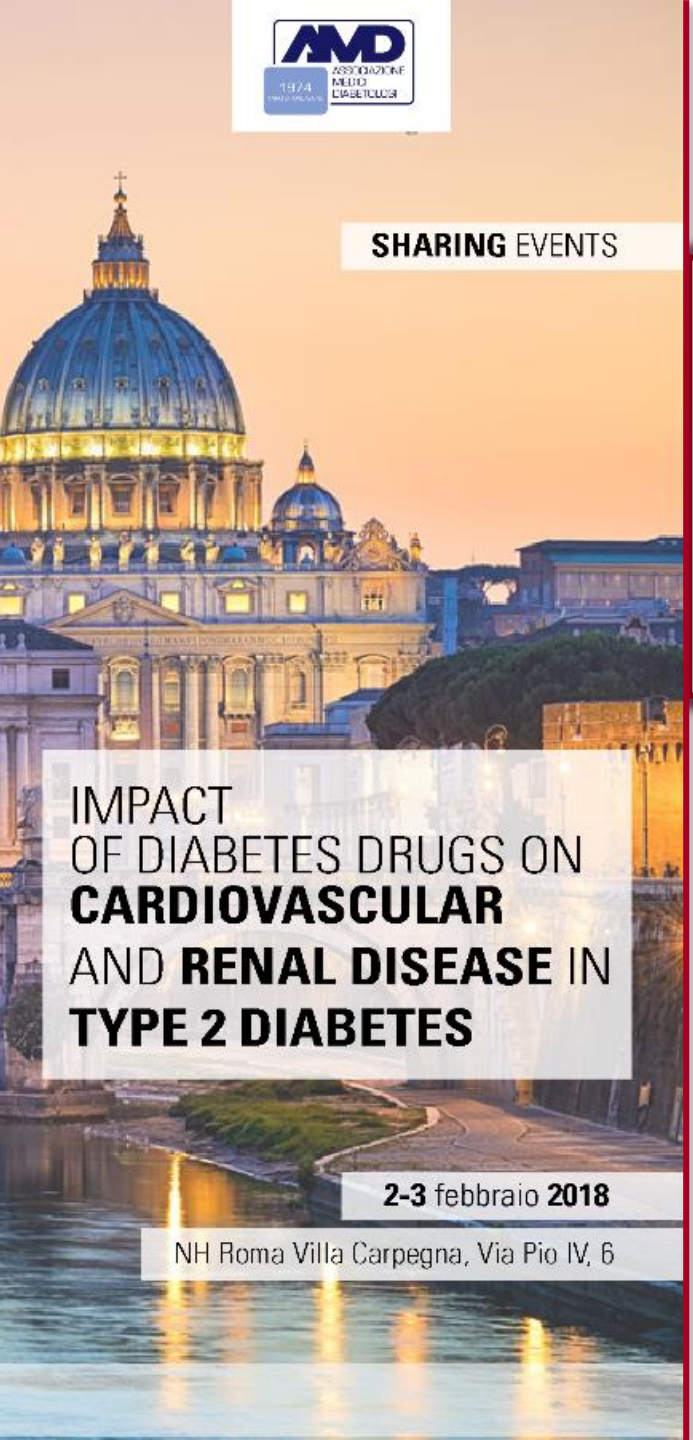

Type 2 diabetes: where are we now and where are we going ?

Professor Paolo Pozzilli

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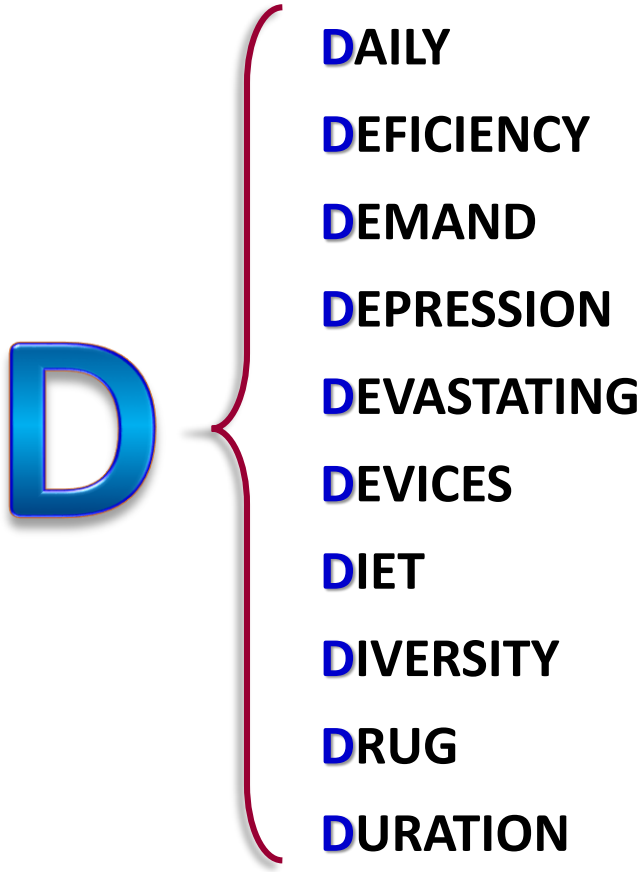
Centre of Immunobiology, Barts & The London School of Medicine, Queen Mary, University of London, UK

UNIVERSITA' CAMPUS BIO-MEDICO DI ROMA

Barts and The London
Queen Mary's School of Medicine and Dentistry

Diabetes, the disease of the 10 Ds



Maddaloni E., Pozzilli P., Endocrine, 2017

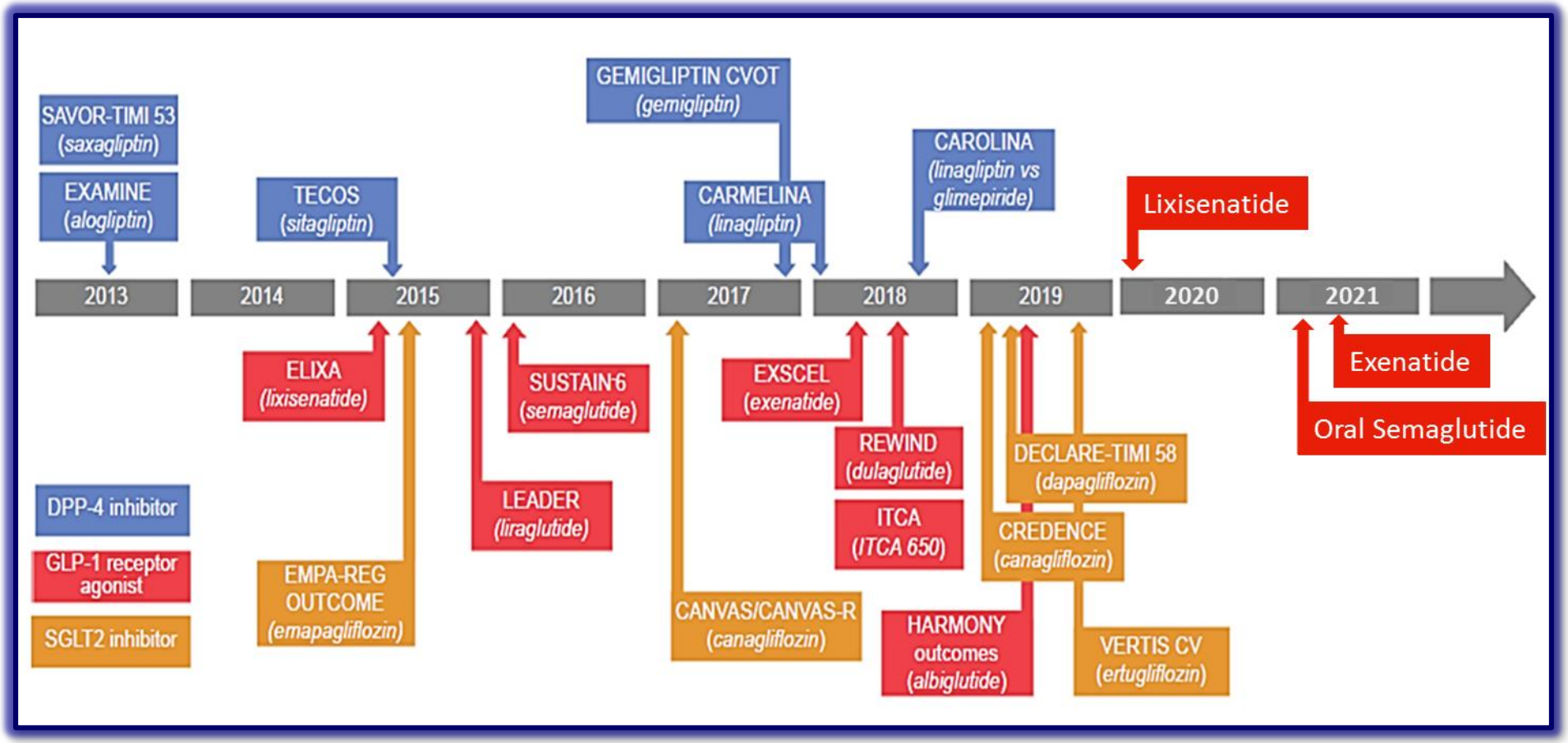
Type 2 diabetes and cardiovascular disease risk

Diabetes is a chronic disease associated with long-term vascular complications

Type 2 diabetes is a multisystem disorder that is also independently associated with a nearly twofold excess risk for a broad range of adverse cardiovascular outcomes including coronary heart disease (CHD), stroke, and cardiovascular death.

Effective strategies to mitigate cardiovascular risk and prevent or reduce the occurrence of microvascular complications are the cornerstone of treatment for patients with diabetes.

