Trial Updates in Type 2 Diabetes: Cardiovascular Outcomes and Clinical Implications

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Disclosures

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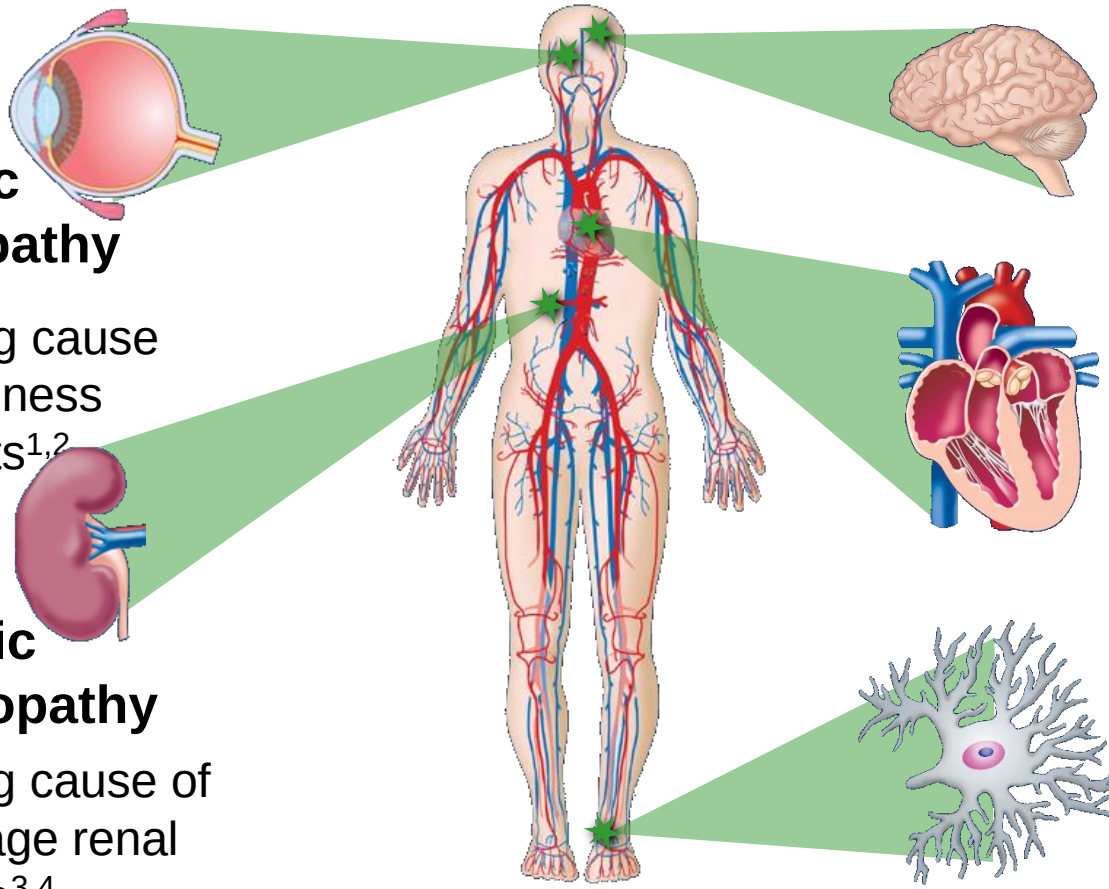
Complications of Diabetes



Diabetic Retinopathy

Leading cause of blindness in adults[1,2]

Diabetic Nephropathy

Leading cause of end-stage renal disease[3,4]

Stroke

2- to 4-fold increase in cardiovascular mortality and stroke[5]

Cardiovascular Disease

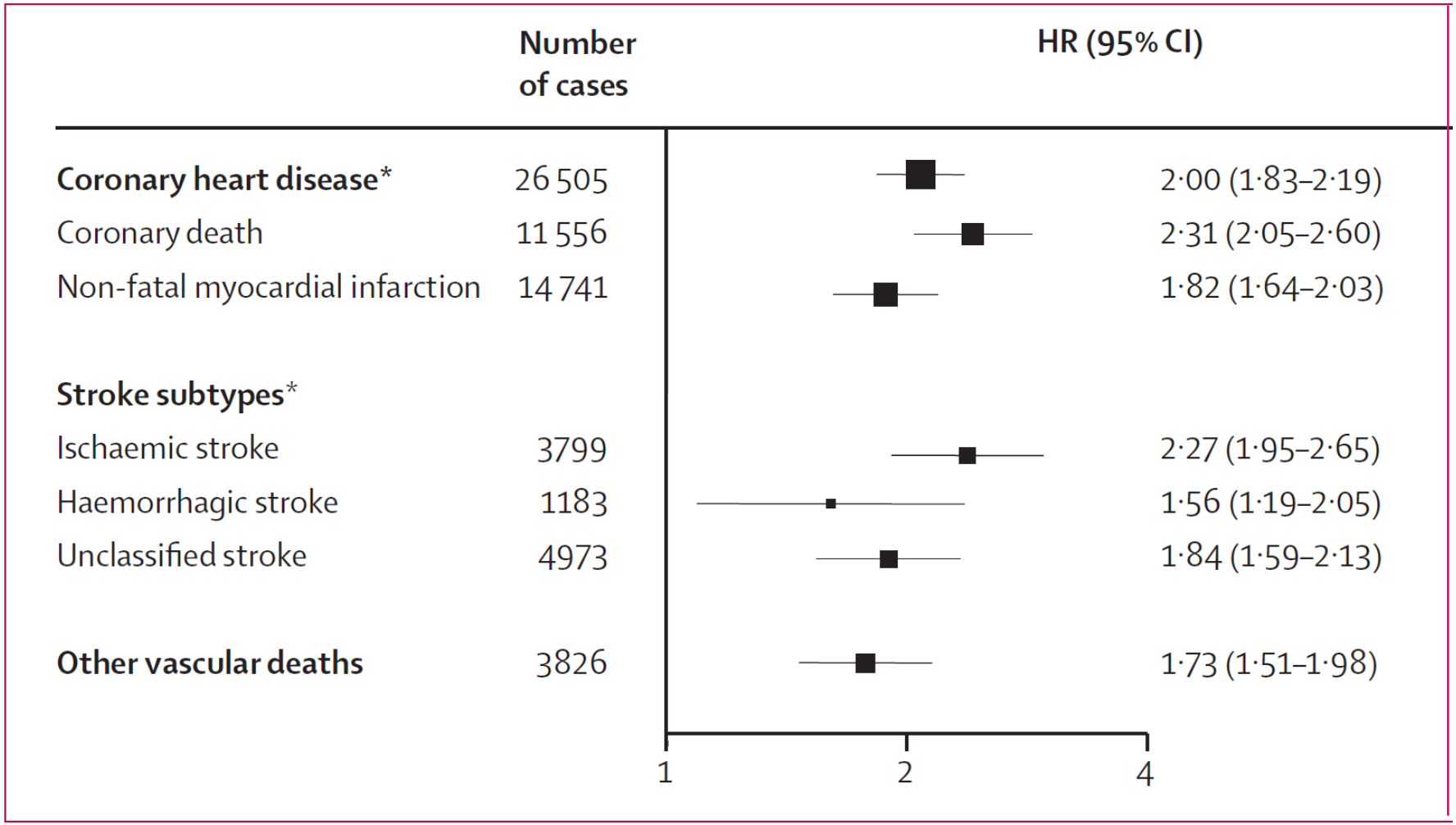
8/10 individuals with diabetes die from CVD

Diabetic Neuropathy

Leading cause of non-traumatic lower extremity amputations[7,8]

