



Lessen van recente CV eindpunt trials in T2DM



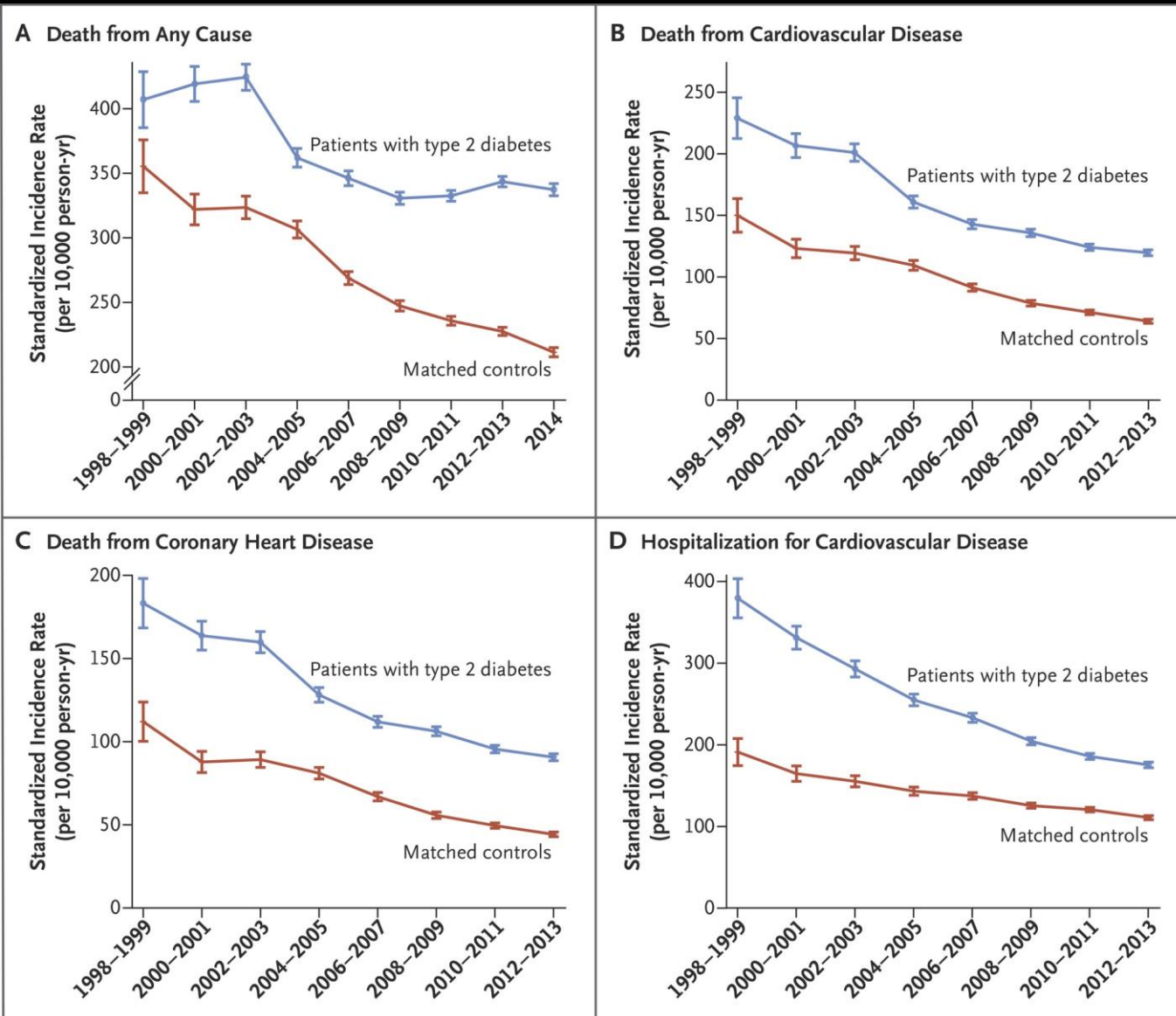
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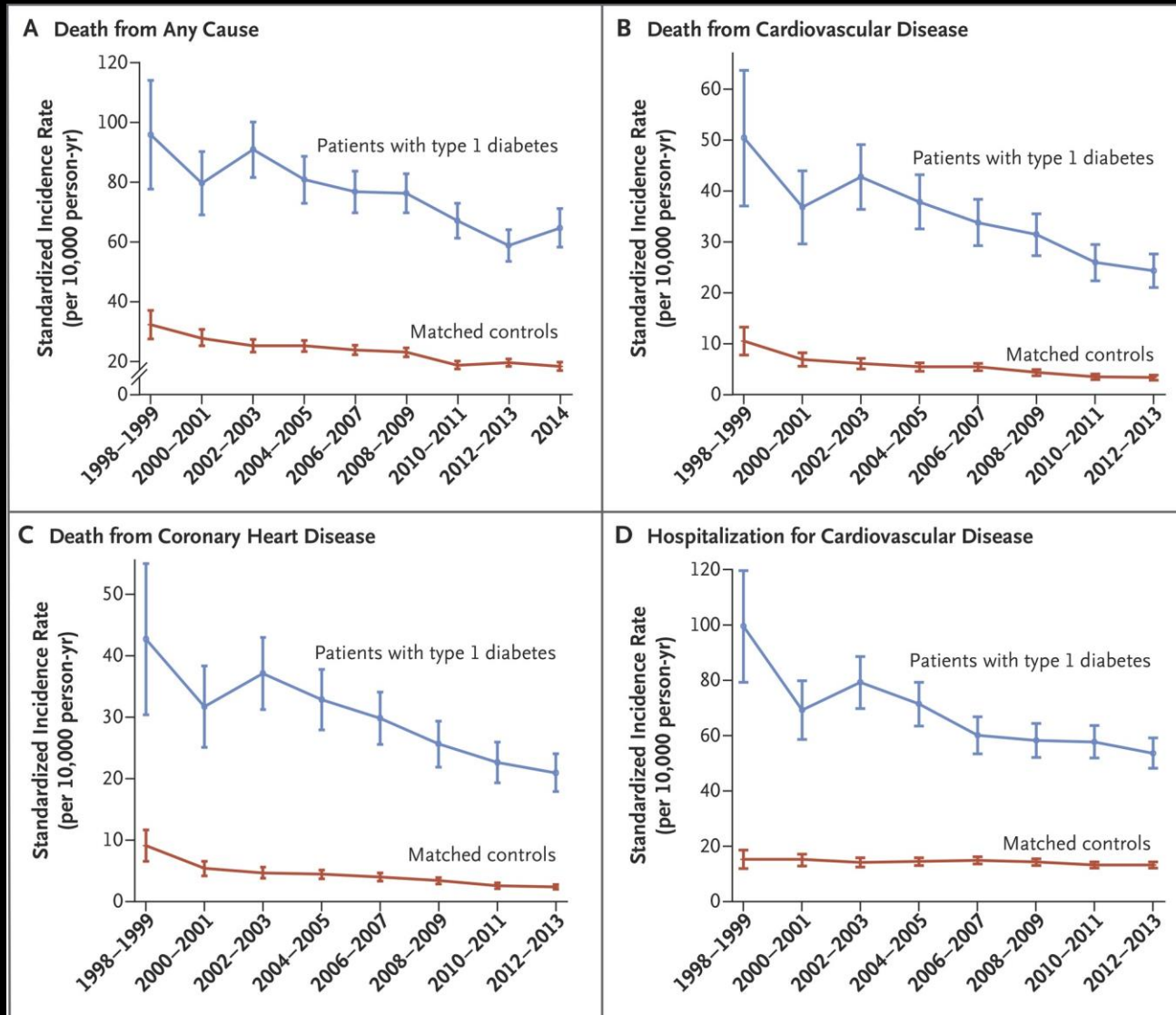
Disclosures

(potentiële) belangenverstrengeling	
<p>Voor bijeenkomst mogelijk relevante relaties met bedrijven</p> <p>Nascholingen, speakers fee</p> <p>adviesorganen</p>	<p>Bedrijfsnamen</p> <p>MSD, Boehringer Ingelheim, Astrazeneca Sanofi, Janssen, Novo Nordisk</p> <p>Astrazeneca, Amgen</p>

Major Cardiovascular Outcomes in Patients with Type 2 Diabetes and Matched Controls.



Major Cardiovascular Outcomes in Patients with Type 1 Diabetes and Matched Controls.



Casus

Vrouw 62 jaar

6 jaar diabetes; TIA, myocard infarct, ex-rookster en PAD

Fit en vitaal

BMI: 35,5 Kg/m²

Metformine 2 dd 850mg, statine wordt niet verdragen, Ezetimibe 1 dd 10mg;
ascal, ACE-remmer

LDL-C: 3,5 mmol/L

RR 150/70

Lab is verder niets op aan te merken, eGFR 62 ml/min

HbA1c opgelopen naar 68 (streefwaarde 53)

Wat nu?

Casus (aandachtspunten)

Vrouw 62 jaar

6 jaar diabetes; TIA, myocard infarct, ex-rookster en PAD

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BMI: 35,5 Kg/m²

Metformine 2 dd 850mg, statine wordt niet verdragen, Ezetimibe 1 dd 10mg; ascal, ACE-remmer

LDL-C: 3,5 mmol/L

RR 150/70

Lab is niets op aan te merken, eGFR 62 ml/min

HbA1c opgelopen naar 68 (streefwaarde 53)

Aandachtspunten:

Obesitas!