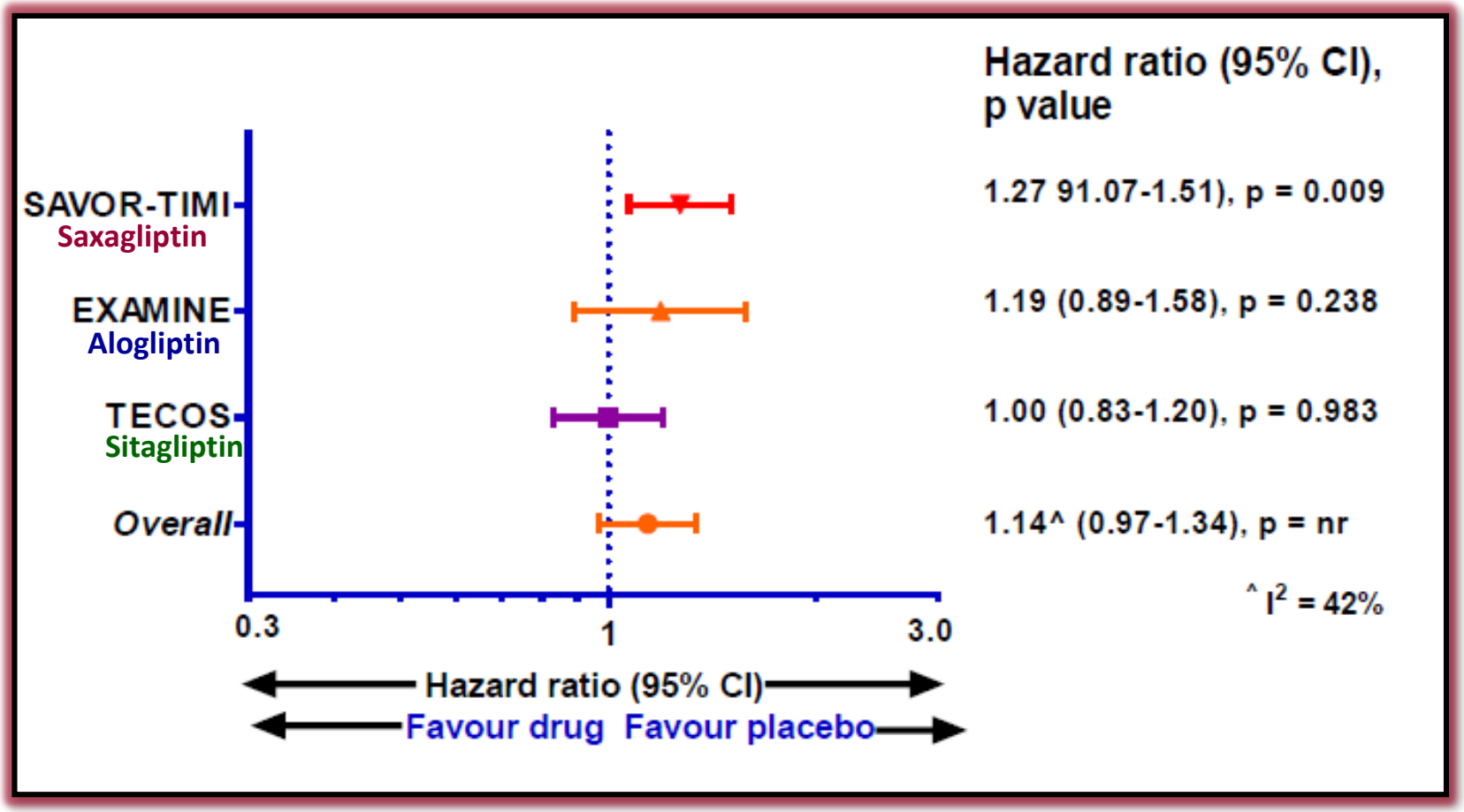
Completed and ongoing cardiovascular outcome trials in type 2 diabetes



Modified from: Schernthaner G. et al., Therapeutics and Clinical Risk Management 2017

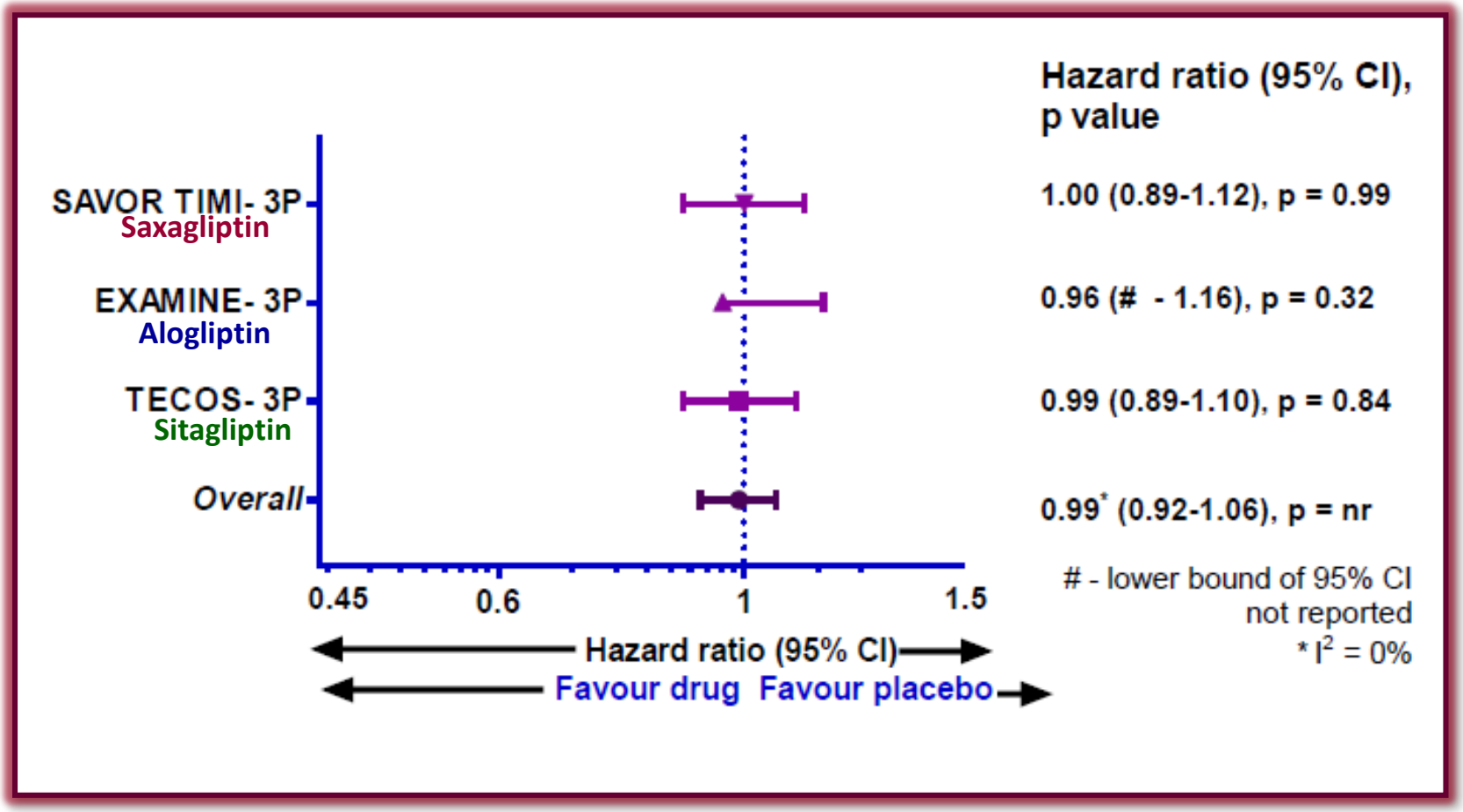
DPP-4 inhibitors and GLP-1 analogues

Heart failure in DPP-4Is CV outcome trials and meta-analysis



Singh AK et al., Expert Review of Clinical Pharmacology 2017

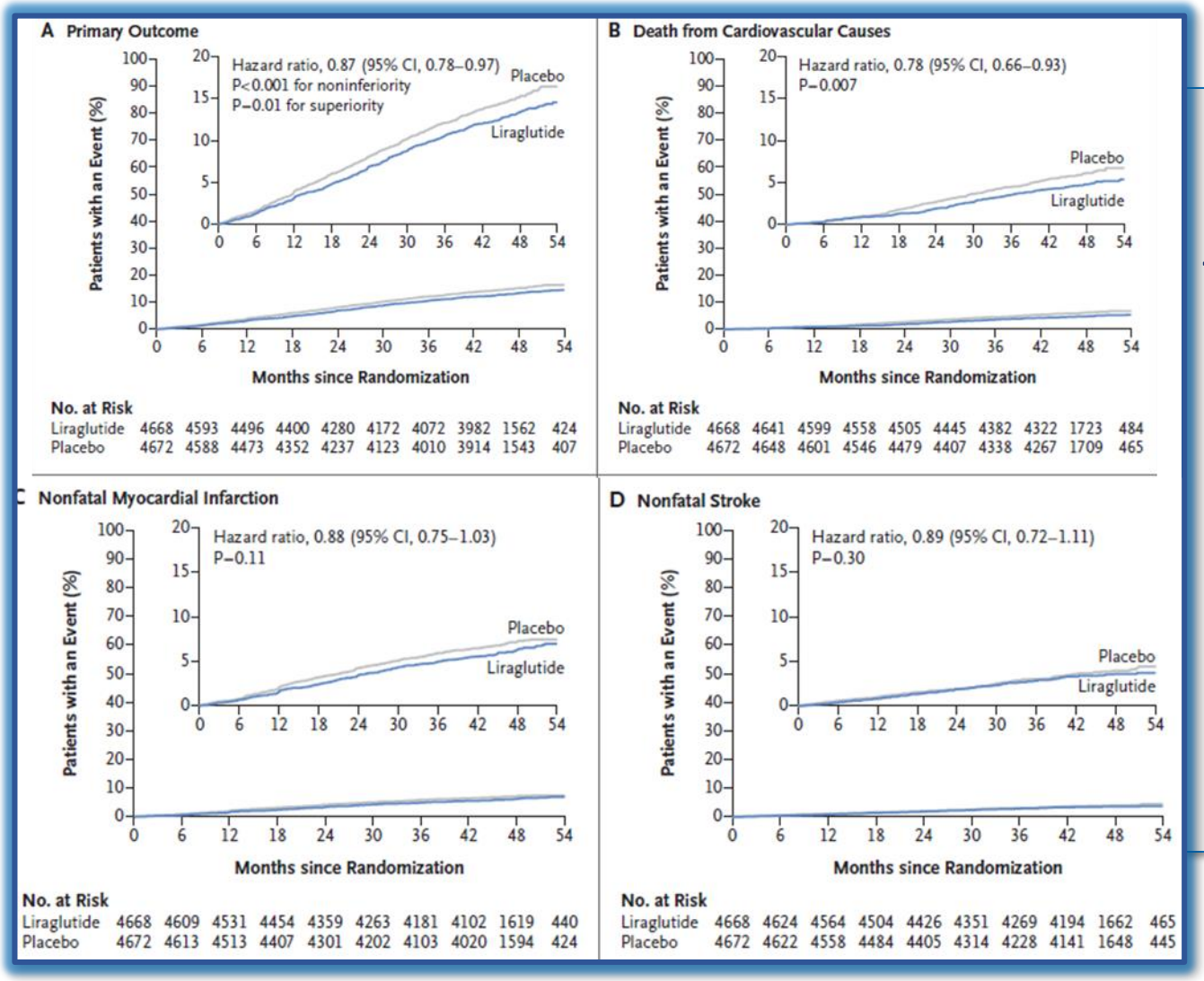
3-P MACE in DPP-4Is CV outcome trials and meta-analysis