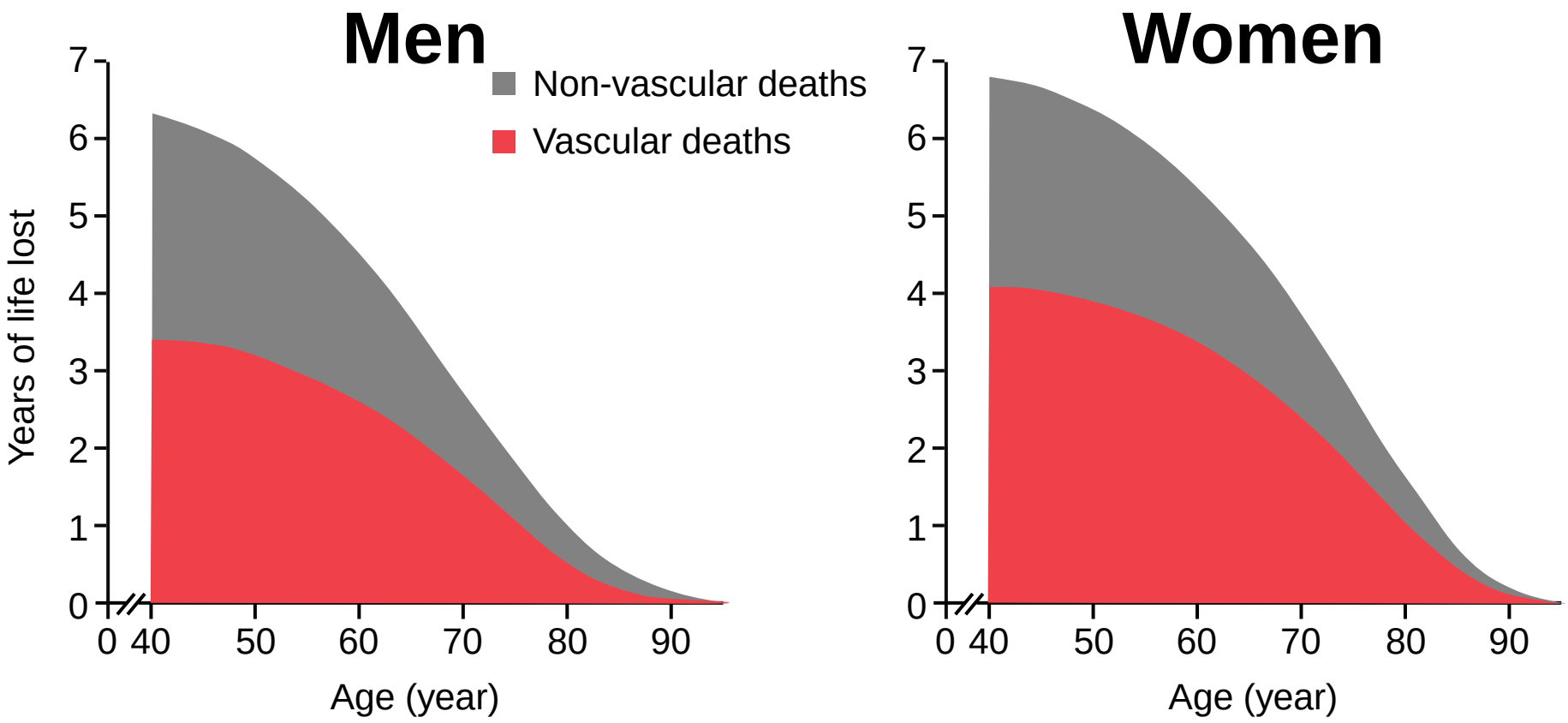
ON average diabetes doubles CVD risk

Emerging Risk Factor Collaboration (2010) Lancet



Hazard ratios for vascular outcomes DM vs. no DM

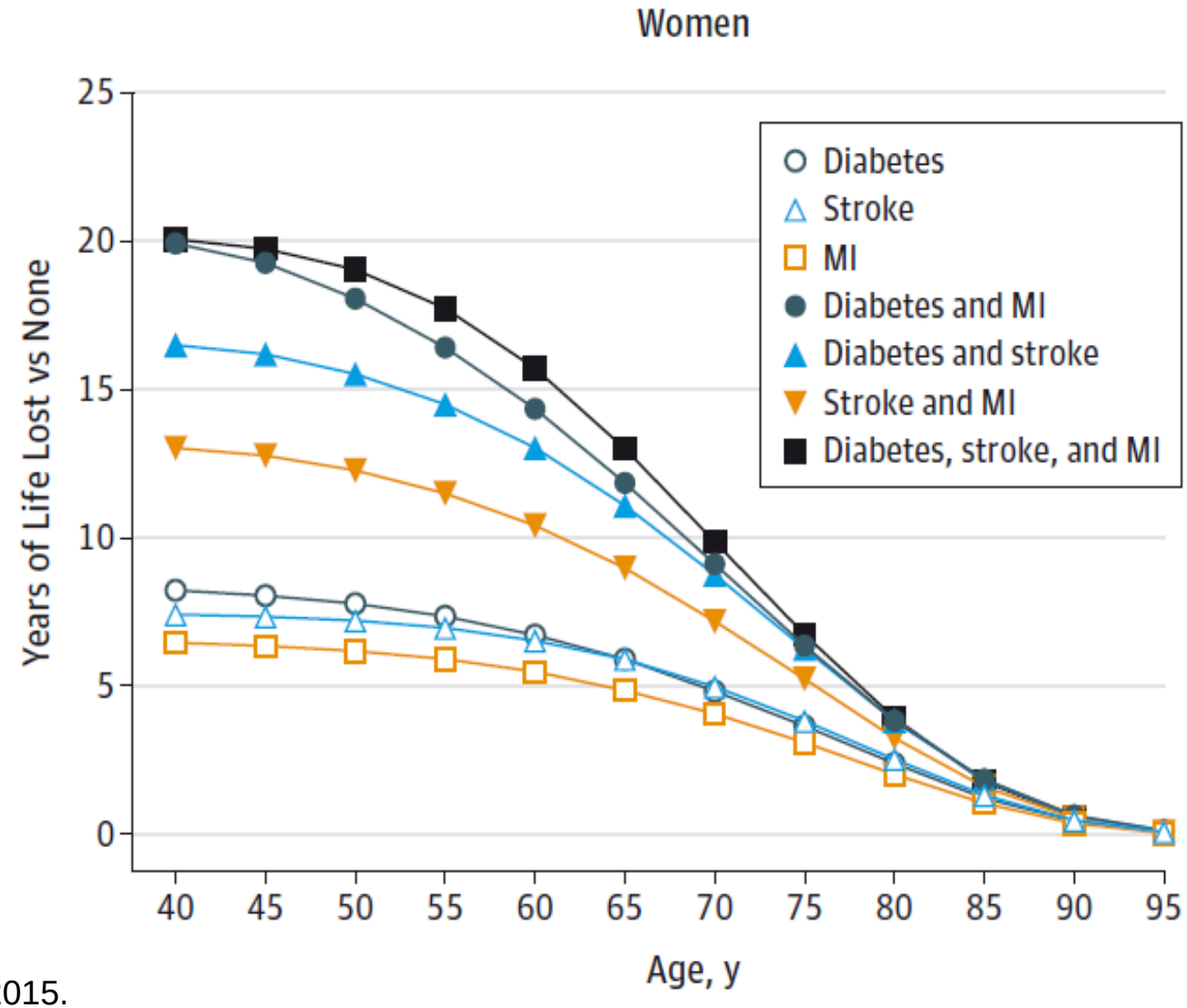
Diabetes is associated with significant loss of life years



On average, a 50-year old with diabetes but no history of vascular disease is ~6 years younger at time of death than a counterpart without diabetes

Seshasai et al. N Engl J Med 2011;364:829-41.