Looptraining of interventie?

LDL-C niet op streefwaarde (3 statines geprobeerd? Re-challenge? PCSK9-i?)

Bloeddruk moet naar 140 systolisch (ACE-i verhogen? diureticum?)

HbA1c: aanscherpen glucose regulatie!!

MAAR.....

Intensive glucose lowering trials: Summary of ACCORD, ADVANCE and VADT

	ACCORD*	ADVANCE	VADT
A1C (%) (Intensive vs. Std)	6.4 vs. 7.5 †	6.4 vs. 7.0 †	6.9 vs. 8.4 †
Nonfatal MI (%) (Intensive vs. Std)	3.6 vs 4.6% †	2.7 vs. 2.8	6.3 vs. 6.1
CV Death (%) (Intensive vs. Std)	2.6 vs. 1.8 † (1.35 Hazard Ratio)	4.5 vs. 5.2	2.1 vs. 1.7
Microvascular	-	nephropathy ↓ 21% retinopathy ↓ 5% NS	-
Take home	↓ risk MIs, but ↑ risk death in intensive arm	Glucose control has no impact on CV events, but ↓ Microvascular risk	Glucose control has no impact on CV events

*ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial halted intensive glucose group (2/6/08) † significant difference between intensive and standard group

ACCORD Study Group, NEJM 2008, 358:2545-2559.

ADVANCE Collaborative Group, NEJM 2008, 358:2560-2572.

VADT Study Results ADA Scientific Session San Francisco, 2008

In Press, Diabetes Obesity and Metabolism, 2008

Updates on cardiovascular outcome trials in DM since 2008 (FDA guidance)

(Schnell et al; Cardiovasc Diabetol 2017; 16:128)

DPP4 inhibitors

SAVOR-TIMI53
EXAMINE
TECOS

CARMELINA*
MK-3102*
ALBIGLUTIDE TRIAL*

GLP1-RA

ELIXA
LEADER
SUSTAIN-6
EXSCEL

REWIND*
ITCA650*

Insulin

DEVOTE
ORIGIN

SGLT2-i

EMPA-REG
CANVAS

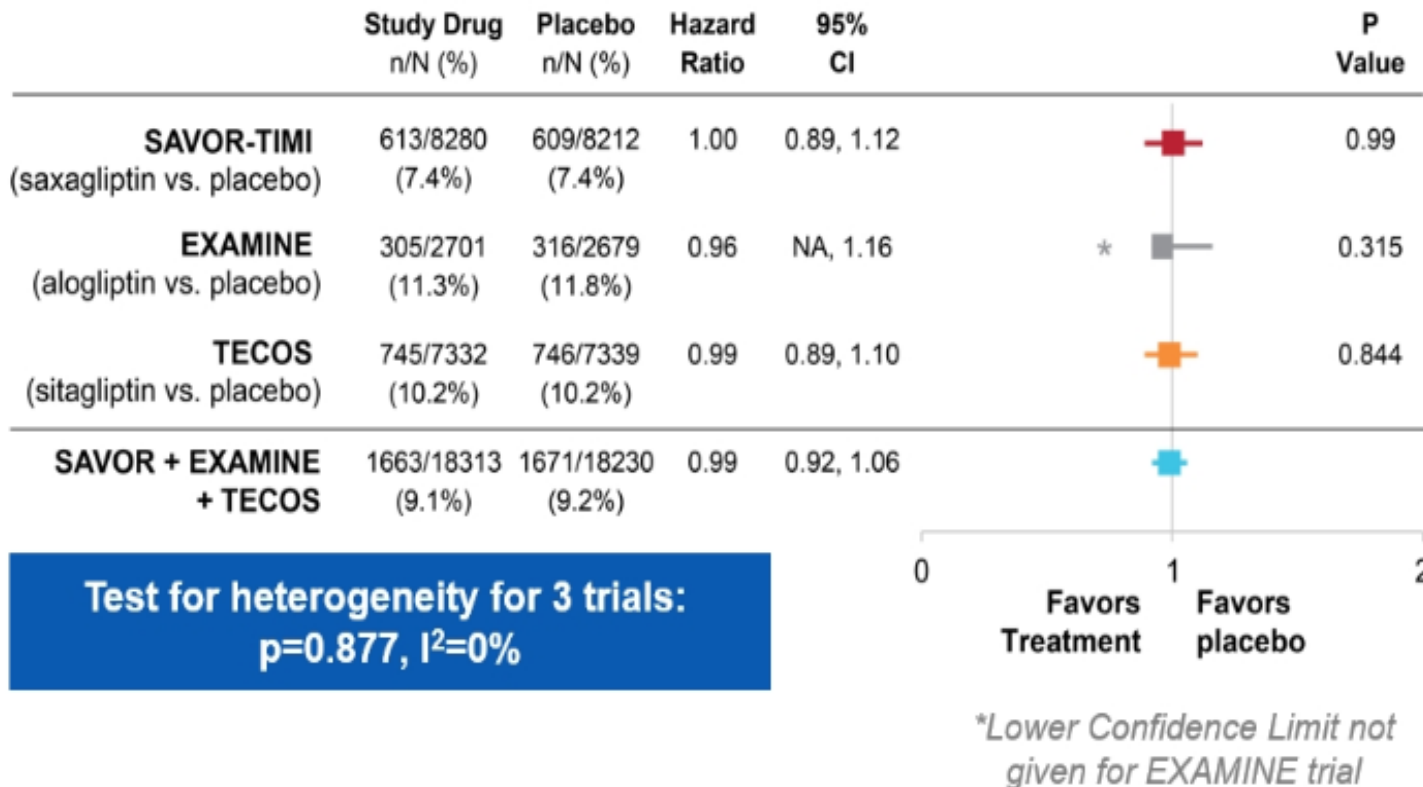
DECLARE-TIMI*
VERTIS*

ACARBOSE

ACE

DPP4-inhibitors

SAVOR-TIMI 53, EXAMINE and TECOS: Meta-analysis of MACE Events



1. Scirica BM et al. *N Engl J Med* 2013; 369: 1317-1326
2. White WB et al. *N Engl J Med* 2013; 369: 1327-1335
3. Green JB et al. *N Engl J Med* 2015;373:232-42

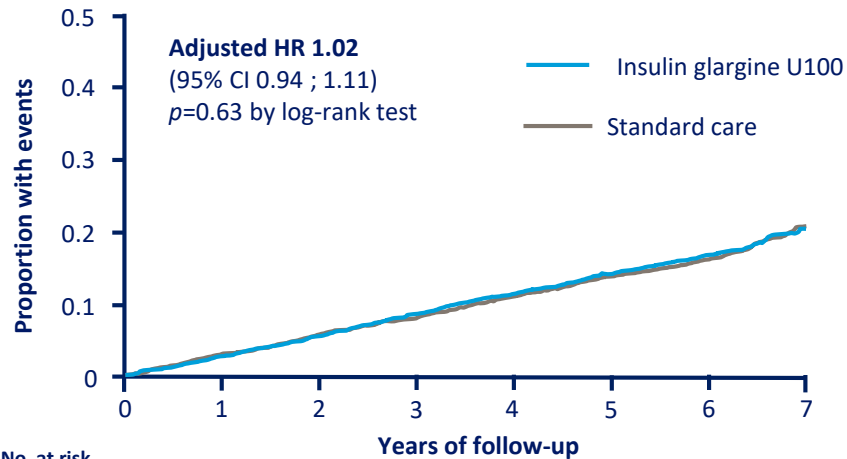
**Deze studies waren
opgezet om veiligheid
aan te tonen (non-inferiority)**

INSULIN

ORIGIN, DEVOTE: geen significante verschillen op MACE

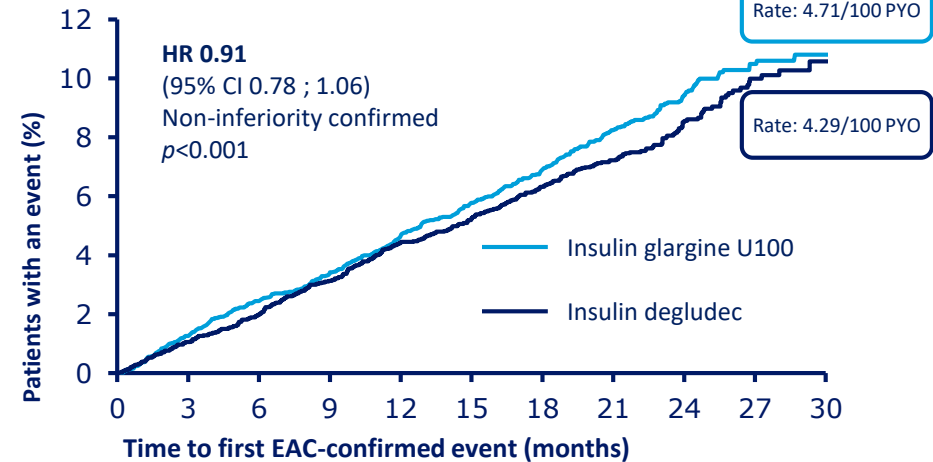
Tijd tot het eerste optreden van cardiovasculaire sterfte, niet-fatale myocardinfarct of niet-fatale beroerte