Singh AK et al., Expert Review of Clinical Pharmacology 2017

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

the LEADER Trial



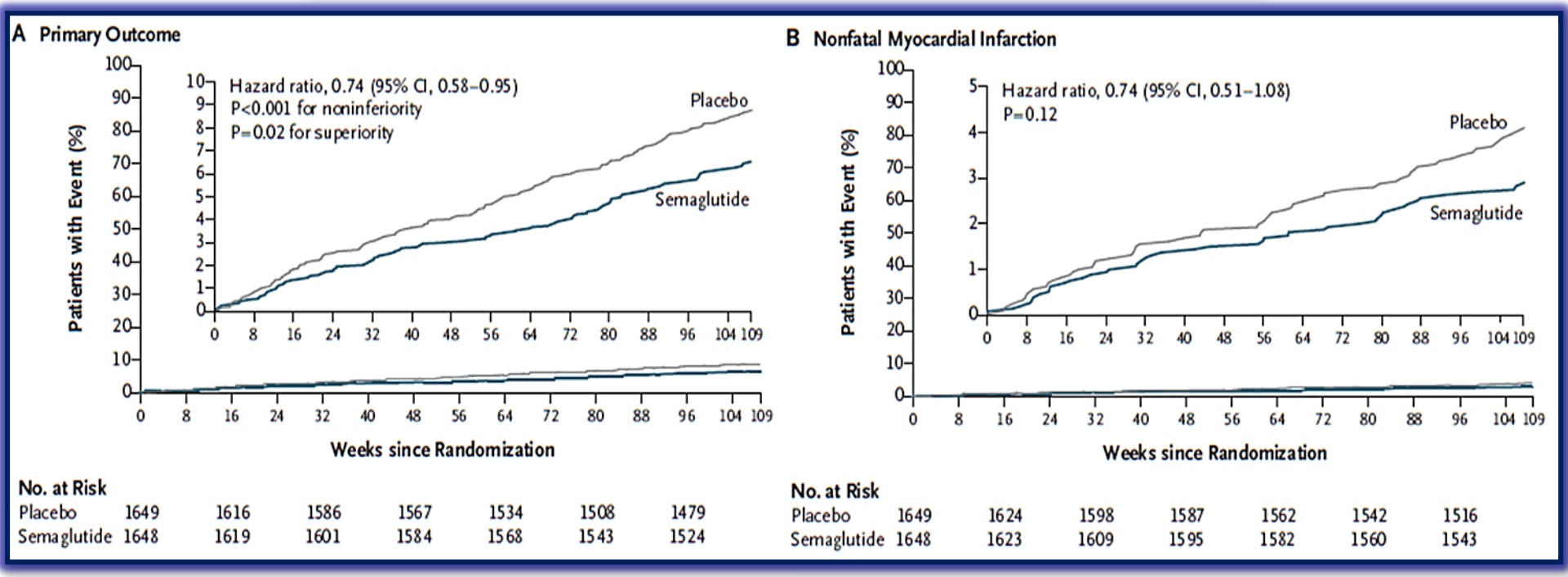
In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, non fatal myocardial infarction, or non fatal stroke among patients with type 2 diabetes was lower with liraglutide than with placebo.

Marso SP. et al., NEJM, 2016

The NEW ENGLAND JOURNAL of MEDICINE

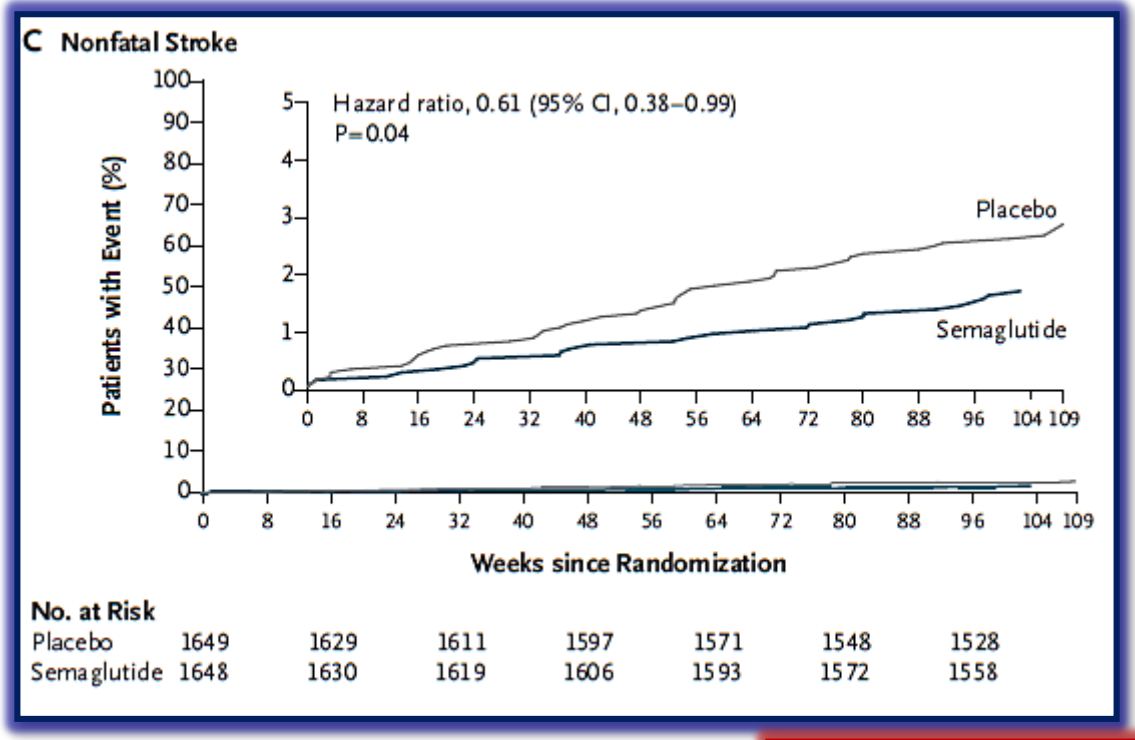
ORIGINAL ARTICLE

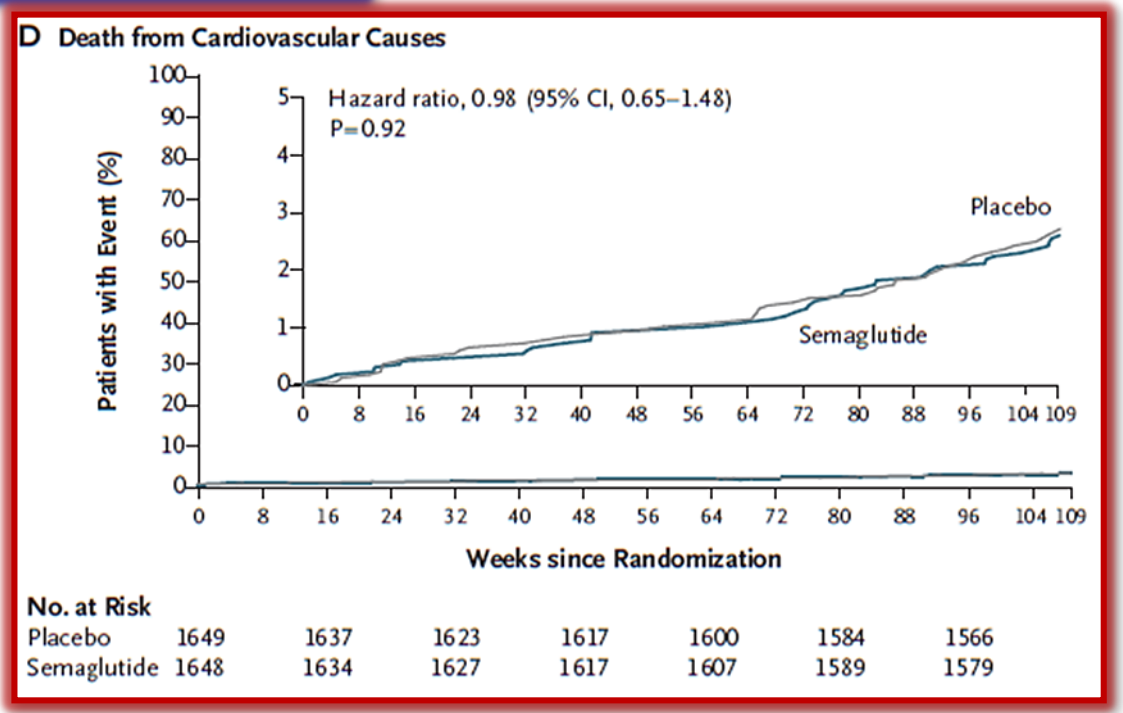
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes



In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, non fatal myocardial infarction, or non fatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the non inferiority of semaglutide.

Marso SP et al., N Engl J Med 2016



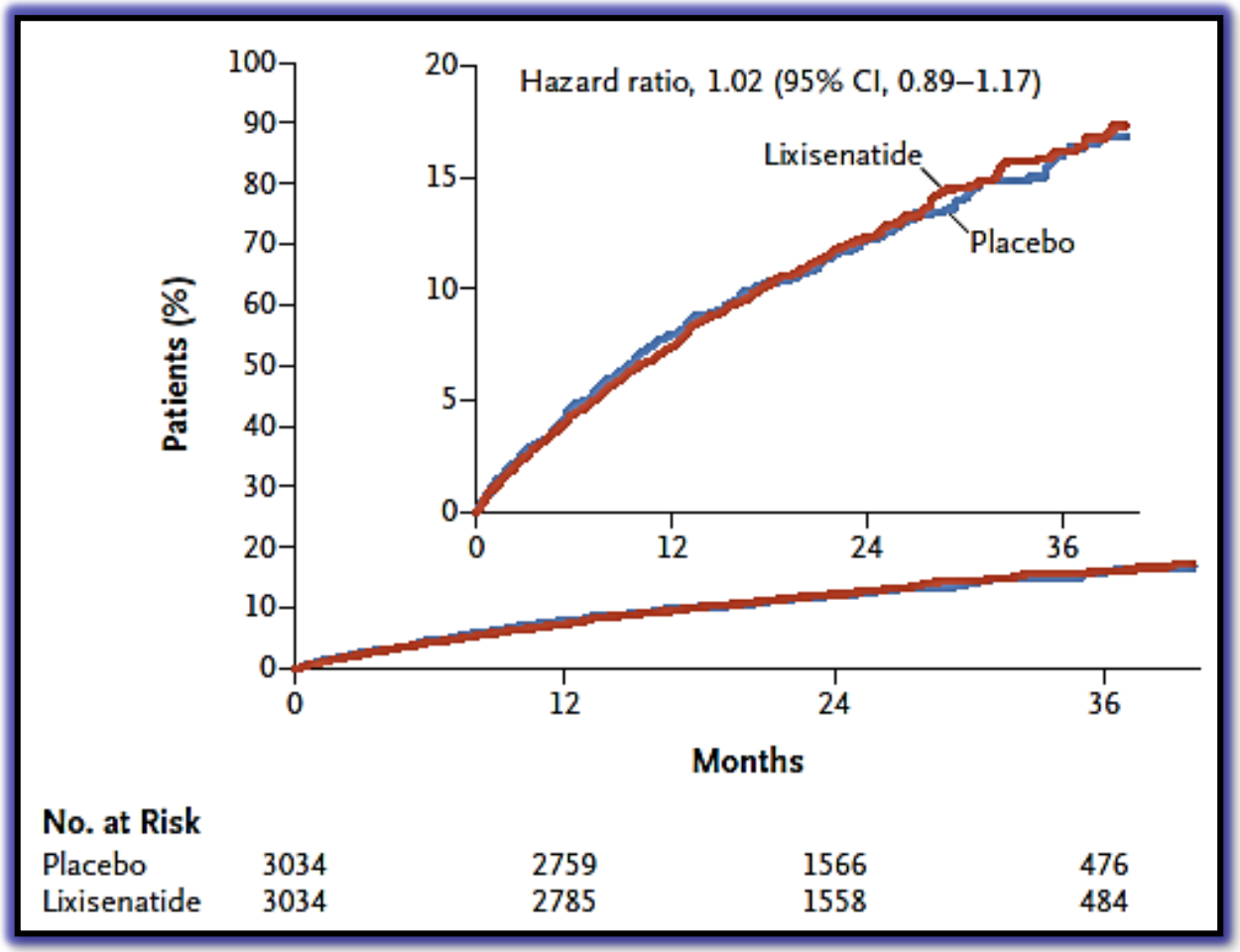


Marso SP et al., N Engl J Med 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