Diabetes PLUS prior CVD begets high premature mortality



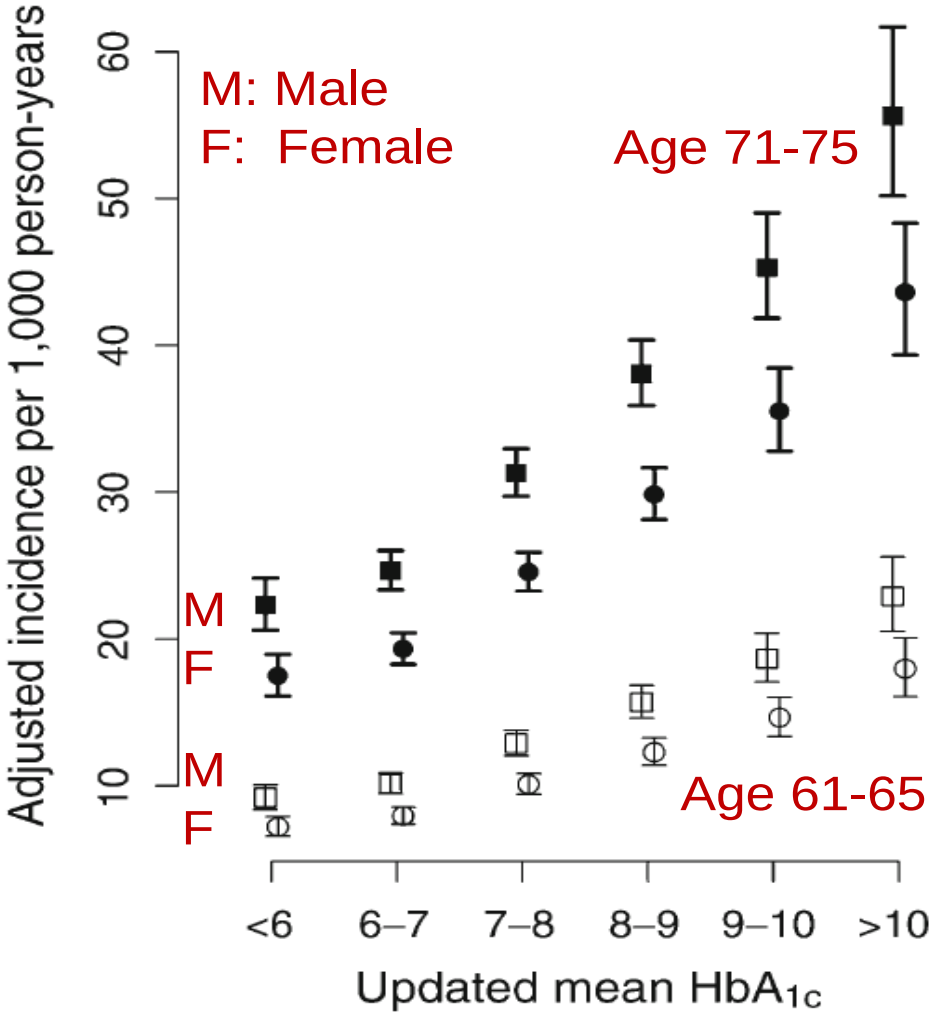
ERFC *JAMA* 2015.

Type 2 DM: A1c & Heart Failure

- **N=83,021 from Swedish National Register 1998-’03, f/u until HF, death or Dec 31/09**
- **10,969 (13.2%) developed HF during a mean follow-up of 7.2 years**

Overall incidence ~ 2%/y

Independent predictors were HbA1c, older age, male sex, diabetes duration



Lind et al. Diabetologia 2012;55:2946

What works and what may not work for CVD prevention

What works?

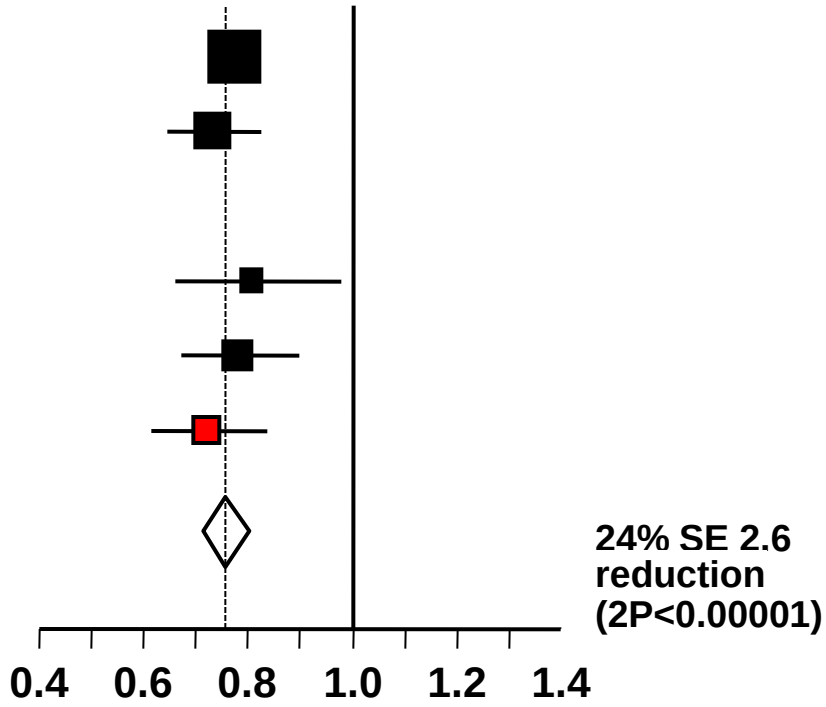
- Statins
- BP reduction
- Smoking cessation
- *Glucose lowering?*
  - *Modality?*

What remains uncertain

- *Lifestyle intervention?*
- Fibrates?
- *Aspirin – primary prevention?*

Statins Work as well in DM as in Non-DM

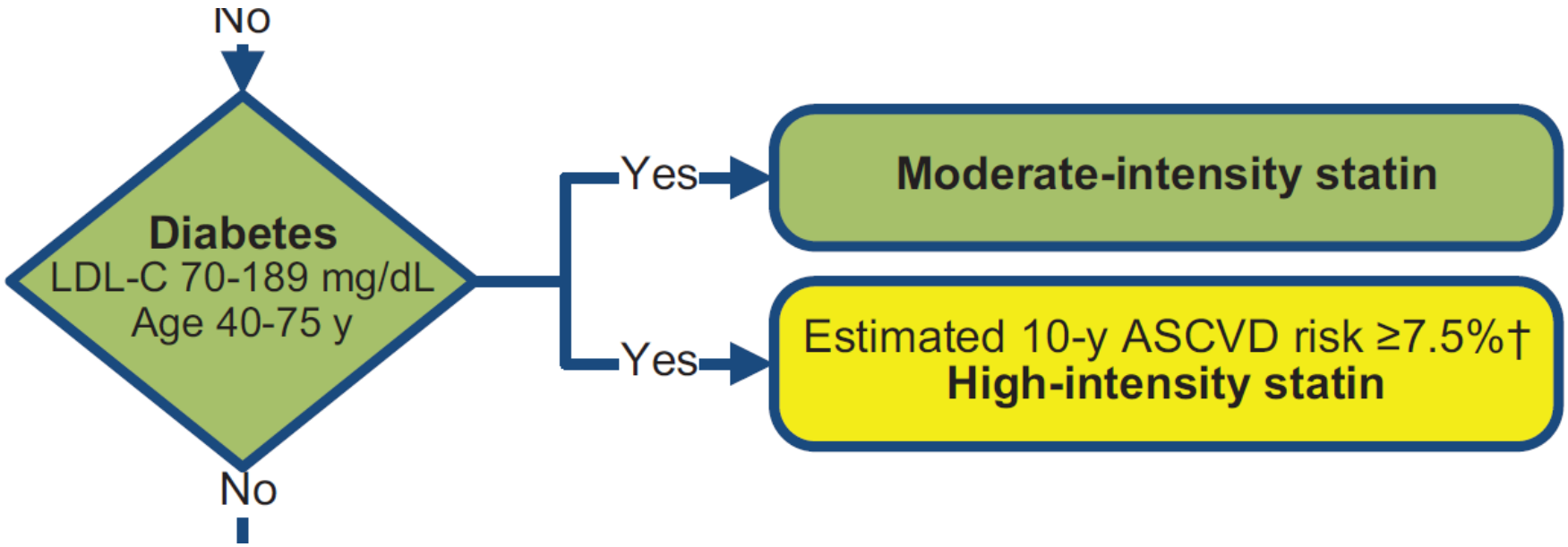
Baseline feature	STATIN (10269)	PLACEBO (10267)
Previous MI	1007	1255
Other CHD (not MI)	452	597
No prior CHD		
CVD	182	215
PVD	332	427
Diabetes	**279**	**369**
ALL PATIENTS	2042 (19.9%)	2606 (25.4%)



20% reduction in risk per ~40 mg/dl reduction in LDL-c

Heart Protection Study (2002) Lancet

Which patients with diabetes recommended for statin?