ORIGIN^{1*}



No. at risk								
Iglar U100	6264	6057	5850	5619	5379	5151	3611	766
Std. care	6273	6043	5847	5632	5415	5156	3639	800

DEVOTE²



IDeg	3818	3765	3721	3699	3611	3563	3504	2851	1767	811	217
Iglar U100	3819	3758	3703	3655	3595	3530	3472	2832	1742	811	205

*Initiated before FDA requirements for mandatory CVOTs. CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; EAC, Event Adjudication Committee; FDA, US Food and Drug Administration; HR, hazard ratio; IDeg, insulin degludec; IGl, insulin glargine; MACE, major adverse cardiac event; MI, myocardial infarction; SoC, standard of care; 100 PYO, per 100 patient-years of observation

1. The ORIGIN trial investigators *N Engl J Med* 2012;367:319–328; 2. Marso et al *N Engl J Med* 2017; Jun 12. doi: 10.1056/NEJMoa1615692 [Epub ahead of print]

GLP1-RA

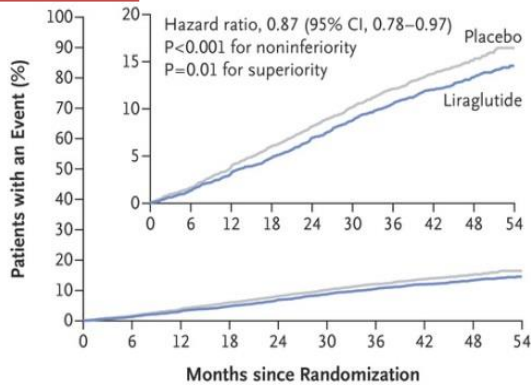
Primary and Exploratory Outcomes

LEADER: Liraglutide in T2DM



The NEW ENGLAND
JOURNAL of MEDICINE

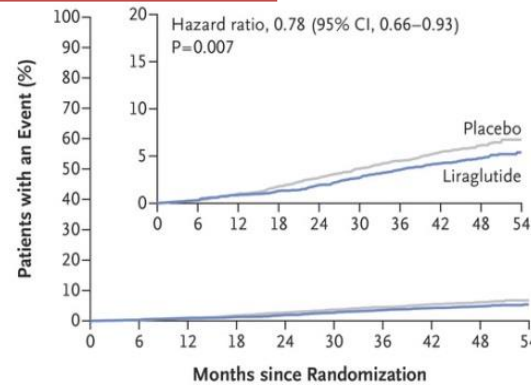
A Primary Outcome



No. at Risk

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

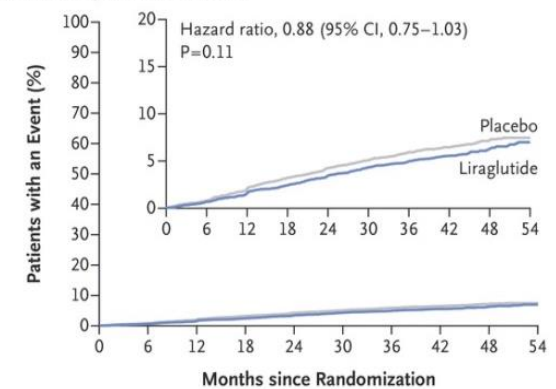
B Death from Cardiovascular Causes



No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

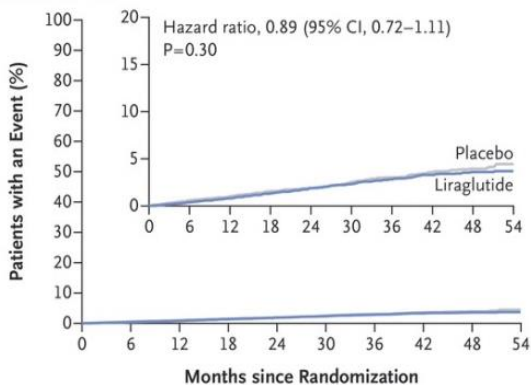
C Nonfatal Myocardial Infarction



No. at Risk

Liraglutide	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Placebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

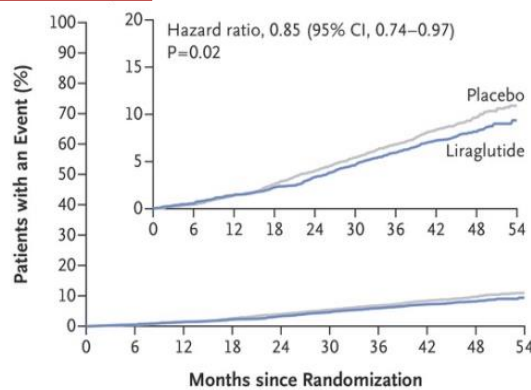
D Nonfatal Stroke



No. at Risk

Liraglutide	4668	4624	4564	4504	4426	4351	4269	4194	1662	465
Placebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	445

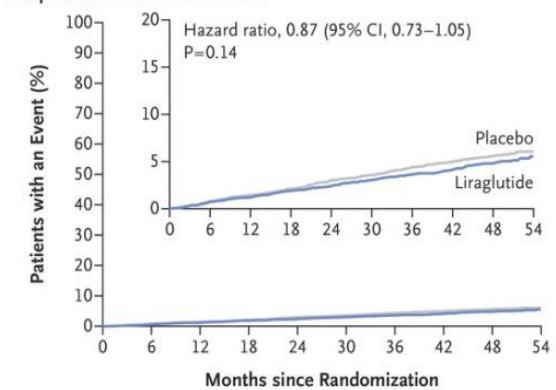
E Death from Any Cause



No. at Risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

F Hospitalization for Heart Failure

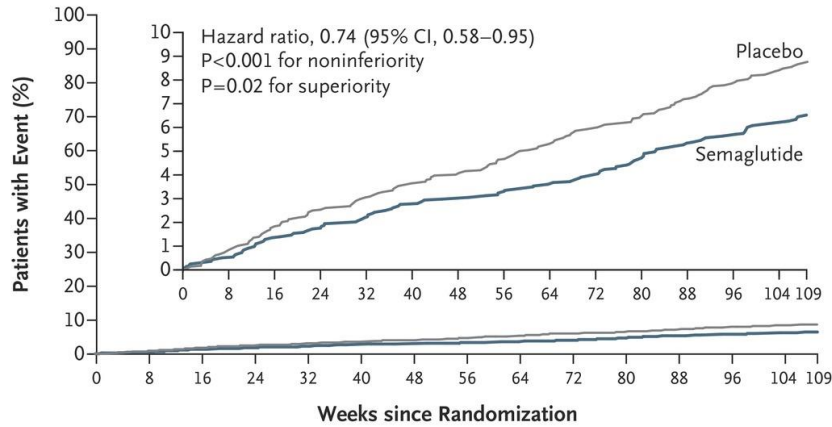


No. at Risk

Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

GLP1-RA SUSTAIN-6 (semaglutide once weekly) Cardiovascular Outcomes.

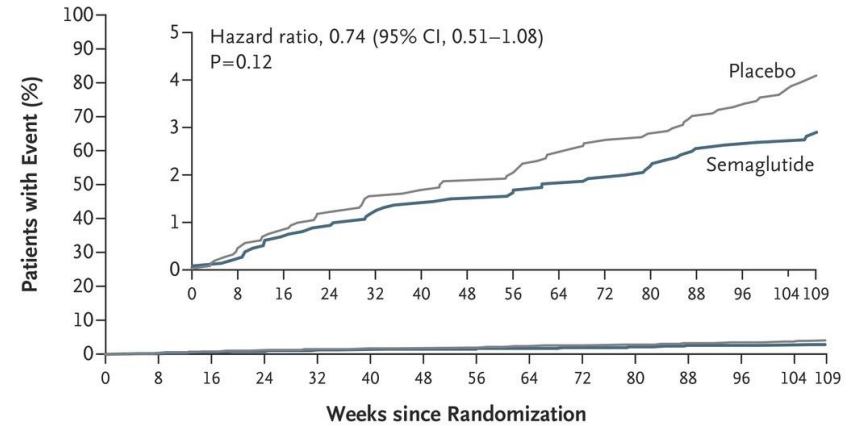
A Primary Outcome



No. at Risk

Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

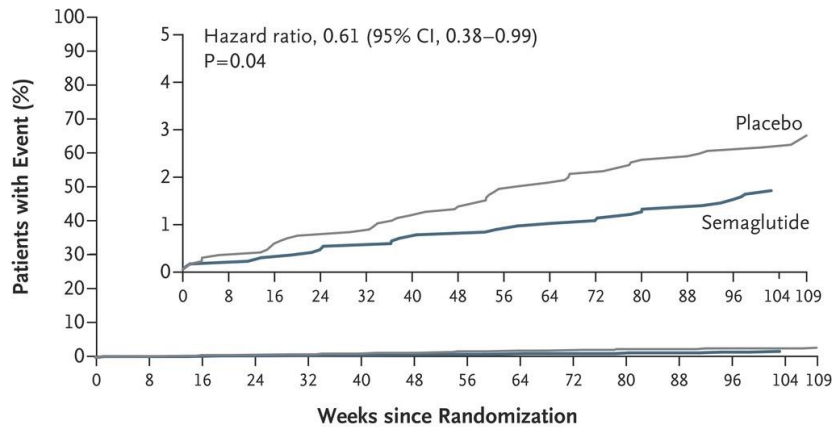
B Nonfatal Myocardial Infarction



No. at Risk

Placebo	1649	1624	1598	1587	1562	1542	1516
Semaglutide	1648	1623	1609	1595	1582	1560	1543