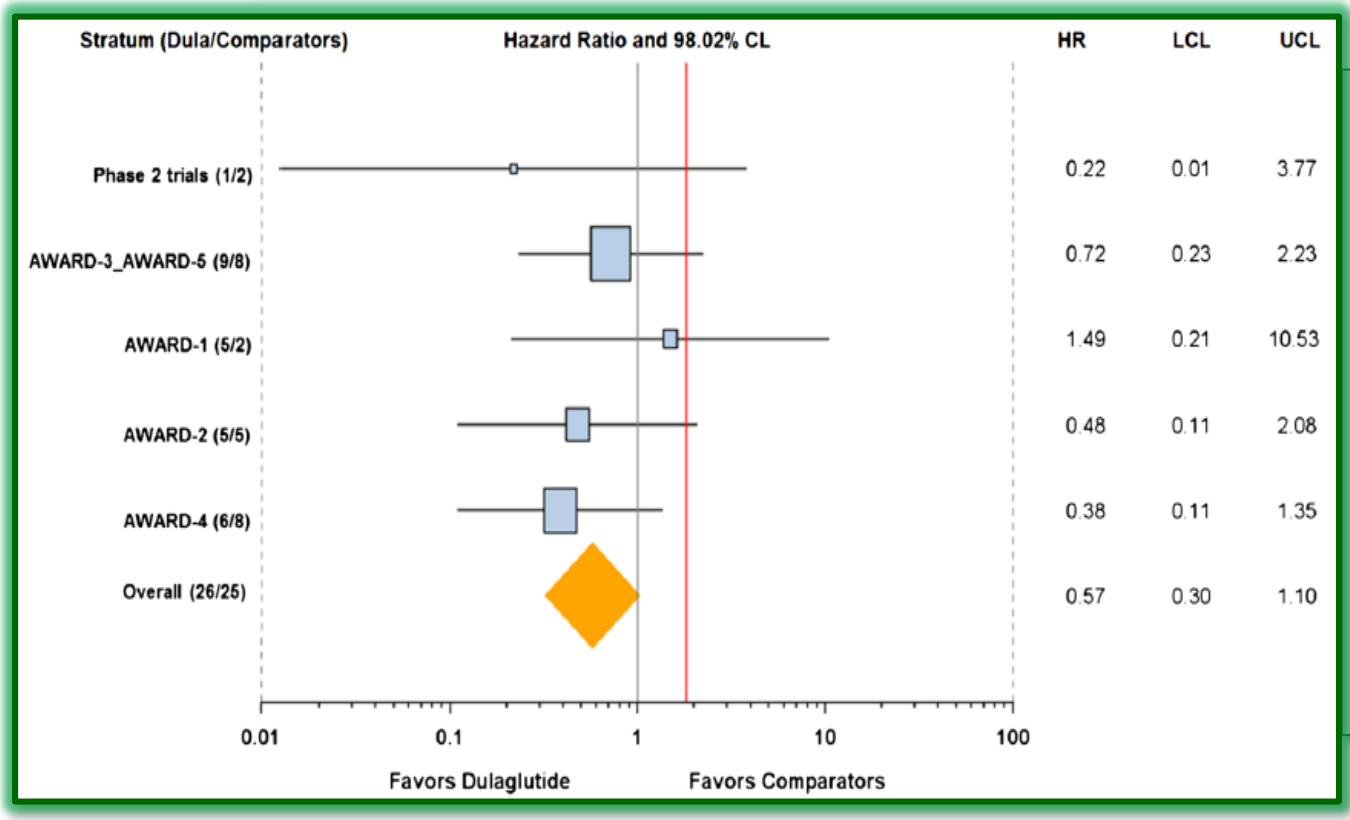
Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome



In patients with type 2 diabetes and a recent acute coronary syndrome, the addition of lixisenatide to usual care did not significantly alter the rate of major cardiovascular events or other serious adverse events.

Pfeffer MA et al., N Engl J Med 2015

Cardiovascular safety for once-weekly dulaglutide in type 2 diabetes: a pre-specified meta-analysis of prospectively adjudicated cardiovascular events

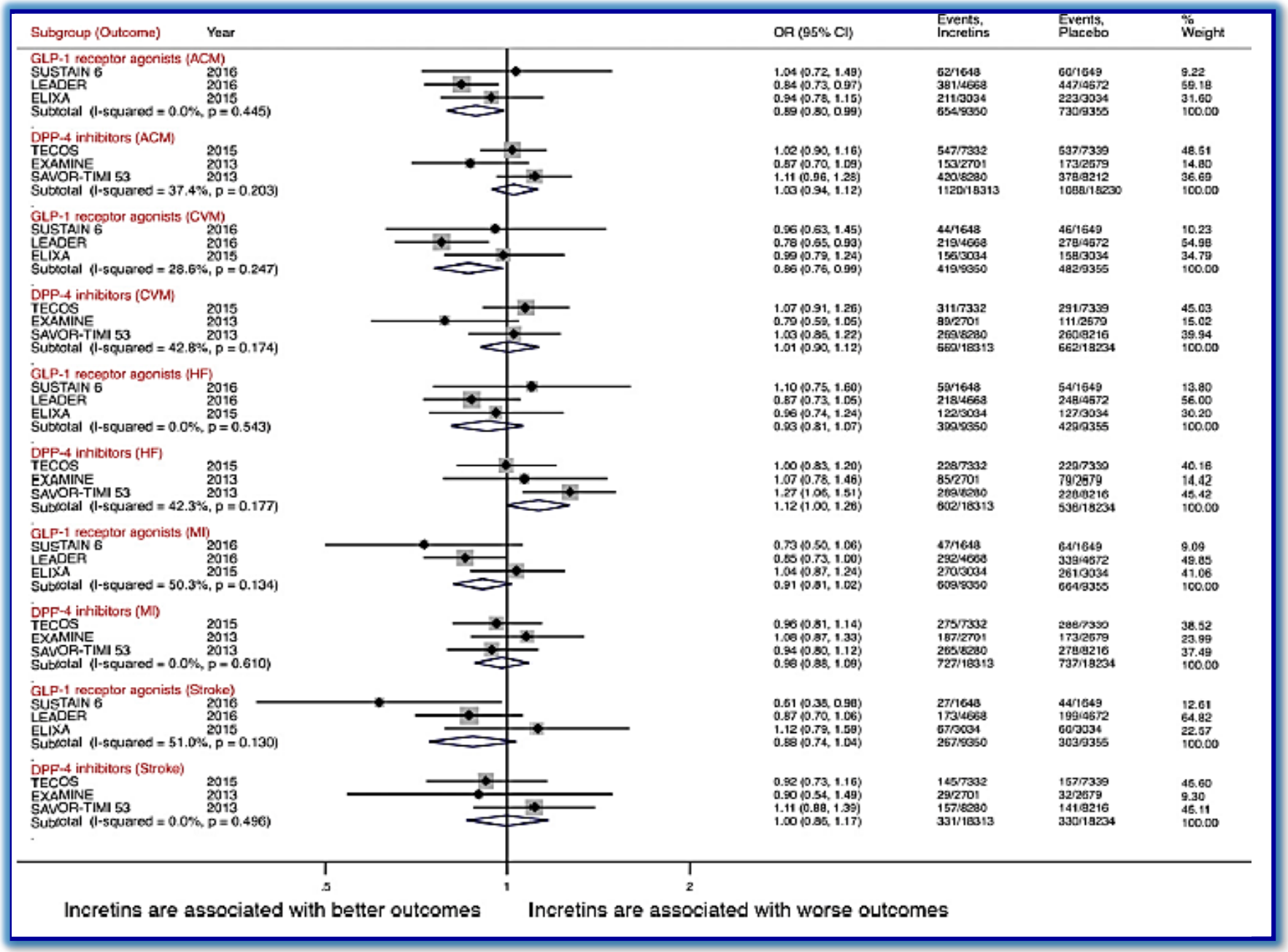


These results suggest that dulaglutide does not increase the risk of major CV events in T2D patients. The ongoing CV outcomes study, investigating CV events with a weekly dulaglutide (REWIND), will further assess CV safety of dulaglutide

Forest plot of the primary 4-component MACE endpoint by stratum. A comparison of the primary analysis results (HR [98.02 % CI]) in each stratum (study or combinations of studies by which the primary analysis was stratified) with the overall result. Numbers of CV events per each treatment group (Dula/Comparators) are indicated in the parentheses in the y-axis under Stratum

Ferdinand KC et al. Cardiovasc Diabetol, 2016

Incretins and CV outcomes



Elgendy IY et al., International Journal of Cardiology, 2017

SGLT-2 inhibitors

Ongoing and recently completed major CV outcomes trials of SGLT2 inhibitors

Drug name	Abbreviated name of the trial	Phase of the trial	Primary outcomes	Key result
Empagliflozin	EMPA-REG Outcome	Completed	CV death, non-fatal MI, non-fatal stroke	Significantly lower rates of death from cardiovascular causes; hospitalization for heart failure; death from any cause among Empagliflozin groups
Canagliflozin	CANVAS	Phase III	CV death, non-fatal MI, nonfatal stroke	To be declared in 2017/2018
Canagliflozin	CANVAS-R	Phase IV	Progression of albuminuria	To be declared in 2017
Canagliflozin	CREDENCE	Phase III	ESKD, S-creatinine doubling, renal/CV death	To be declared in 2019
Dapagliflozin	DECLARE-TIMI 58	Phase III	CV death, non-fatal MI, non-fatal ischaemic stroke	To be declared in 2019
Ertugliflozin	Ertugliflozin CVOT	Phase III	CV death, non-fatal MI, or non-fatal stroke	To be declared in 2020