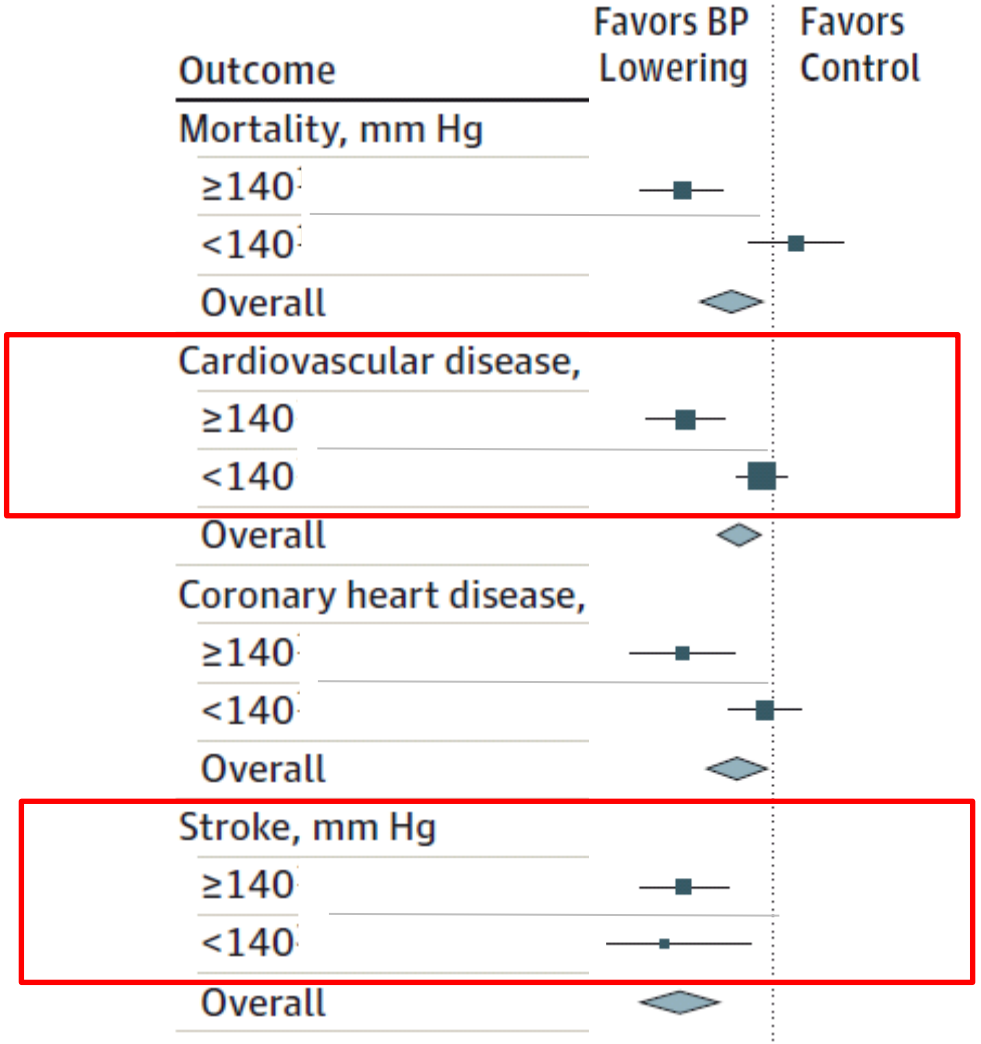
- **If aged < 40 or >75 and LDL-c <190**
  - Measure risk score and consider if:
    - Additional ASCVD risk factors: obesity, FH premature CAD, smoking, hypertension, LDL > 100 mg/dl.
    - Presence of CKD, retinopathy
    - CRP >2mg/l, CAC >=300 Agatston unit, ABI <0.9

Stone (2014) JACC

Original Investigation

Blood Pressure Lowering in Type 2 Diabetes
A Systematic Review and Meta-analysis

Connor A. Emdin, HBSc; Kazem Rahimi, DM, MSc; Bruce Neal, PhD; Thomas Callender, MBChB; Vlado Perkovic, PhD; Anushka Patel, PhD



Emdin et al (2015) JAMA

SBP target: 140 most, 130 select but relax in elderly? (150 when >80 yrs)

- **For most outcomes, risk reduction max <140 SBP[1]**
- **<130 SBP further reductions in stroke, retinopathy and albuminuria[1]**
- **DBP < 70 associated with increased mortality in older adults[2]**
- **All BP meds work – though CCBs less stroke, ARBs and diuretics, less HF[1]**
  - Beta-blockers least impressive