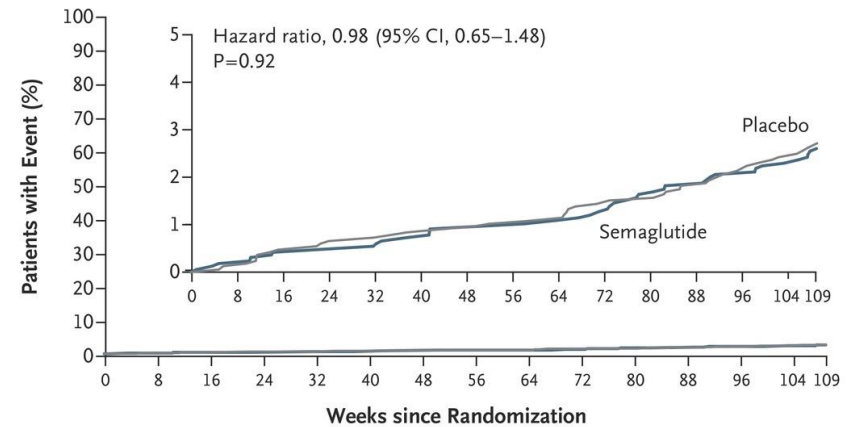
C Nonfatal Stroke



No. at Risk

Placebo	1649	1629	1611	1597	1571	1548	1528
Semaglutide	1648	1630	1619	1606	1593	1572	1558

D Death from Cardiovascular Causes



No. at Risk

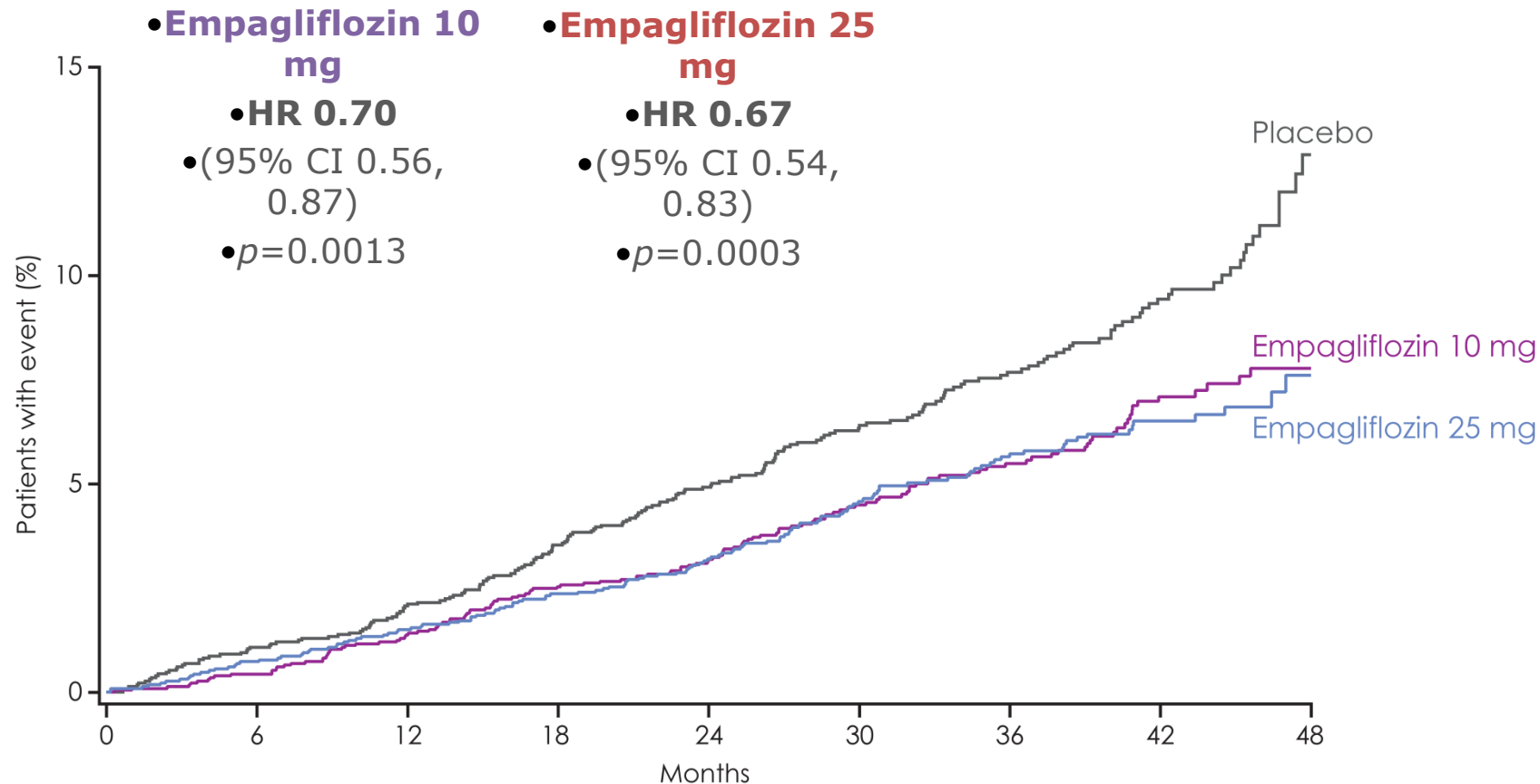
Placebo	1649	1637	1623	1617	1600	1584	1566
Semaglutide	1648	1634	1627	1617	1607	1589	1579

Comparison between 4 large GLP1-RA CVOT's

	N	inclusion	Duration	HbA1c baseline	HbA1c change	CV Outcome
ELIXA (lixisenatide 1dd1) 2015	6068	T2DM +CVD or RF	25 Months	7,6%	-0,27%	HR: 1,02 (ns) Non-inferior
LEADER (liraglutide 1dd1) 2016	9340	T2DM+CVD or RF	3,8 yrs	8,7%	-0,40%	0,78 (<0.001) Superior
SUSTAIN-6 (semaglutide 1w1) 2016	3297	T2DM + CVD or RF	104 weeks	8,7%	-0,70%	0,74 (<0.001) Superior
EXSCEL (exenatide 1w1) 2017	14752	T2DM+CVD or RF	3.2 yrs	8,0%	-0,70%	0,91 (P=0.06) Non-inferior