Ghosh RK et al., International Journal of Cardiology, 2016

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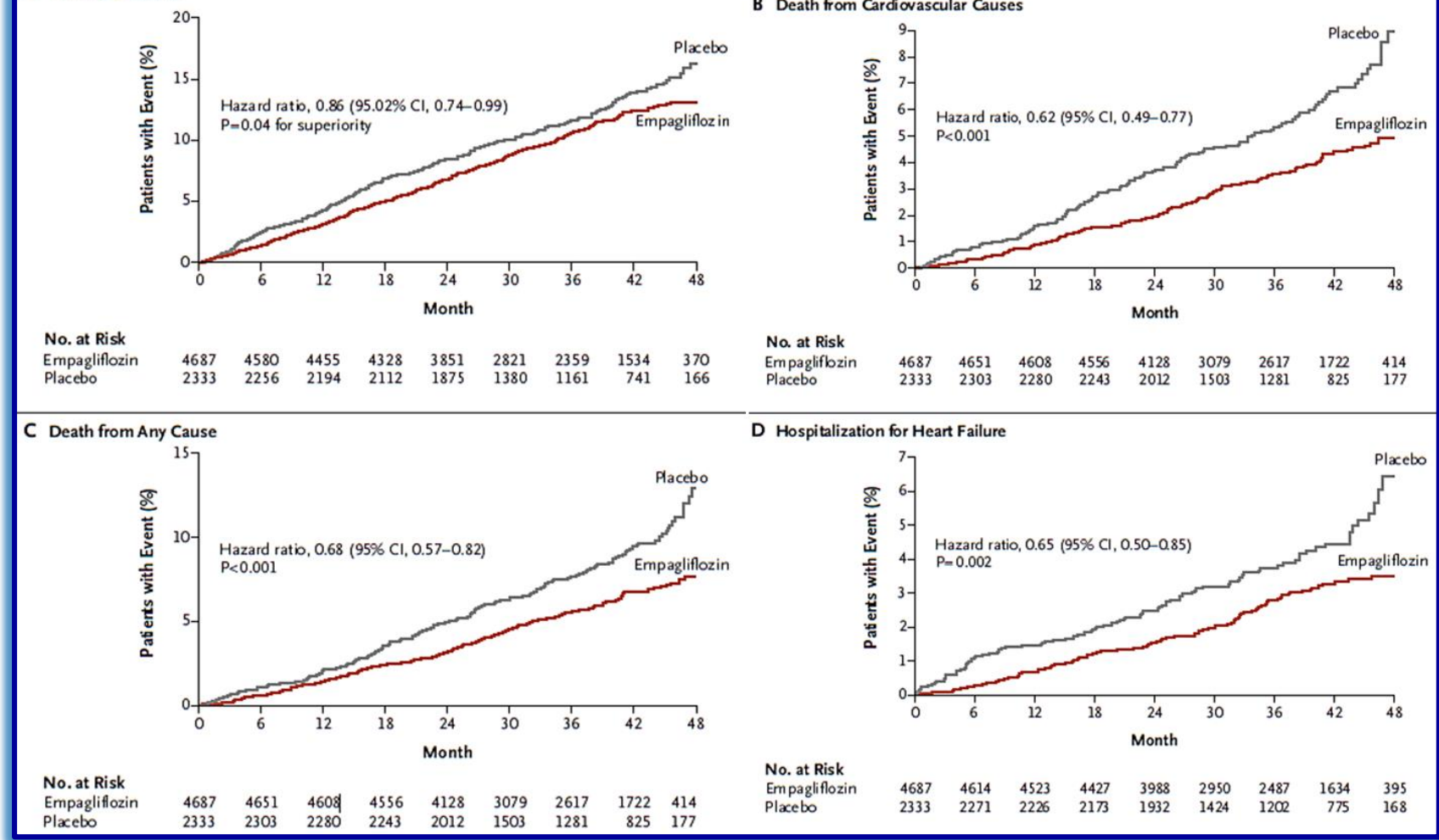
ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

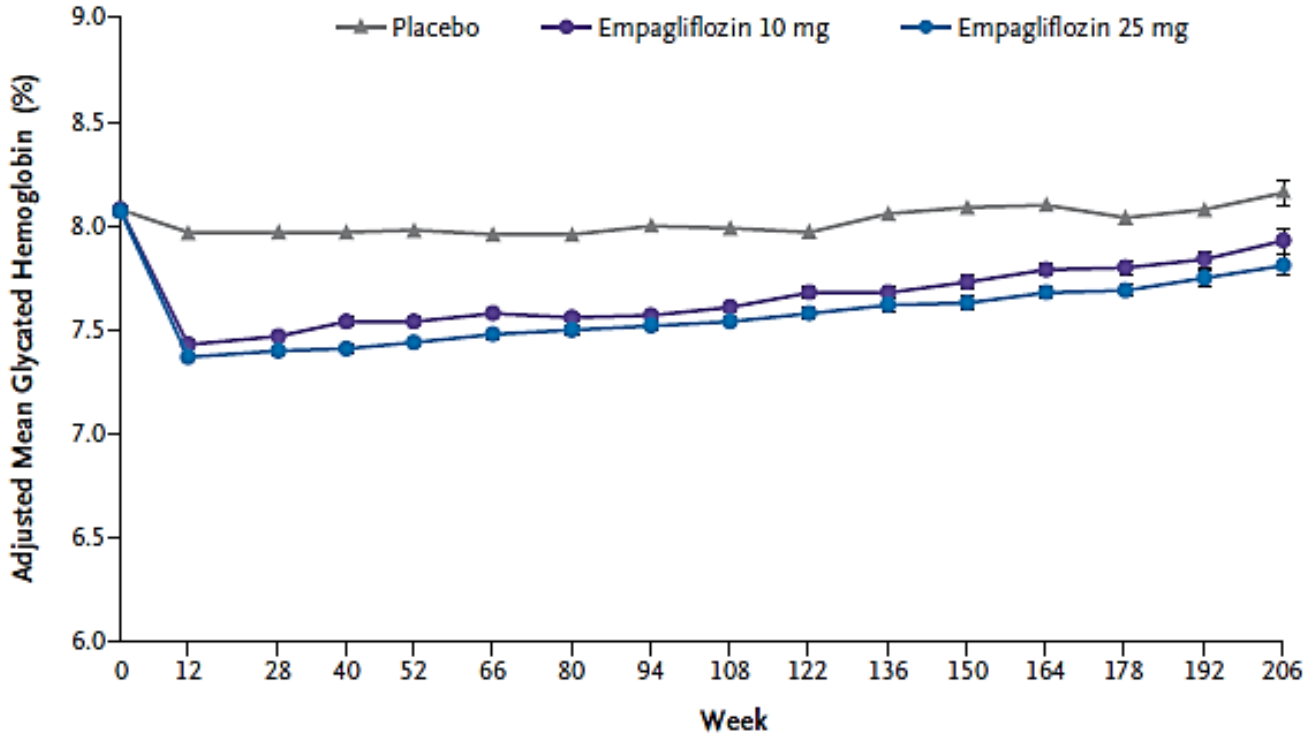
EmpaReg Outcome Trial

Cardiovascular Outcomes and Death from Any Cause



Zinman B. et al., NEJM, 2015

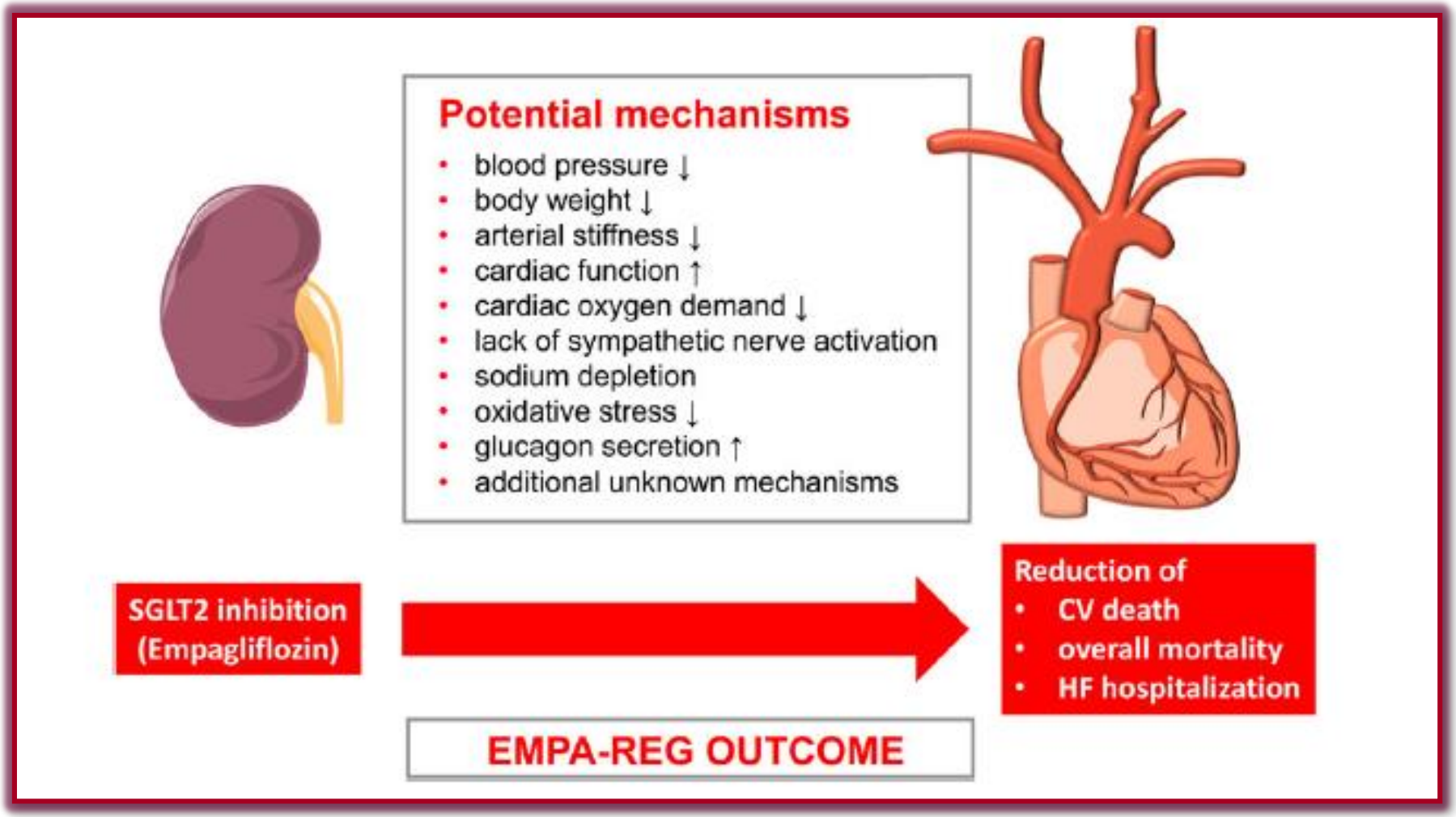
Glycated Haemoglobin Levels



No. at Risk

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	2058	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

Zinman B. et al., NEJM, 2015



Potential mechanisms involved in the reduction of cardiovascular events (cardiovascular death, total mortality, and heart failure hospitalization) observed in the EMPA-REG OUTCOME trial in T2D patients with prevalent atherosclerotic cardiovascular disease.