Emdin et al JAMA 2015 2 ADA Standards of Care 2016

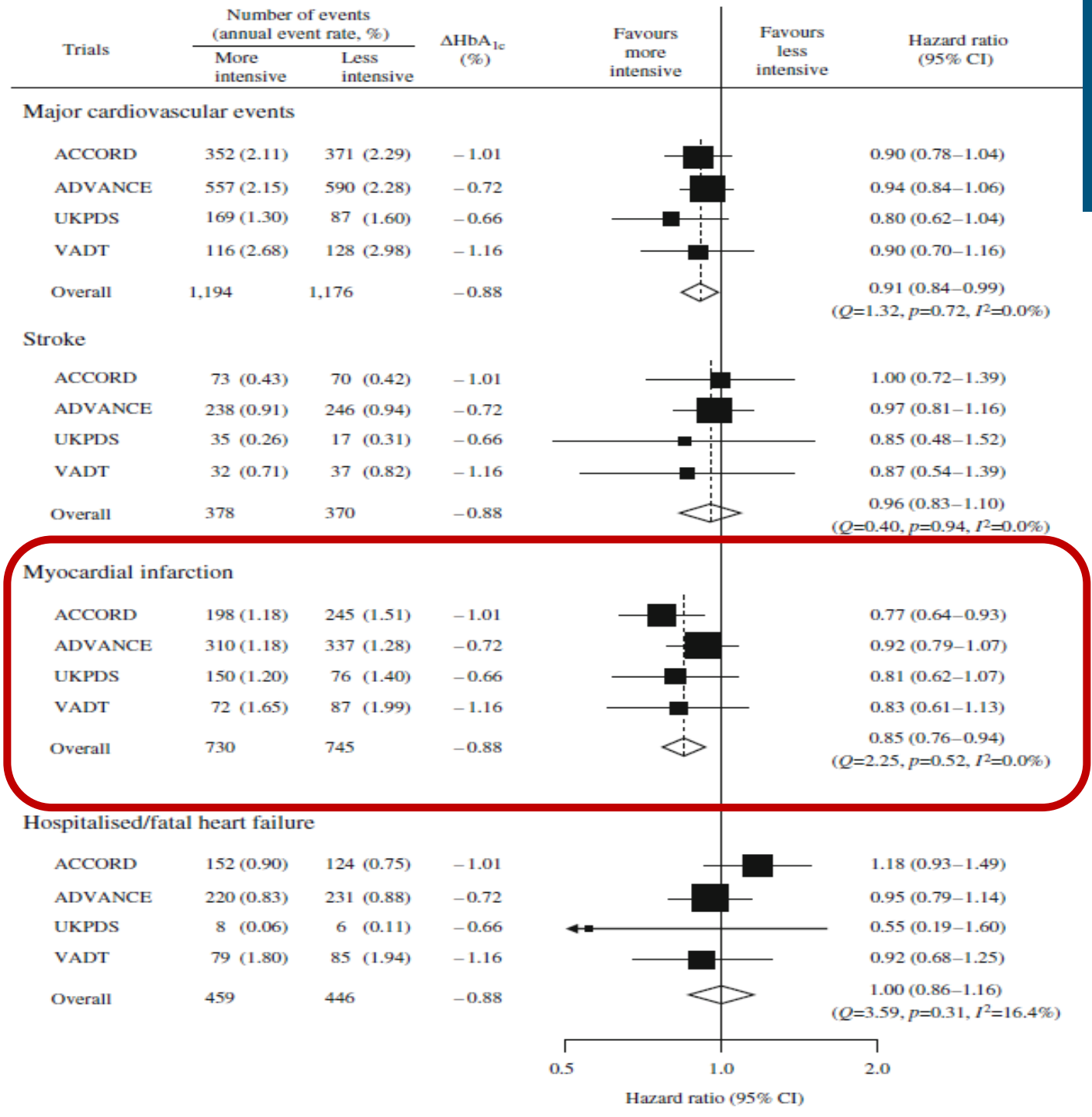
Type 2 DM: Glucose Lowering Trials

Study	Duration (yrs)	N	Glycemia	
			Target	Achieved A1c
UKPDS	10	3867	FPG < 6 (110)	7.0% vs. 7.9%
ACCORD	3.5	10251	A1C < 6.0%	6.4% vs. 7.5%
ADVANCE	5	11140	A1C < 6.5%	6.5% vs. 7.3%
VADT	6.3	1791	A1C < 6.0%	6.9% vs. 8.4%

UKPDS - Lancet 1998:837-853; ACCORD - NEJM 2011:818-828
ADVANCE - NEJM 2008:2560-72; VADT - NEJM 360;129-39

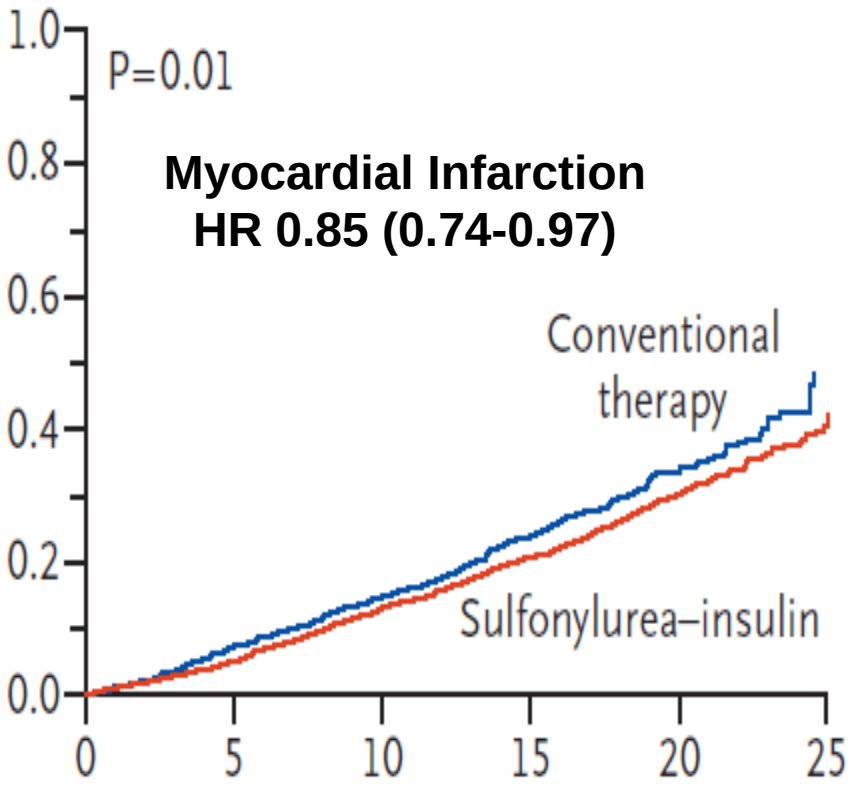
Meta-Analysis of Glucose Lowering Trials