SGLT2-i

EMPA-REG: All-cause mortality



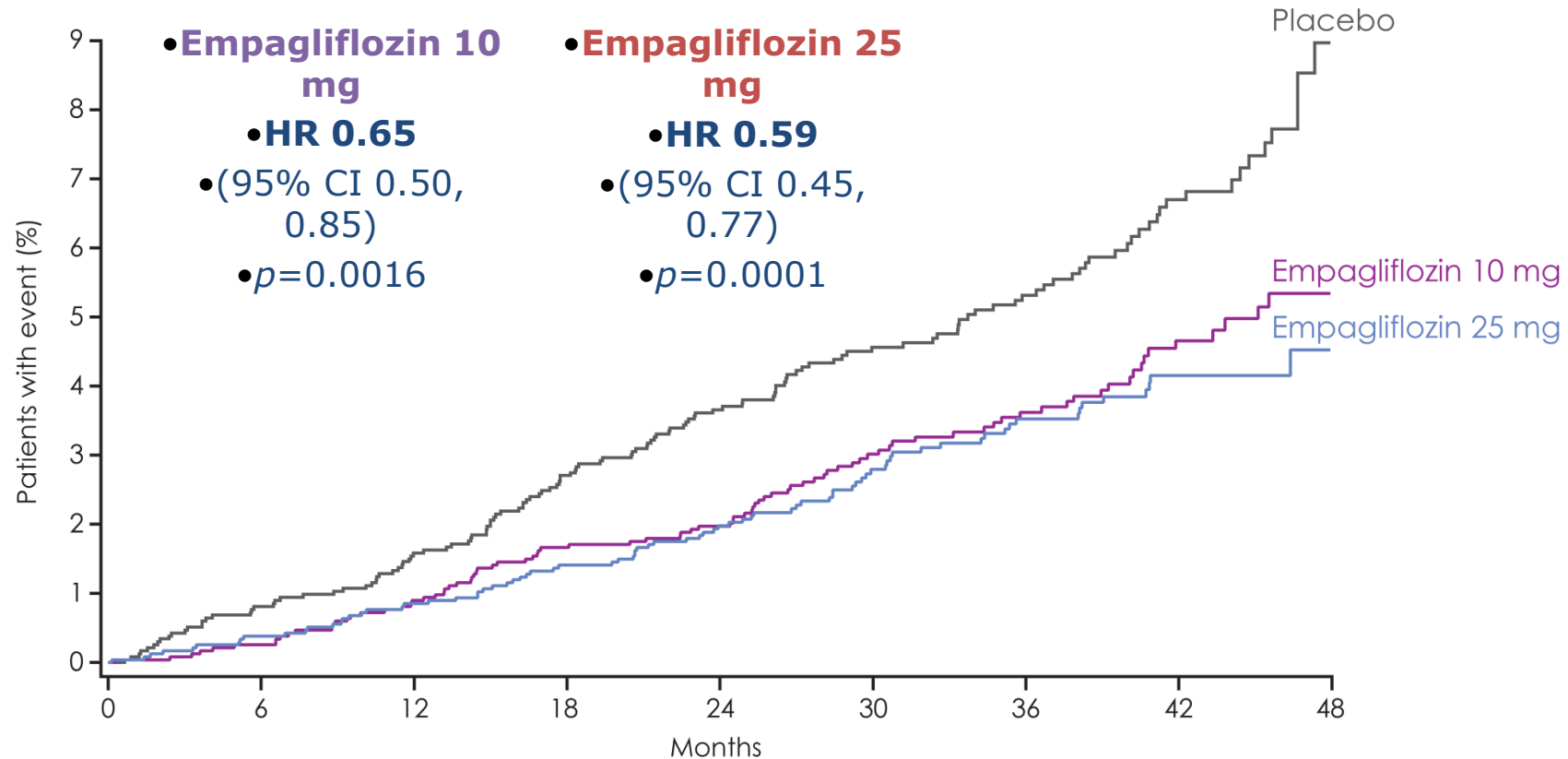
No. of patients

Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Kaplan-Meier estimate. HR, hazard ratio

SGLT2-i

EMPA-REG: CV death



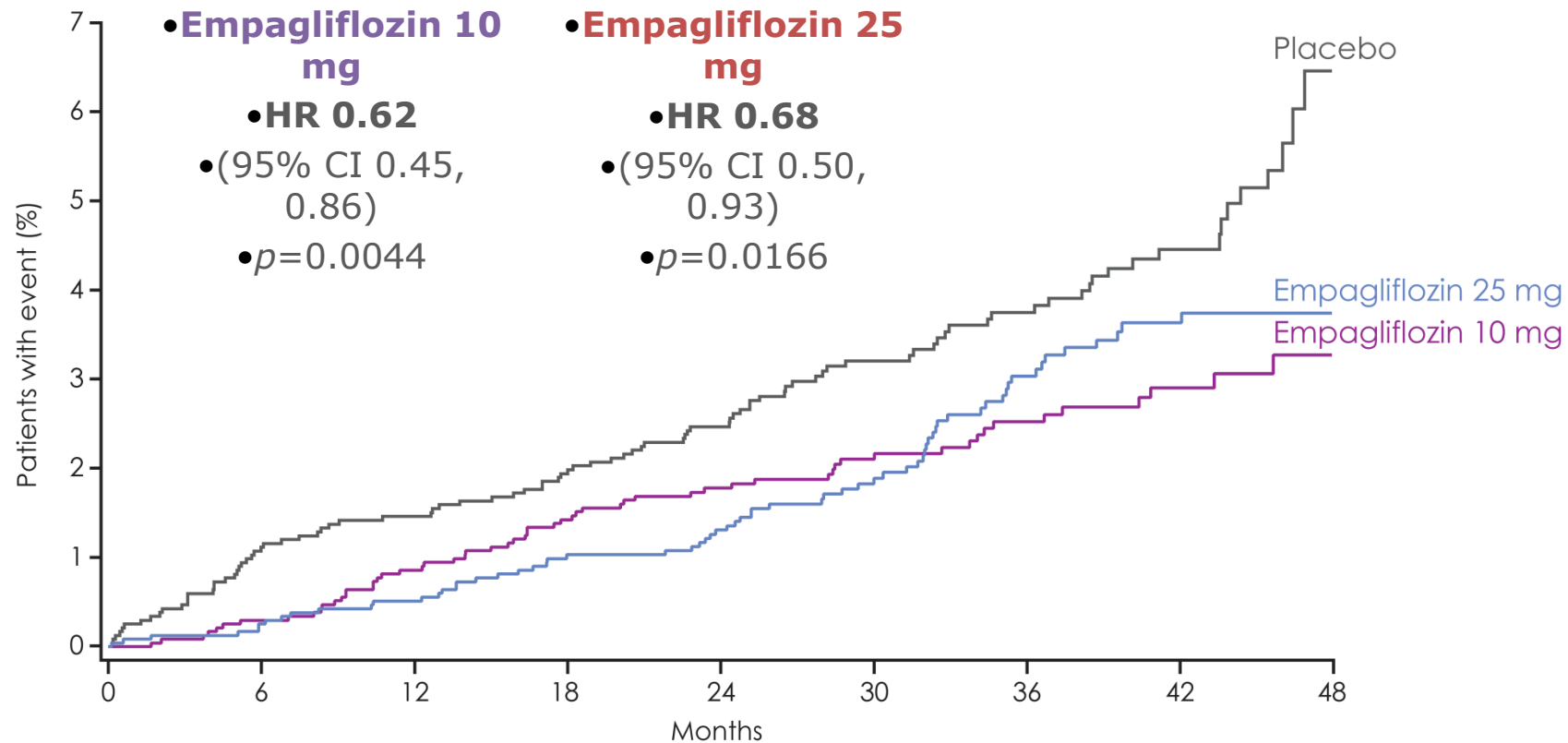
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Cumulative incidence function. HR, hazard ratio

SGLT2-i

EMPA-REG: Hospitalization for heart failure



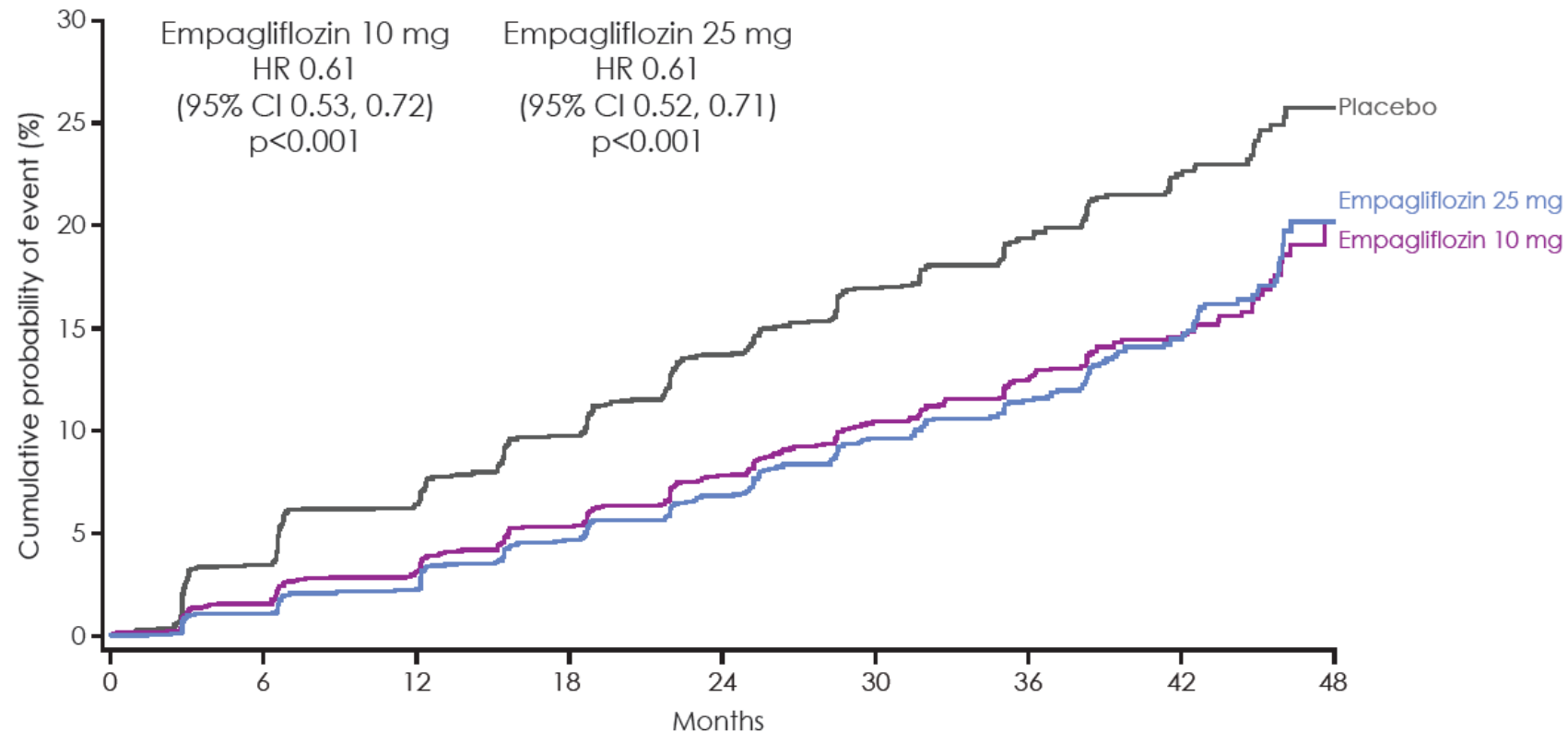
No. of patients

Empagliflozin 10 mg	2345	2306	2256	2204	1981	1473	1240	804	188
Empagliflozin 25 mg	2342	2308	2267	2223	2007	1477	1247	830	207
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function. HR, hazard ratio