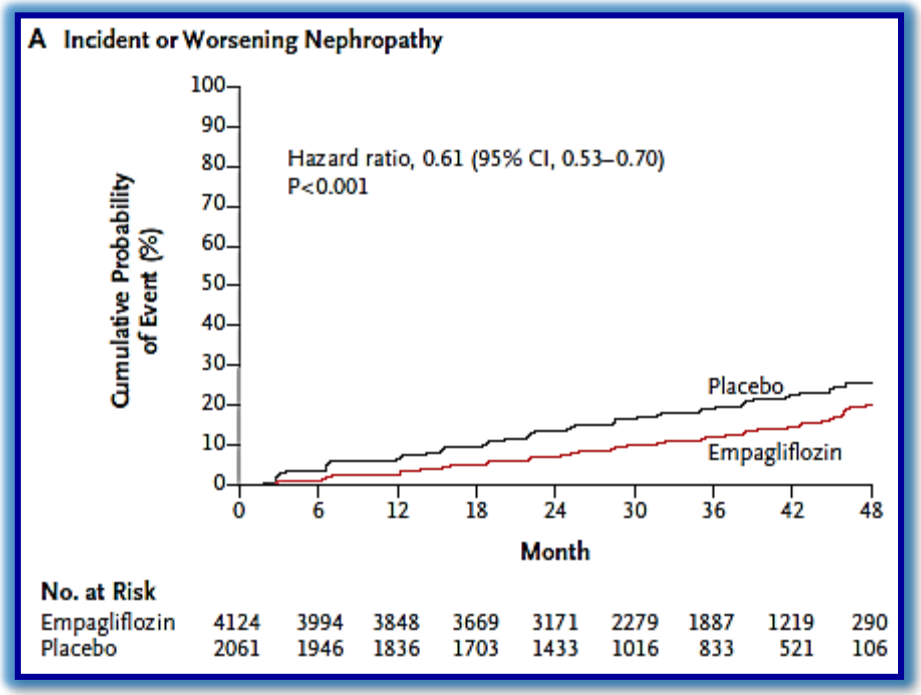
Marx N. et al., European Heart Journal, 2016

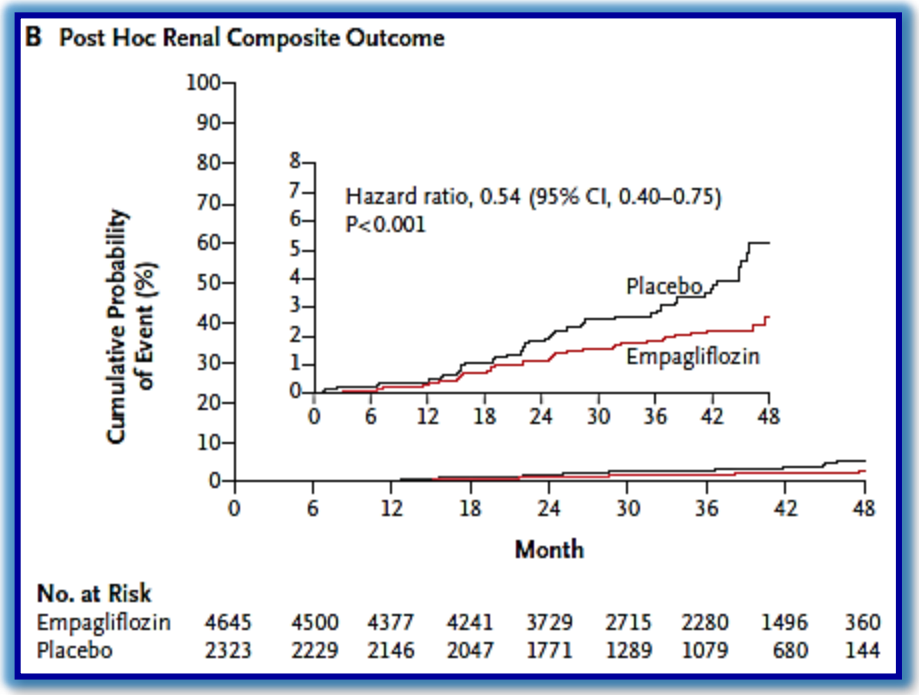
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

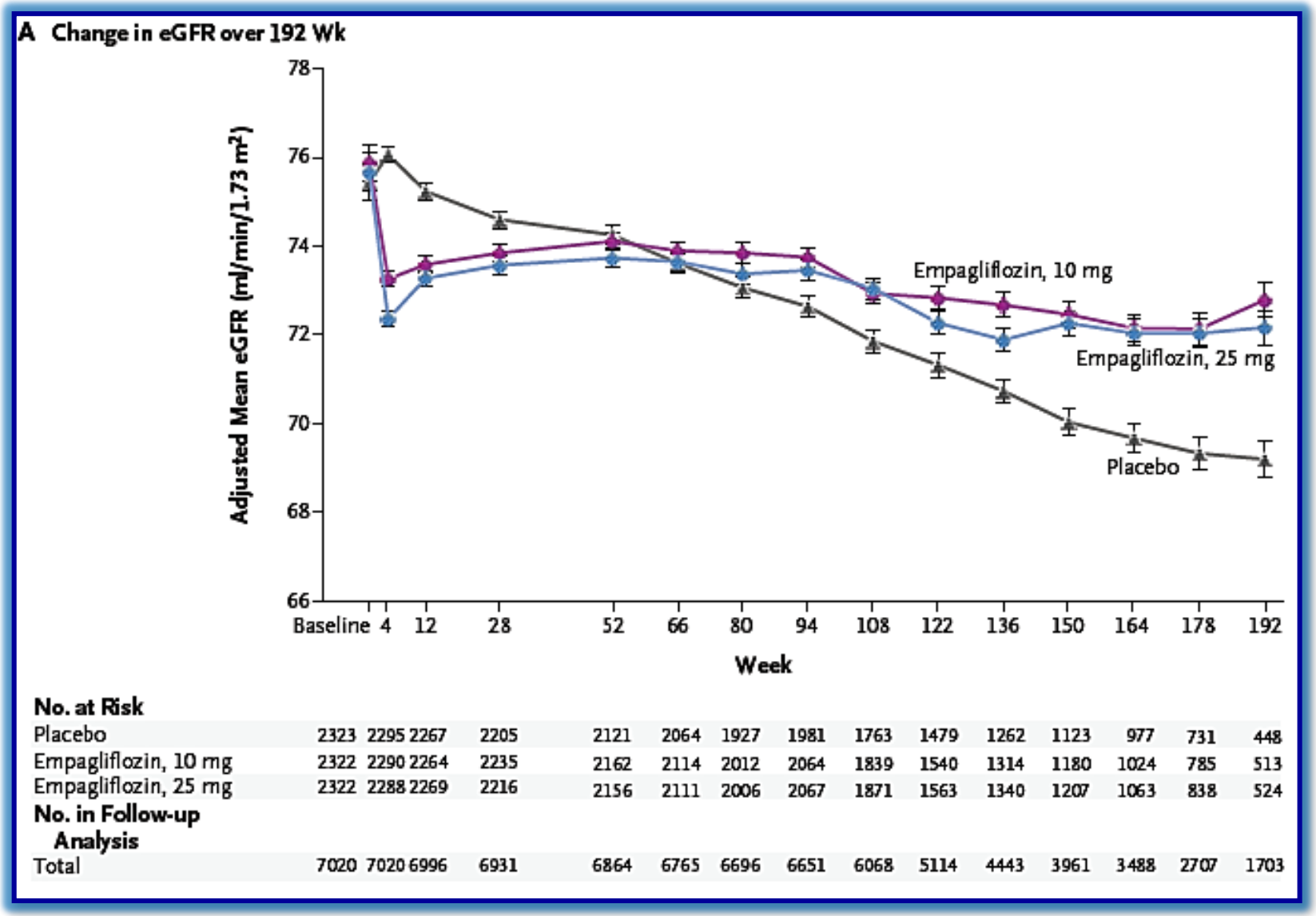
Analysis of Two Key Renal Outcomes





Wanner C. et al., NEJM, 2016

Renal Function over Time: estimated glomerular filtration rate (eGFR) over a period of 192 weeks



No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

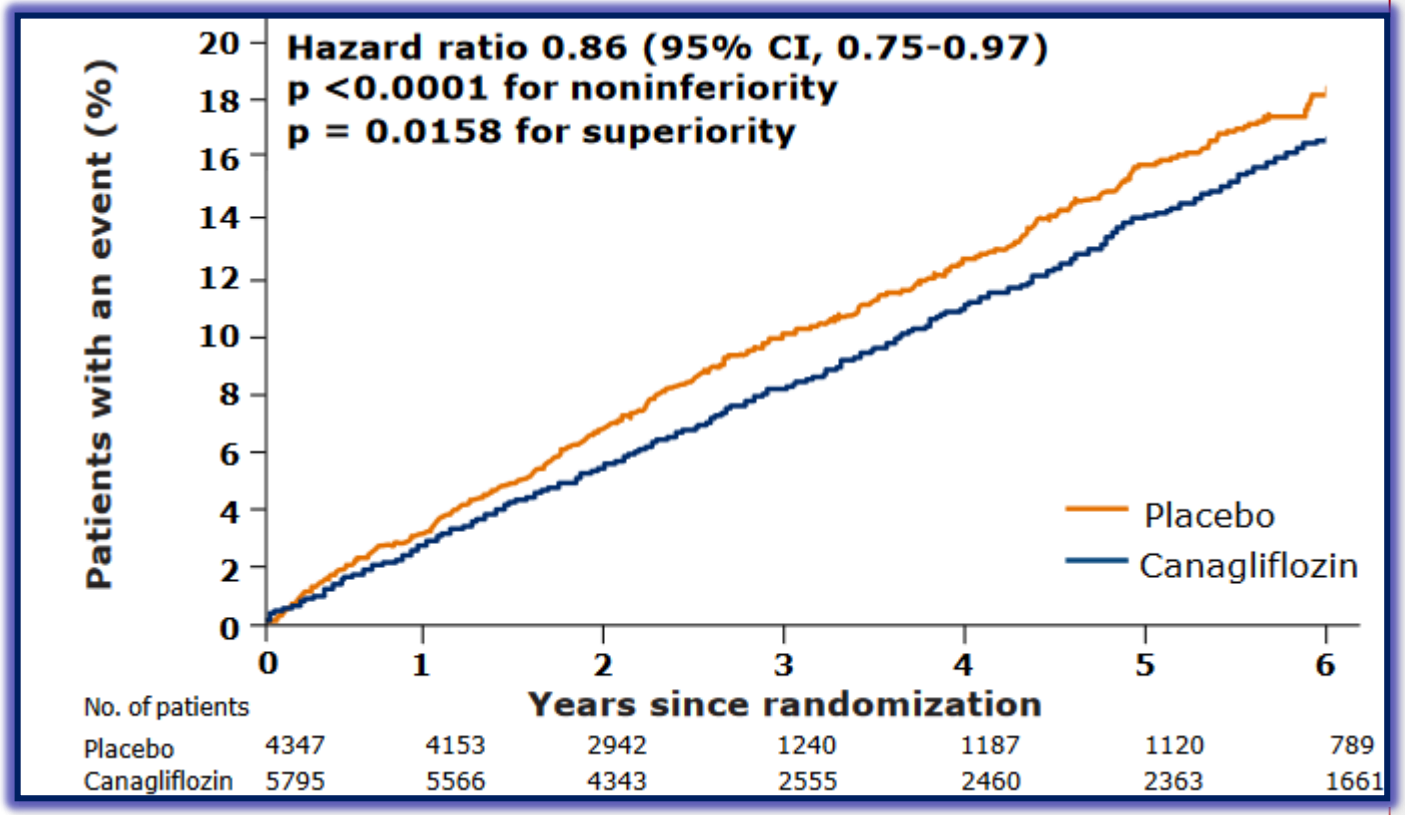
Wanner C. et al., NEJM, 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