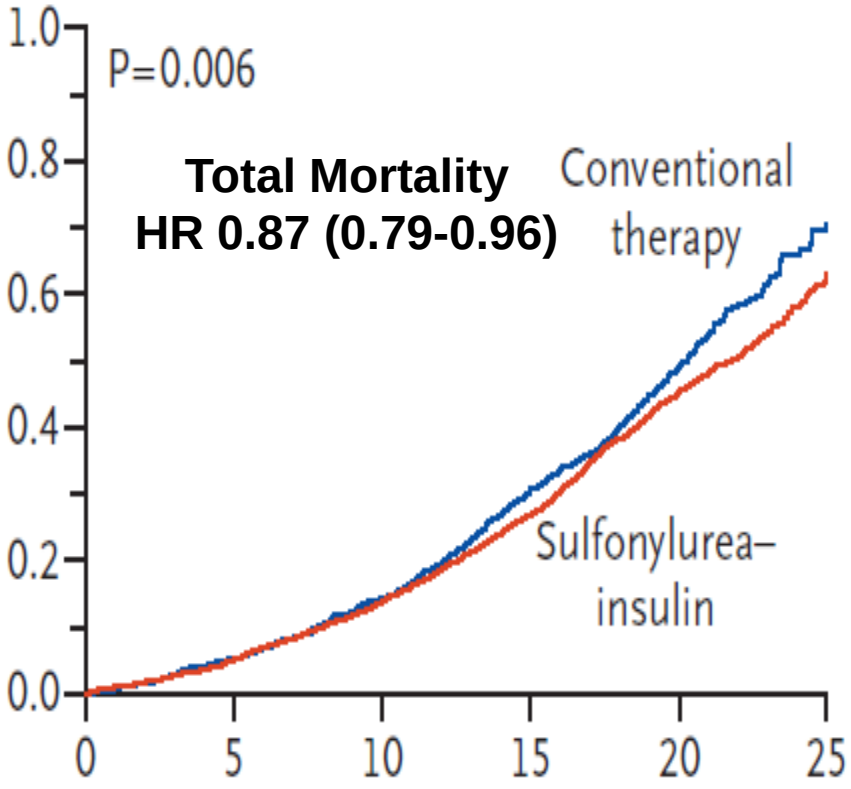
ACCORD
ADVANCE
UKPDS (@ 5y)
VADT



Turnbull et al. Diabetologia 2009;2288

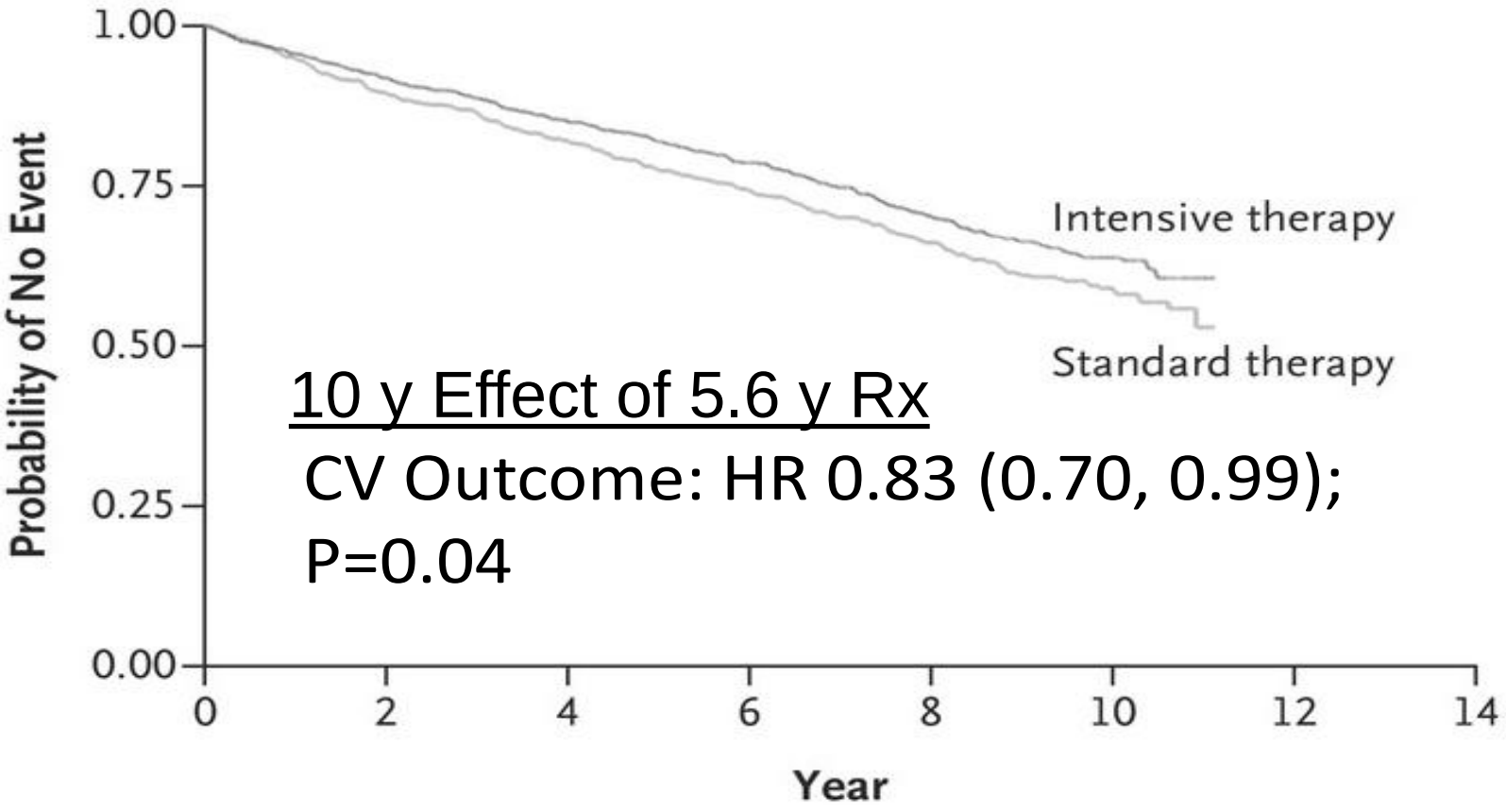
Legacy Effects: New T2DM
UKPDS F/U NEJM 2008;359:1-13





Legacy Effects: Advanced T2DM

VADT F/U NEJM 2015;372:2197

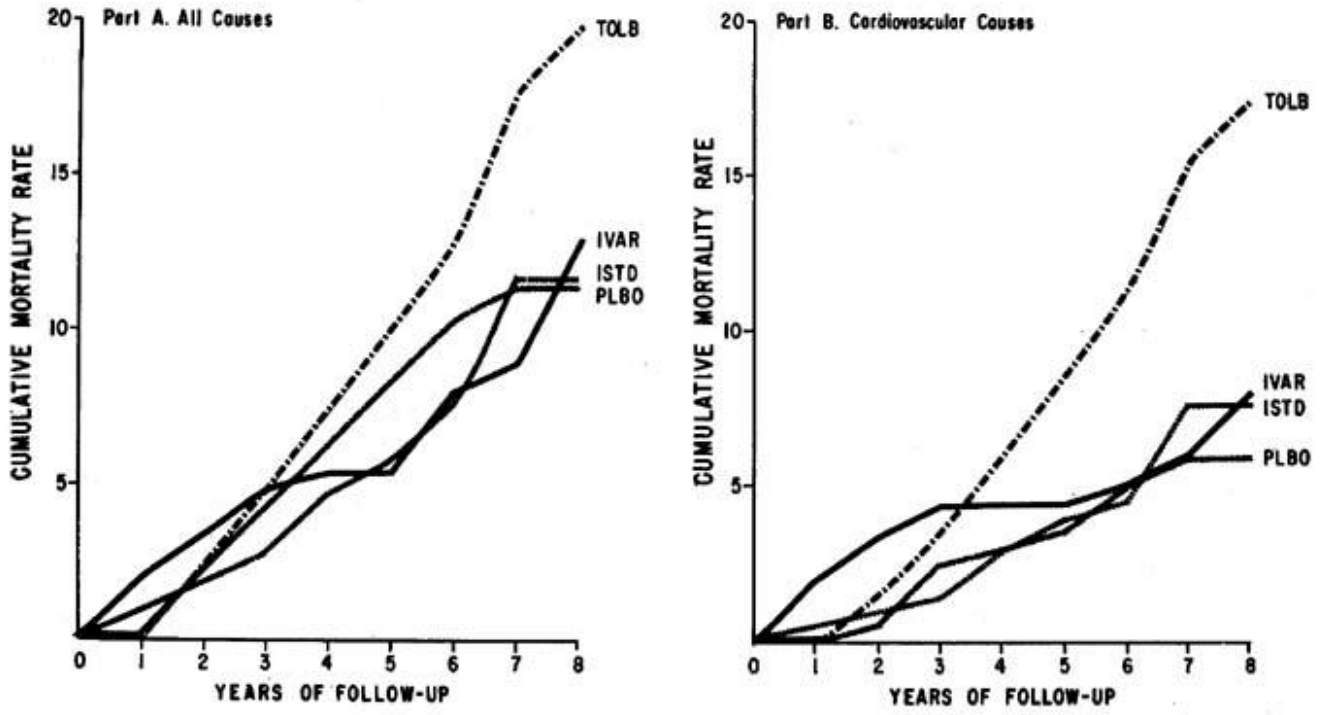


10 y Effect of 5.6 y Rx

CV Outcome: HR 0.83 (0.70, 0.99);