SGLT2-i

EMPA-REG: New onset or worsening nephropathy

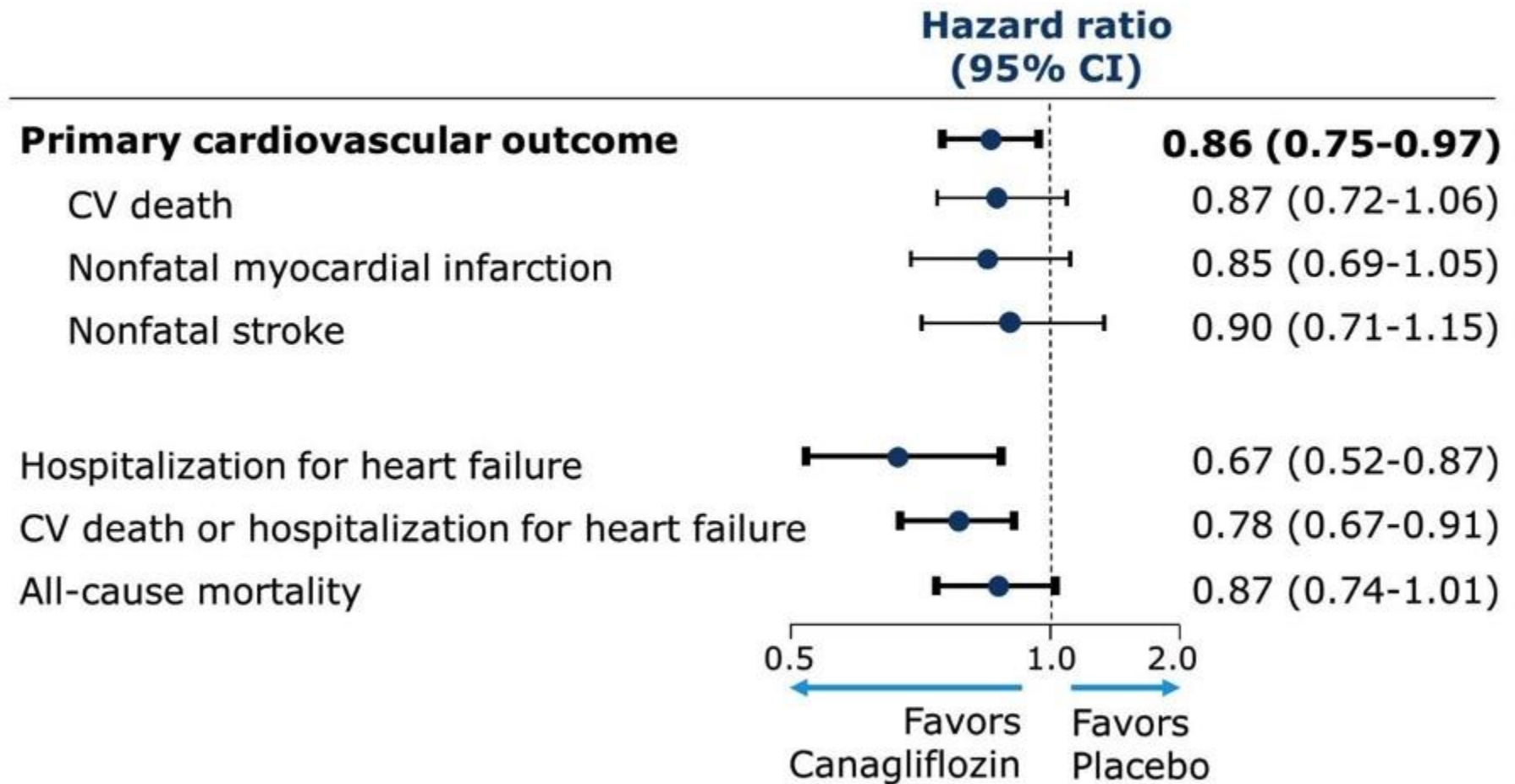


No. of patients									
Empagliflozin 10 mg	2055	1991	1912	1825	1571	1122	922	593	136
Empagliflozin 25 mg	2069	2003	1936	1844	1600	1157	965	626	154
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Kaplan-Meier estimate. Patients treated with at least one dose of study drug. Hazard ratios are based on Cox regression analyses.
HR, hazard ratio; CI, confidence interval. Pre-specified analyses.

SGLT2-i

Summary CANVAS study program



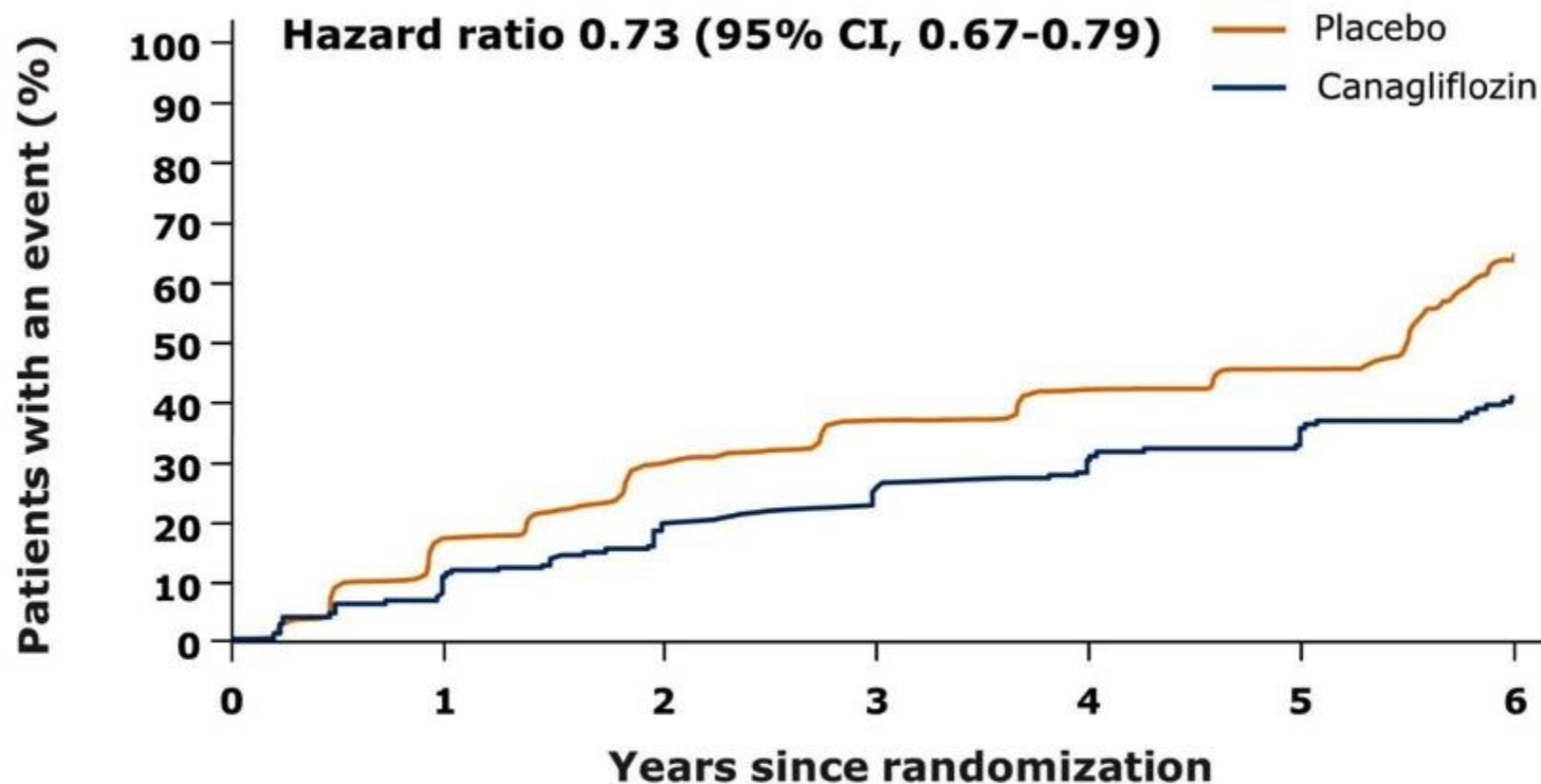
Intent-to-treat analysis

Presented at the 77th Scientific Sessions of the American Diabetes Association;
June 12, 2017; San Diego, CA.

