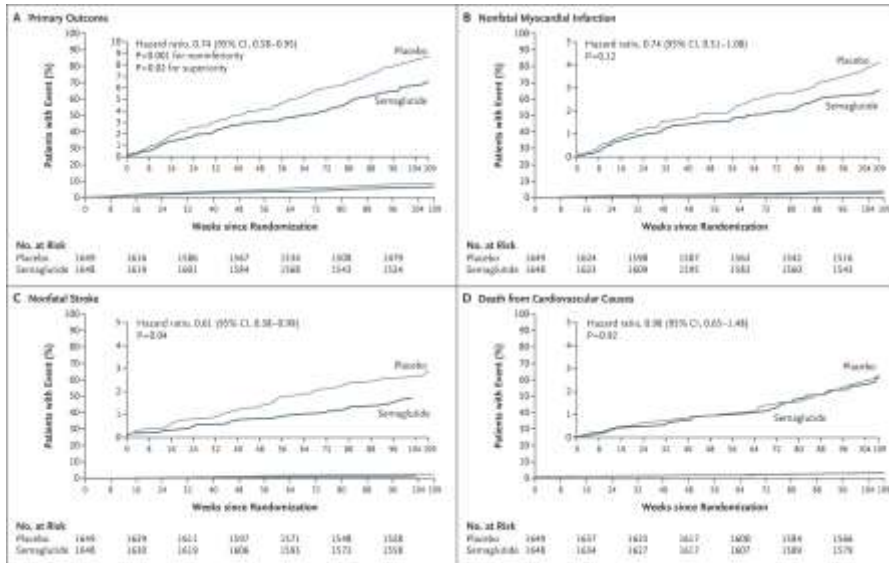
<https://clinicaltrials.gov/ct2/show/NCT01720446>

SUSTAIN-6: CV Death, Non fatal MI, Non fatal Stroke



No. at Risk							
Placebo	1649	1616	1586	1567	1534	1508	1479
Semaqlutide	1648	1619	1601	1584	1568	1543	1524

Marso SP N Engl J Med 2016;375:1834-44



Marso SP N Engl J Med 2016;375:1834-44

SUSTAIN 6:

- In patients with type 2 diabetes who were at high cardiovascular risk, rate of cardiovascular death, nonfatal MI, or non fatal stroke significantly lower among patients receiving semaglutide

Conclusions

- Cardiovascular morbidity and mortality remain the highest risk in patients with diabetes
- New agents including SGLT-2 inhibitors and GLP-1 analogues have shown reductions in cardiovascular mortality and all cause mortality
- The treatment of our patients with diabetes is entering a new era