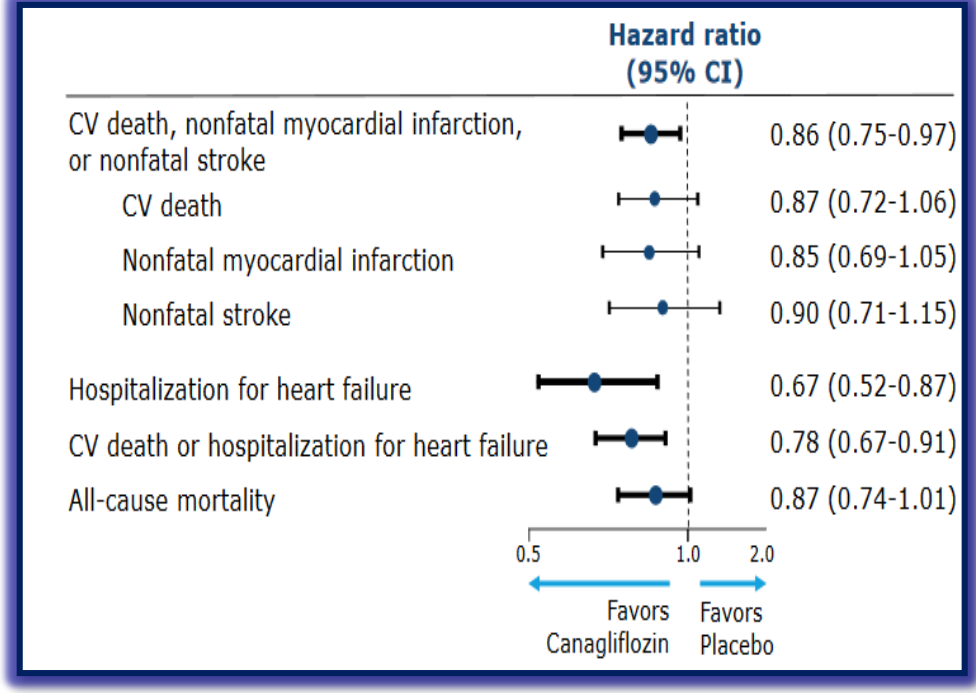
Primary outcome
CV death, nonfatal myocardial infarction or stroke



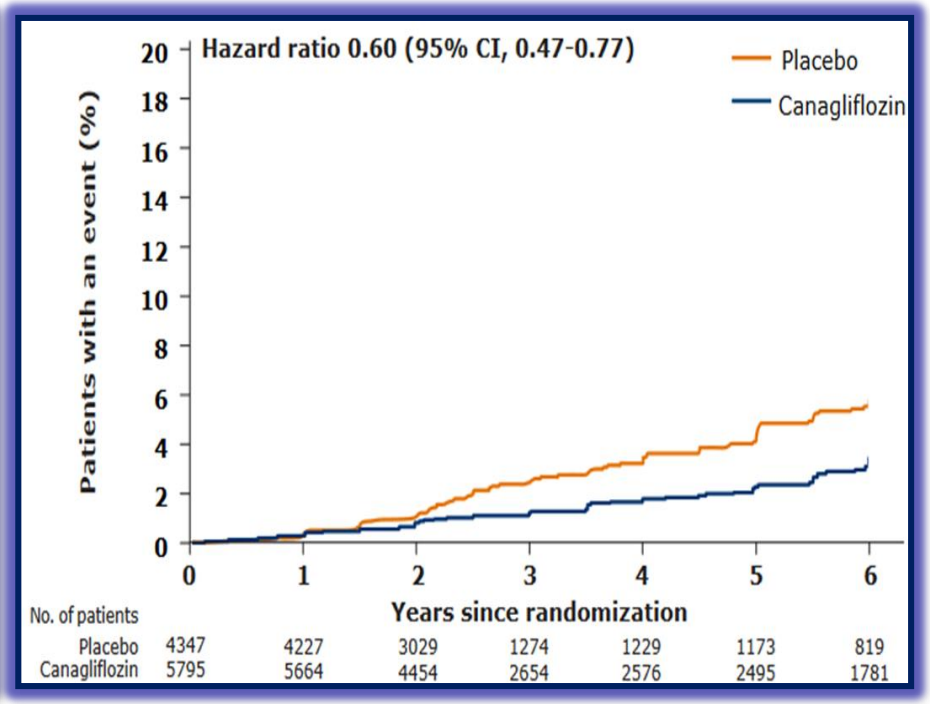
In two trials involving patients with type 2 diabetes and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal.

Neal B. et al., N Engl J Med 2017

Other vascular events and death



Composite of 40% reduction in eGFR, end-stage Renal Disease, or renal death



The CANVAS Program met its primary objective of demonstrating cardiovascular safety, and also showed efficacy of canagliflozin for the prevention of CV events

Neal B. et al., N Engl J Med 2017

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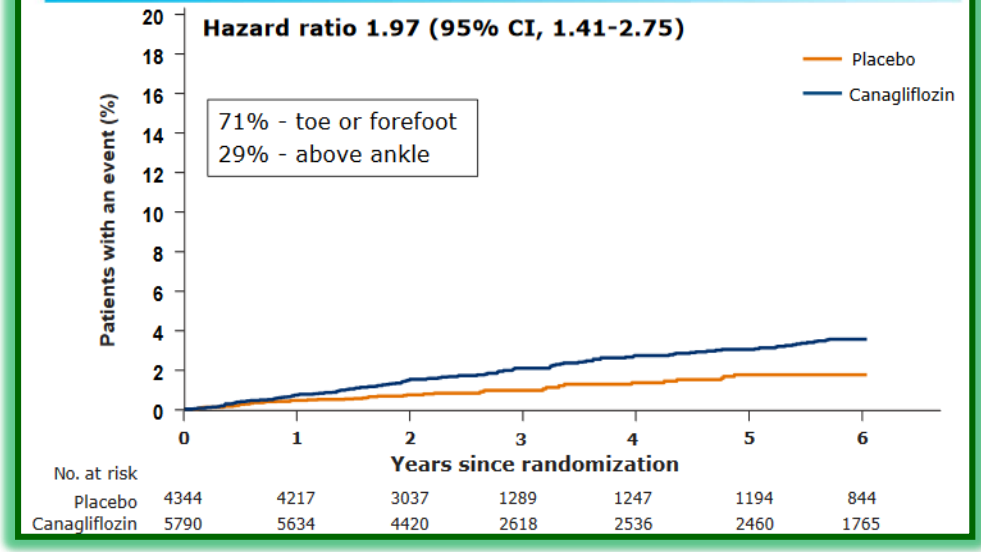
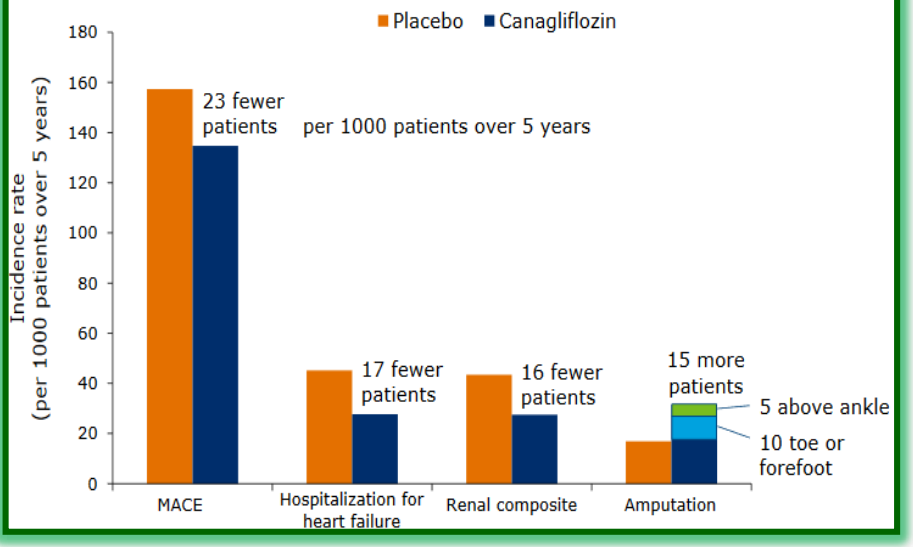
ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Lower-extremity amputations