P=0.04

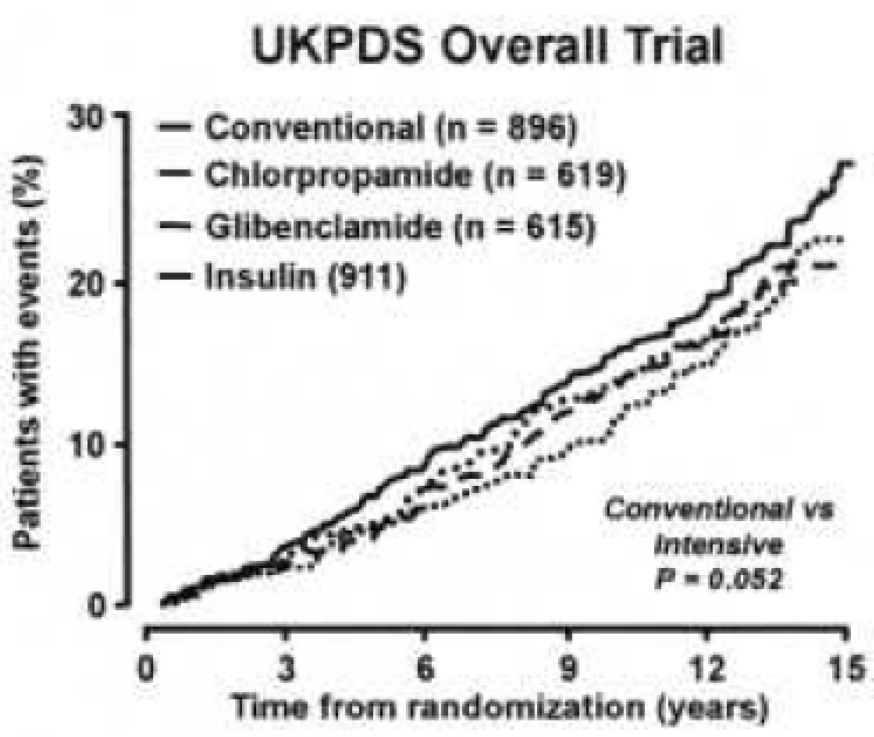
UGDP: Tolbutamide vs insulin vs placebo



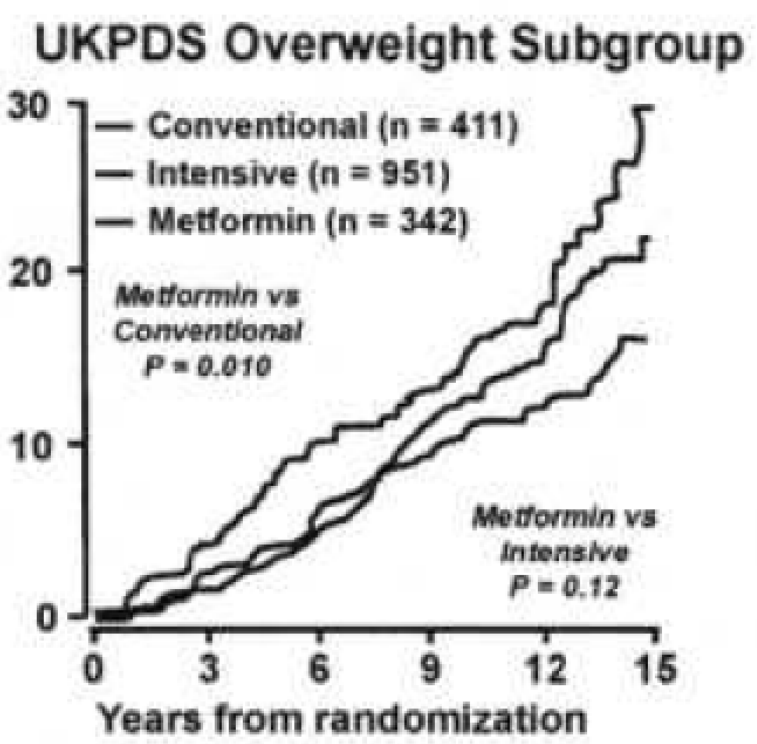
UGDP, Diabetes, 1970

UKPDS Study
Fatal or Nonfatal MI, Sudden Death

[a]

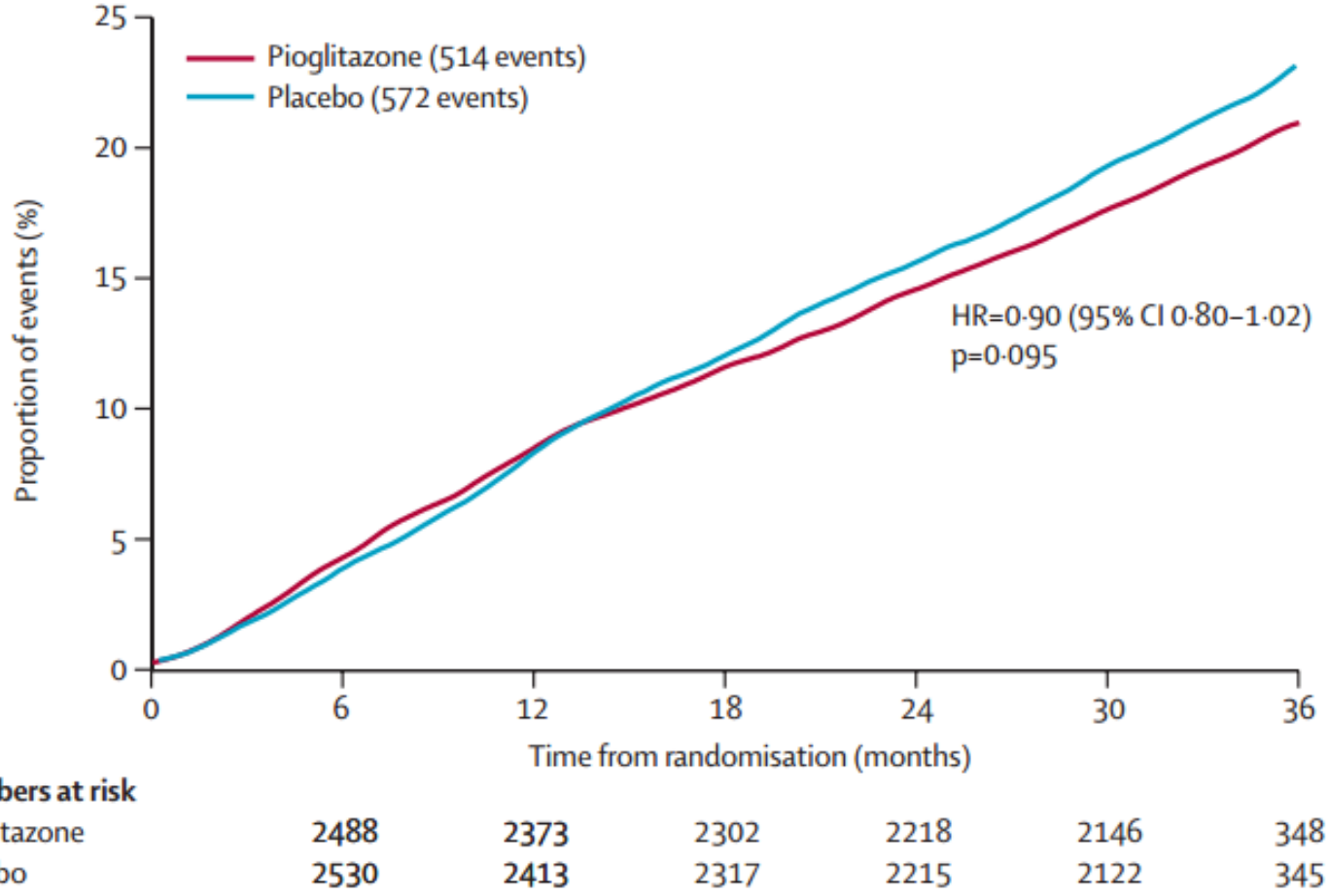


[b]



a. UKPDS Group. *Lancet*. 1998;352:837-853.
b. UKPDS Group. *Lancet*. 1998;352:854-865.