SGLT2-i

CANVAS study program

Progression of Albuminuria



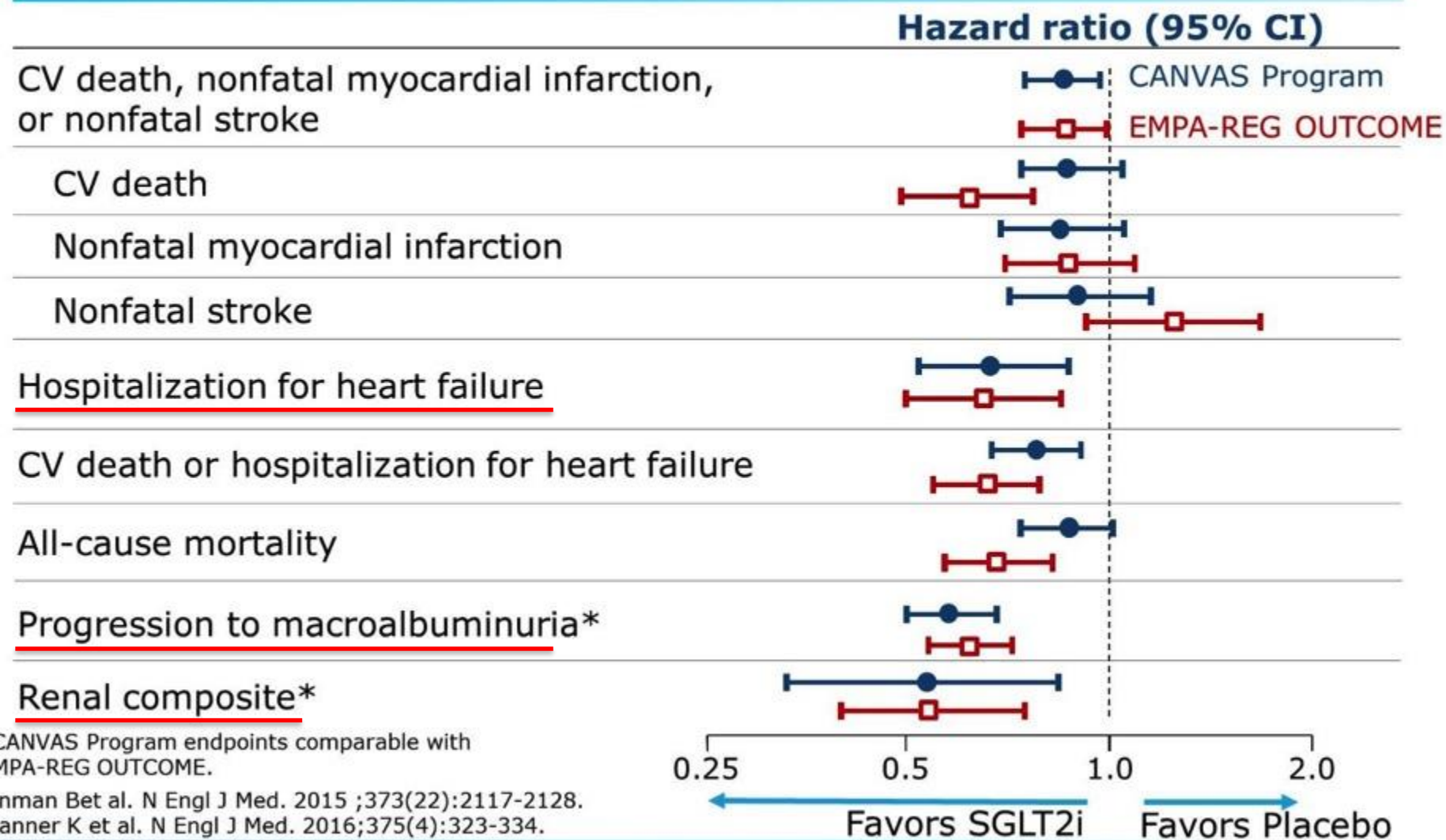
No. of patients

Placebo	3819	3096	1690	724	626	548	303
Canagliflozin	5196	4475	2968	1730	1528	1354	775

Intent-to-treat analysis

Presented at the 77th Scientific Sessions of the American Diabetes Association;
June 12, 2017; San Diego, CA.

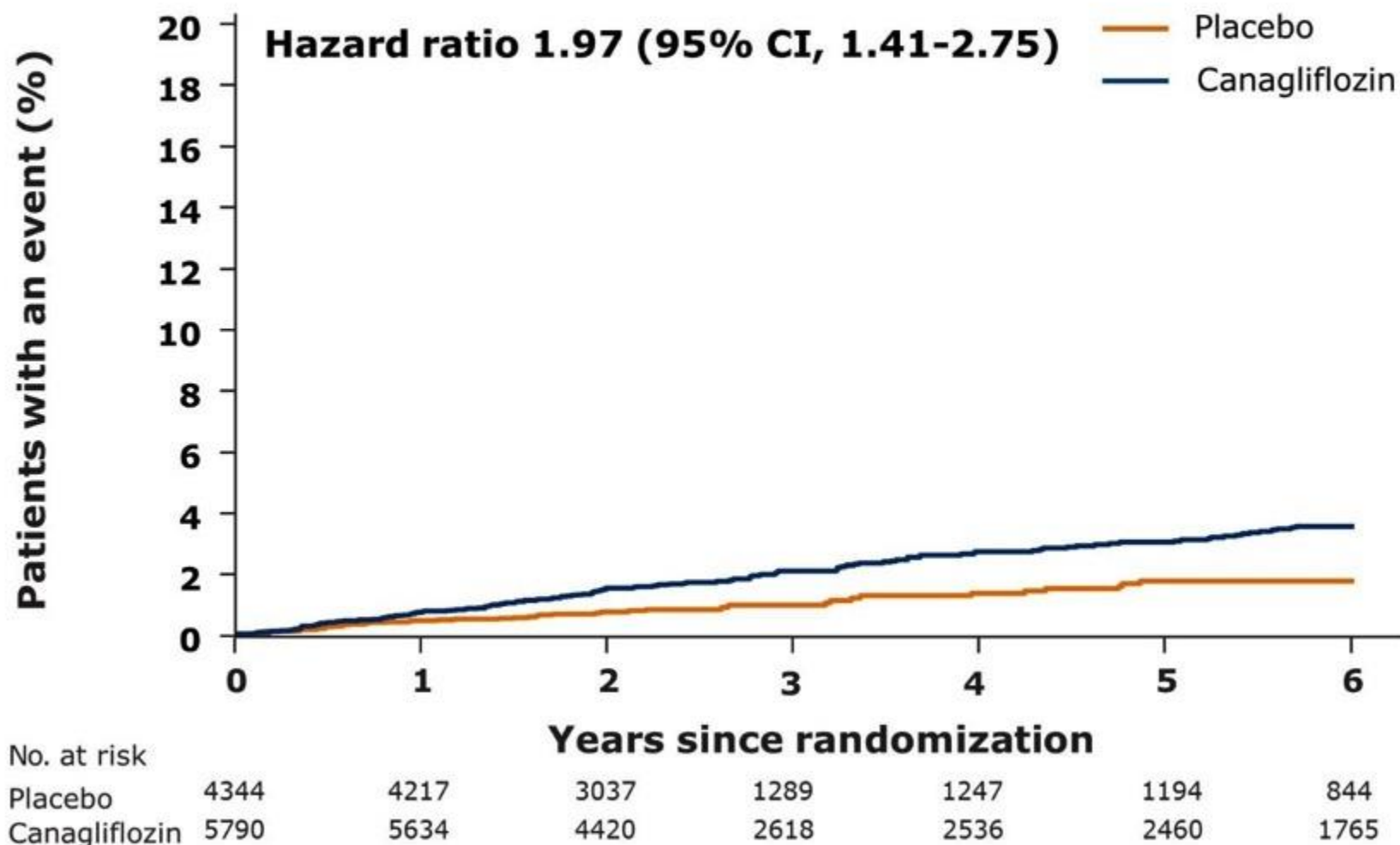
Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME



SGLT2-i

CANVAS study program

Lower-extremity Amputations

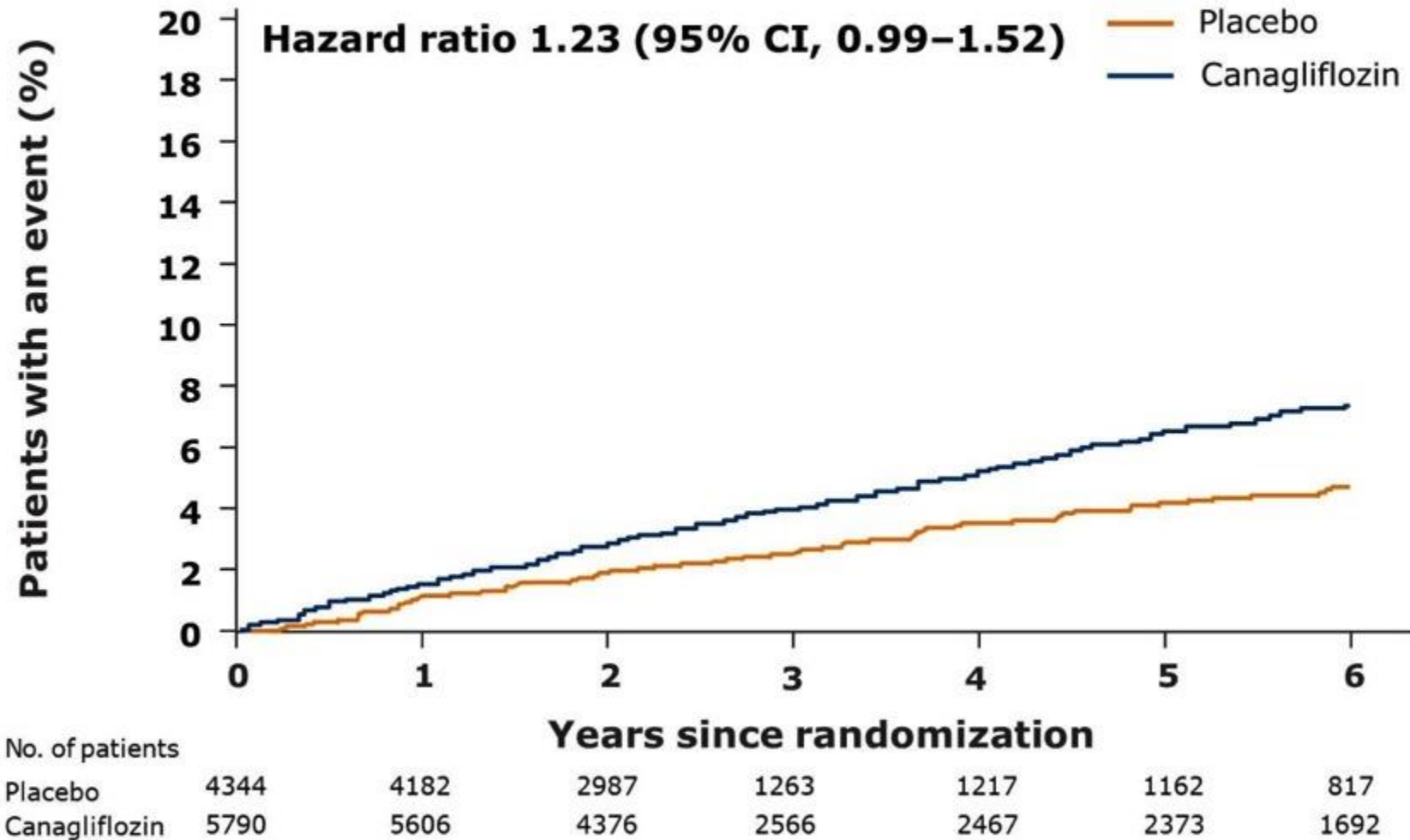


Increased risk communicated to health authorities, investigators, and providers in 2016 based on IDMC letter.

SGLT2-i

CANVAS study program

Low-trauma Fracture



ORIGINAL RESEARCH ARTICLE

ORIGINAL RESEARCH
ARTICLE

Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)

Editorial, see p 260

BACKGROUND: Reduction in cardiovascular death and hospitalization for heart failure (HHF) was recently reported with the sodium-glucose cotransporter-2 inhibitor (SGLT-2i) empagliflozin in patients with type 2 diabetes mellitus who have atherosclerotic cardiovascular disease. We compared HHF and death in patients newly initiated on any SGLT-2i versus other glucose-lowering drugs in 6 countries to determine if these benefits are seen in real-world practice and across SGLT-2i class.

METHODS: Data were collected via medical claims, primary care/hospital records, and national registries from the United States, Norway, Denmark, Sweden, Germany, and the United Kingdom. Propensity score for SGLT-2i initiation was used to match treatment groups. Hazard ratios for HHF, death, and their combination were estimated by country and pooled to determine weighted effect size. Death data were not available for Germany.

RESULTS: After propensity matching, there were 309 056 patients newly initiated on either SGLT-2i or other glucose-lowering drugs (154 528 patients in each treatment group). Canagliflozin, dapagliflozin, and empagliflozin accounted for 53%, 42%, and 5% of the total exposure time in the SGLT-2i class, respectively. Baseline characteristics were balanced between the 2 groups. There were 961 HHF cases during 190 164 person-years follow-up (incidence rate, 0.51/100 person-years). Of 215 622 patients in the United States, Norway, Denmark, Sweden, and the United Kingdom, death occurred in 1334 (incidence rate, 0.87/100 person-years), and HHF or death in 1983 (incidence rate, 1.38/100 person-years). Use of SGLT-2i, versus other glucose-lowering drugs, was associated with lower rates of HHF (hazard ratio, 0.61; 95% confidence interval, 0.51–0.73; $P<0.001$); death (hazard ratio, 0.49; 95% confidence interval, 0.41–0.57; $P<0.001$); and HHF or death (hazard ratio, 0.54; 95% confidence interval, 0.48–0.60; $P<0.001$) with no significant heterogeneity by country.

CONCLUSIONS: In this large multinational study, treatment with SGLT-2i versus other glucose-lowering drugs was associated with a lower risk of HHF and death, suggesting that the benefits seen with empagliflozin in a randomized trial may be a class effect applicable to a broad population of patients with type 2 diabetes mellitus in real-world practice.

CLINICAL TRIAL REGISTRATION: URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT02993614.

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Sources of Funding, see page 257

Key Words: canagliflozin
■ dapagliflozin ■ death ■
diabetes mellitus ■ empagliflozin
■ heart failure ■ sodium glucose
transporter 2

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Overwegingen mbt SGLT-2 remmers en GLP1-RA

- **Kunnen we spreken over een klasse effect?**

Voorlopig nog niet; EMPA-REG en CANVAS laten toch wel iets andere resultaten zien
Liraglutide en semaglutide zijn de enige GLP1-RA die cardioprotectie hebben laten zien (echter: recente meta-analyse!)

- **Klinische betekenis van de renale uitkomsten?**

Vooraf voor de SGLT2-remmers

- **Amputaties en fracturen bij canagliflozine studies?**

Behoeven nader onderzoek; uit meta-analyse voorlopig: geen nadelige effecten

- **Wat behandel je primair met een SGLT2 remmer en GLP1-RA?**

Waarschijnlijk verlaag je primair het CV risico via glucose onafhankelijke mechanismen

- **Inzetten SGL2-remmers bij hartfalen?**

Studies onderweg

Casus

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LDL-C: 3,5 mmol/L

RR 150/70

Lab is niets op aan te merken, eGFR 62 ml/min

HbA1c opgelopen naar 68

Wat nu? Is dit een patiënte voor een SGLT-i of GLP1-RA?

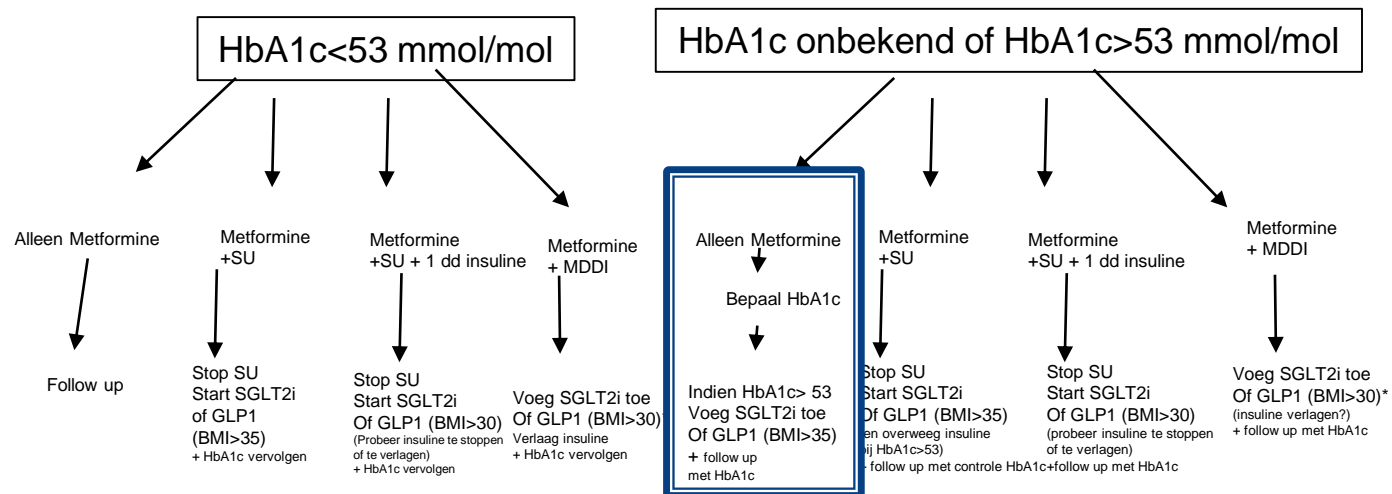
Voorstel inzet SGLT2-i en GLP1-RA bij T2DM en hoog CVR

T2DM met “event” of hoog CVR bij de cardioloog

(cardiovasculair event of clustering van risicofactoren zoals: proteïnurie, retinopathie, PNP, hypertensie, roken, obesitas)
(zonder contraïndicaties voor SGLT2 [eGFR>60 ml/min; geen UWIs])

Cardiovasculair event: hartfalen, coronairsclerose, perifeer vaatlijden, CVA

(Opm: aanpassing van diabetes medicatie alleen door huisarts [terugverwijzing] of internist [verwijzing])



* Nog niet vergoed bij MDDI

Conclusie

1. Empagliflozine: gunstige effecten cardiovasculair, renaal en hartfalen (geldt ook voor canagliflozine)
2. Cave: atypische fracturen en amputaties met canagliflozine (CANVAS)
3. Dapagliflozine studies lopen nog
4. GLP1-RA: liraglutide en semaglutide: positief op MACE (maar andere middelen nog niet)