Benefits and risk

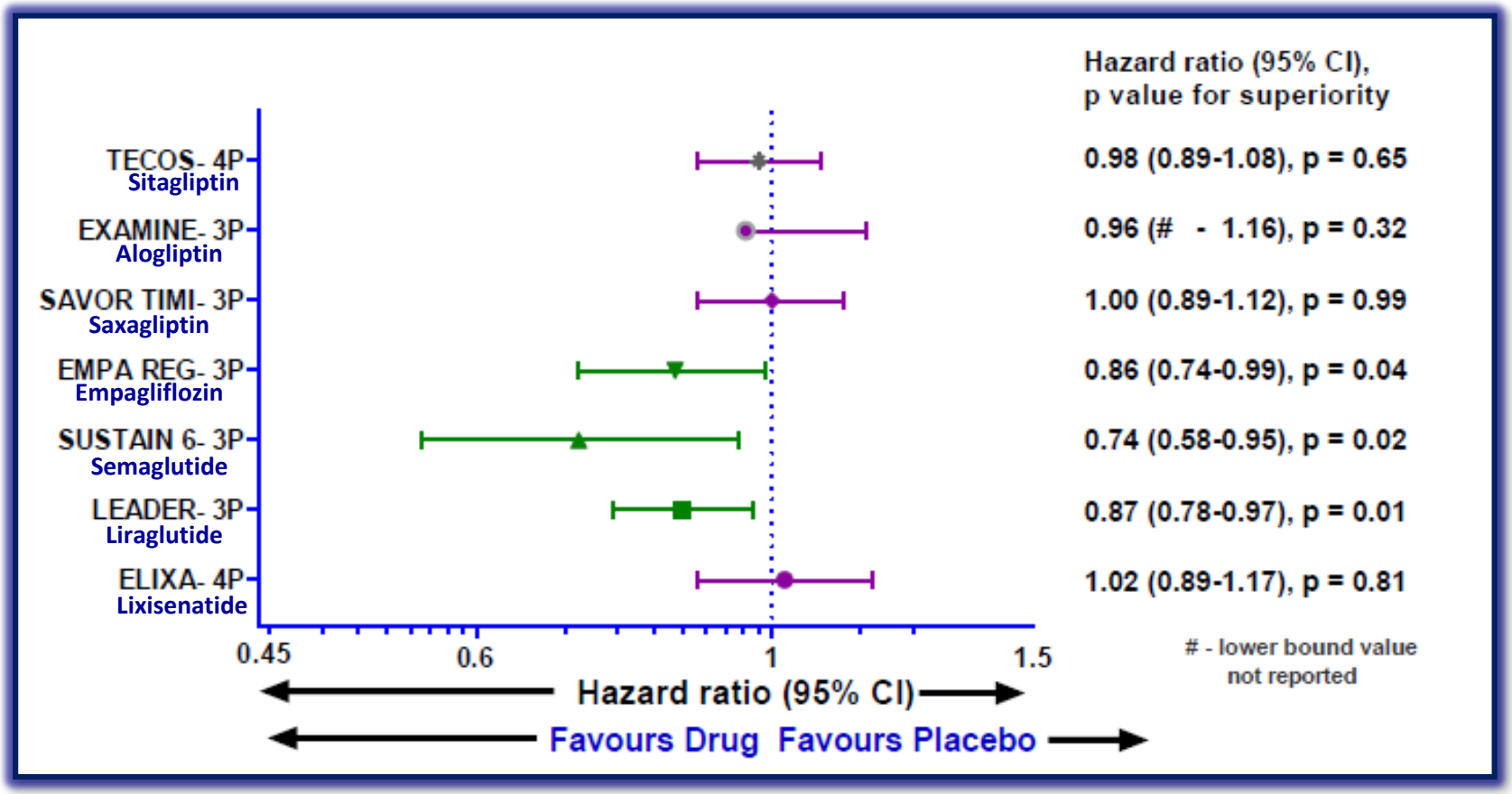


- These data suggest net overall benefit of canagliflozin for most patients with type 2 diabetes and high cardiovascular risk.
- Canagliflozin use was associated with an increased risk of amputation which should be taken into consideration when prescribing this agent.

Neal B. et al., N Engl J Med 2017

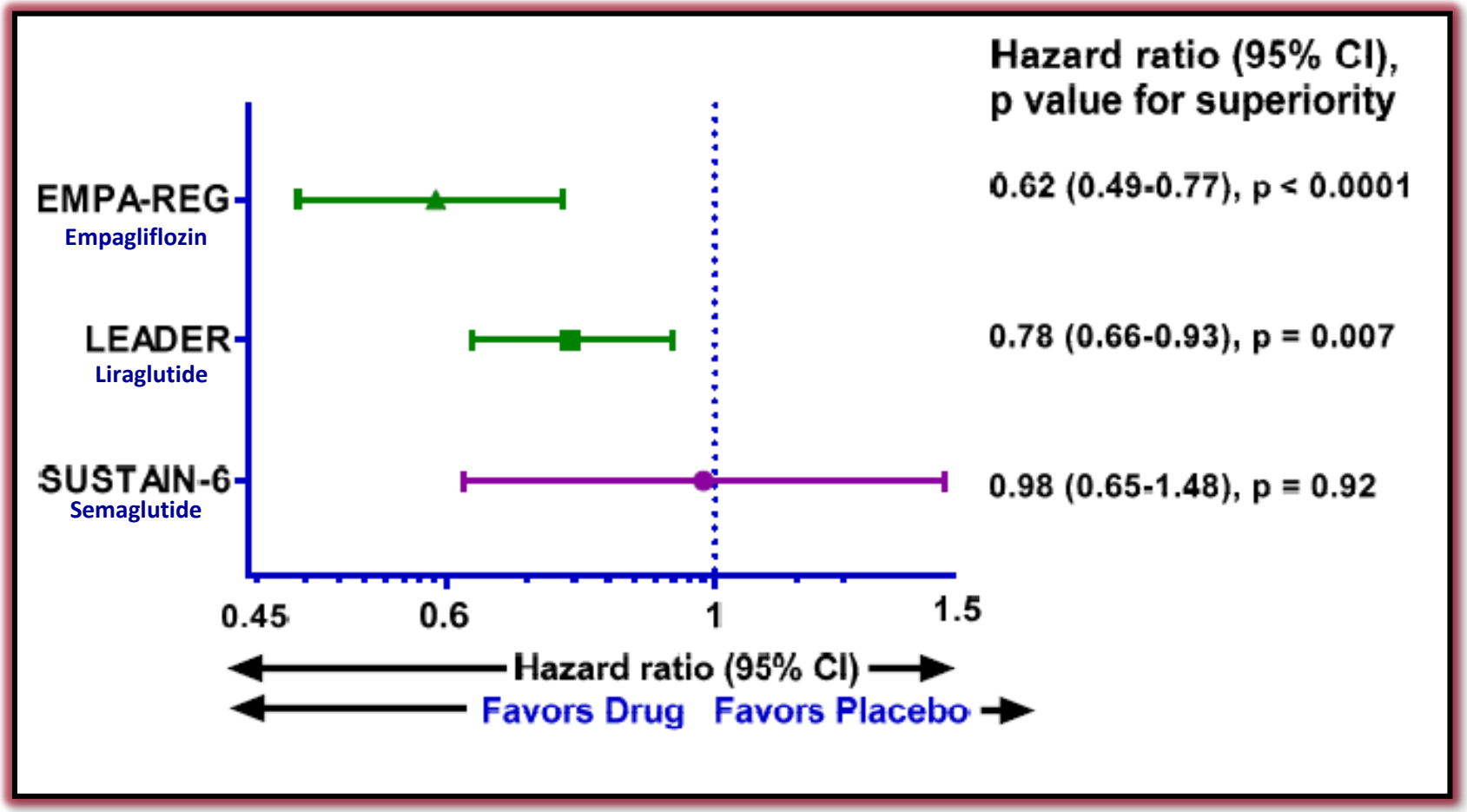
SAVOR-TIMI to SUSTAIN-6: A critical comparison of cardiovascular outcome trials of anti-diabetic drugs

Primary outcomes in all CV outcome trials



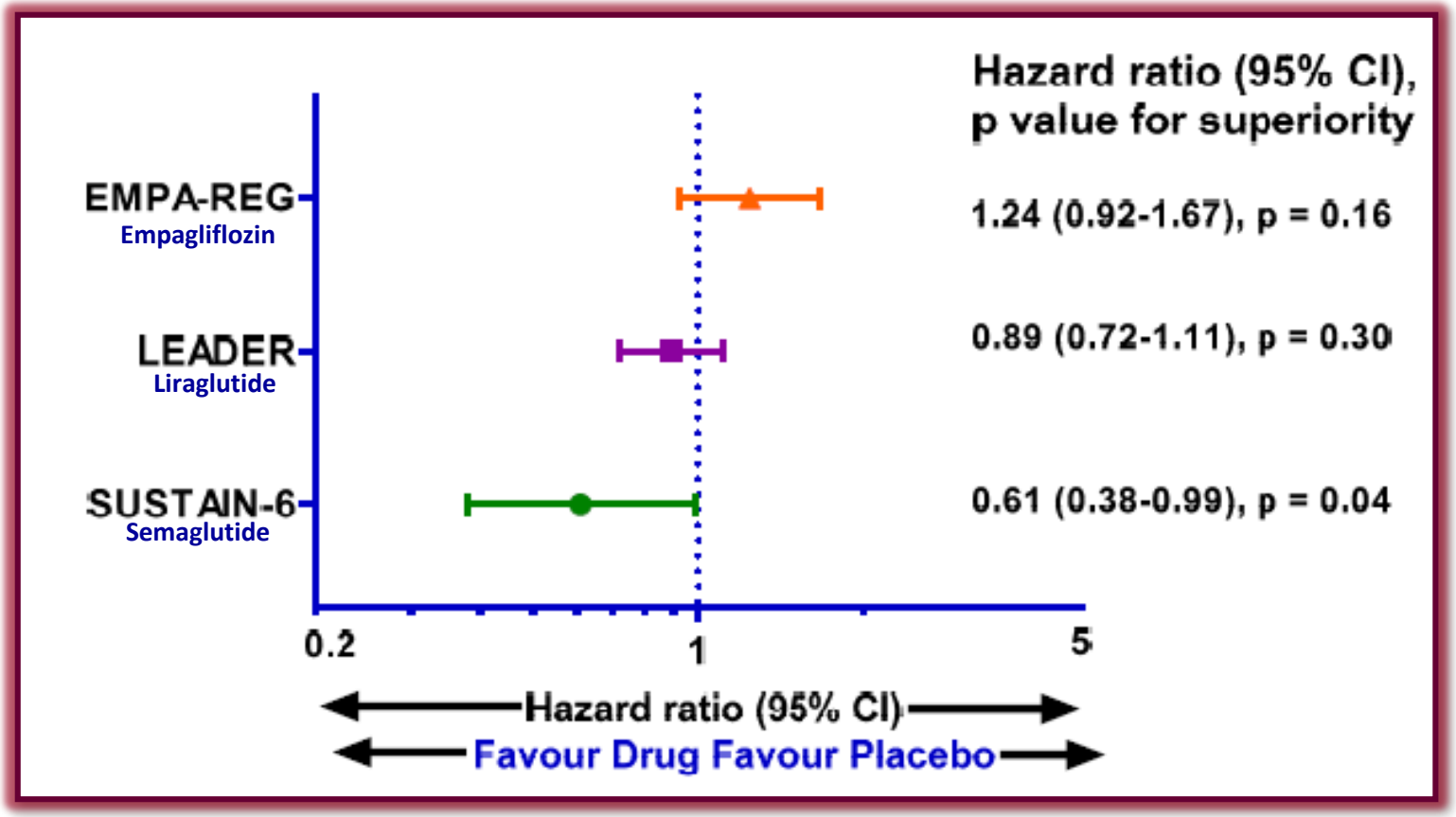
Singh AK et al., Expert Review of Clinical Pharmacology 2017

CV death in 3 CV outcome trials



Singh AK et al., Expert Review of Clinical Pharmacology 2017

Non-fatal stroke in 3 CV outcome trials



Singh AK et al., Expert Review of Clinical Pharmacology 2017

Conclusions

Since the inception of mandatory cardiovascular (CV) safety outcome trial (CVOT) promulgated by US Food and Drug administration in 2008, several trials have been published with 3 different classes of anti-diabetic drugs in T2D.

The three CVOT conducted with saxagliptin, alogliptin and sitagliptin respectively, found them to be CV neutral.

However, both saxagliptin and alogliptin showed an increase in heart failure hospitalization (hHF), while sitagliptin had no such signal.

The CVOT conducted with lixisenatide (ELIXA) was CV-neutral, but both liraglutide (LEADER) and semaglutide (SUSTAIN-6) demonstrated superiority in reducing MACE.

LEADER had concordant reduction in all CV endpoints.
SUSTAIN-6 had most robust reduction in 3P-MACE, although no reduction in the CV-death, all-cause death and hHF were observed.

The trial conducted with empagliflozin (EMPA-REG) found it to be superior in reducing major adverse cardiac events (MACE).