PROspective Actos Clinical Trial In MacroVascular Events (PROactive) Primary Endpoint



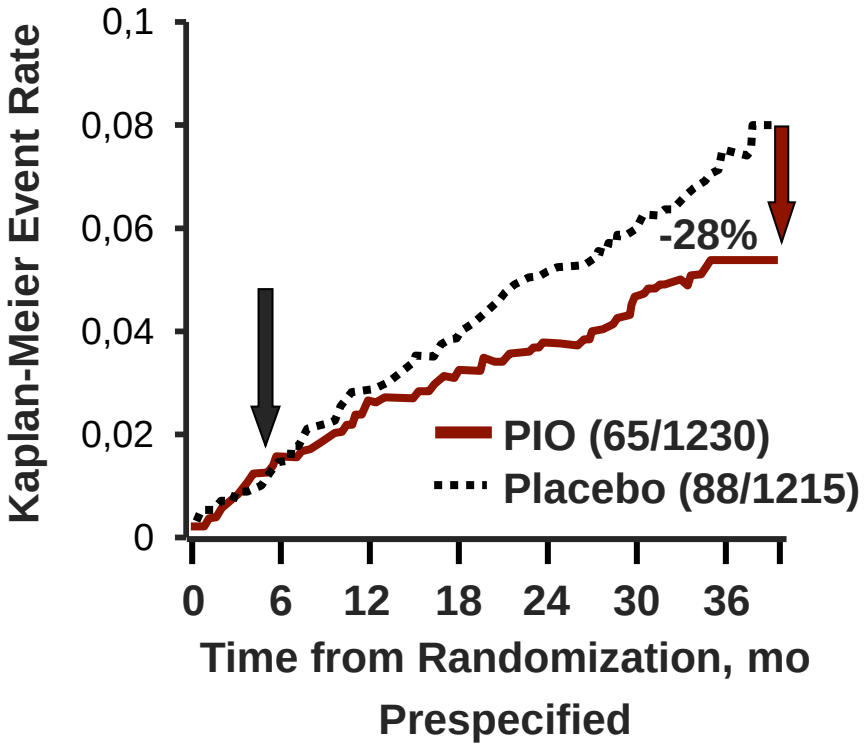
Death, MI, CVA, ACS, Leg Revascularization or Amputation, PCI, or CABG

Dormandy JA, et al. *Lancet*. 2005;366:1279-1289.

PROactive: *Pioglitazone (PIO) Reduces "Hard" Coronary Heart Disease Endpoints*

Time to Fatal/Nonfatal MI (Excluding Silent MI)

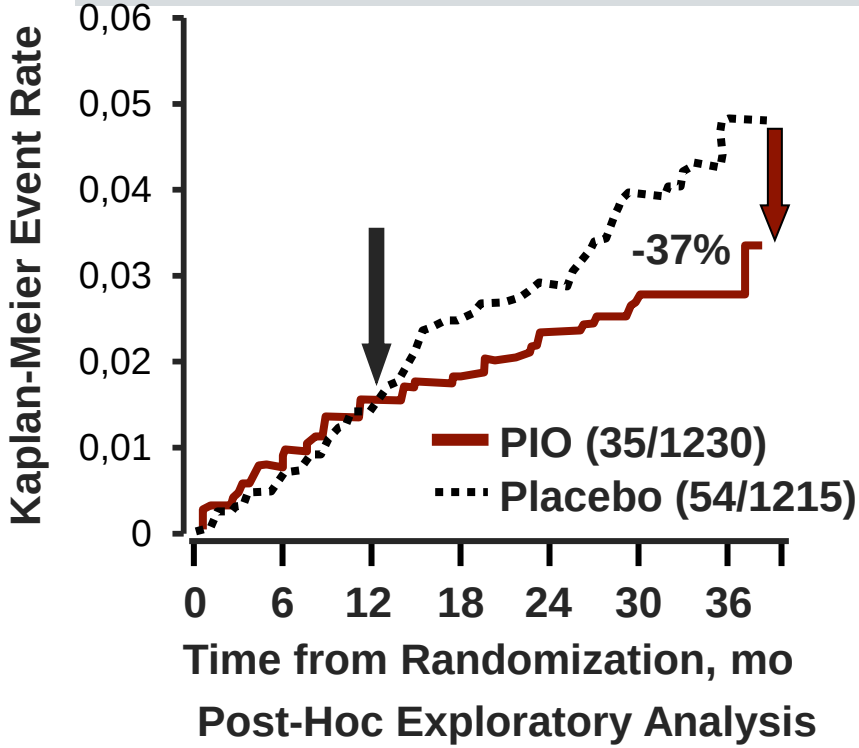
	HR	95% CI	*P* Value
PIO vs placebo	0.72	0.52-0.99	.045



Prespecified

Time to Acute Coronary Syndrome

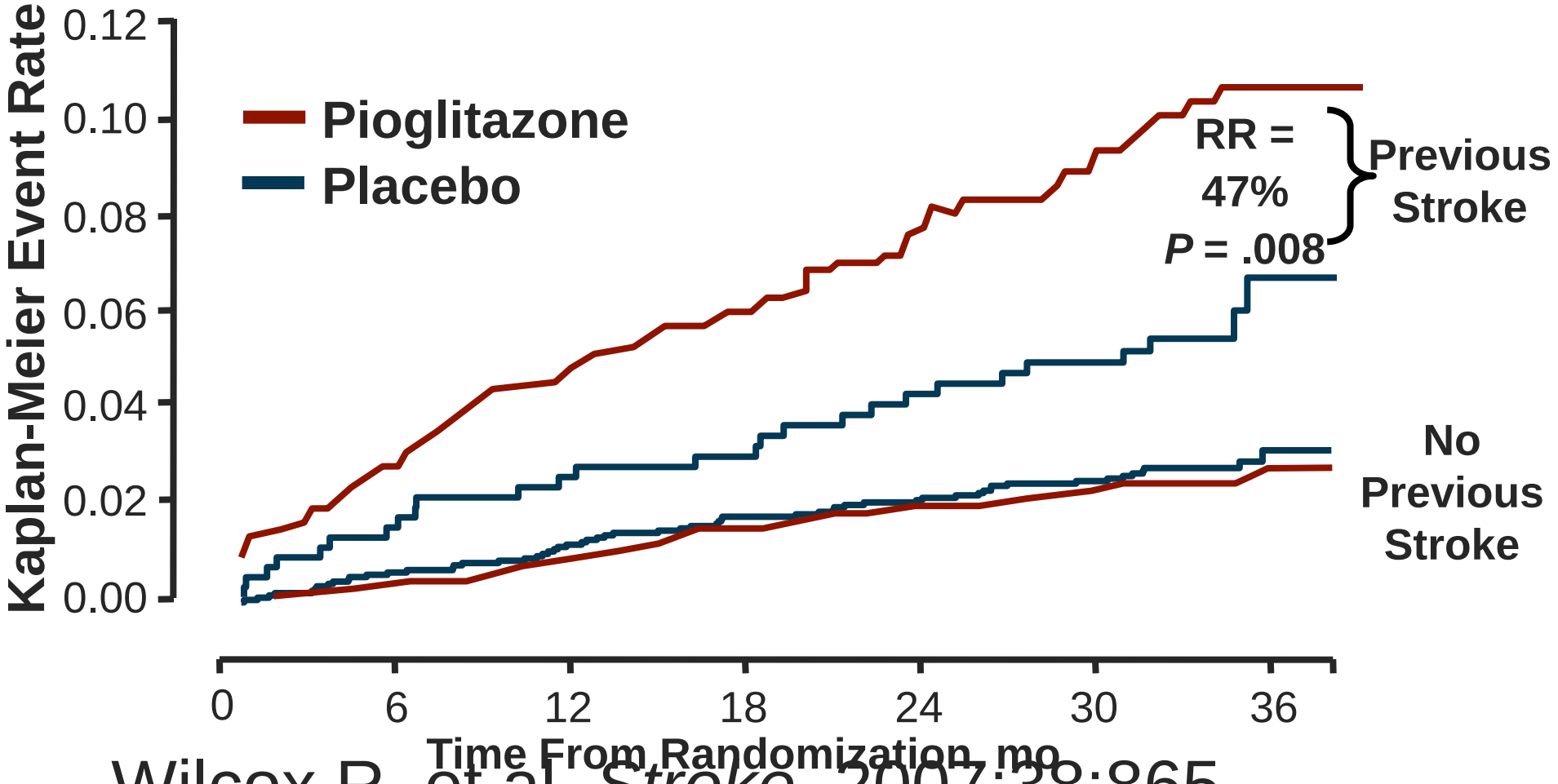
	HR	95% CI	*P* Value
PIO vs placebo	0.63	0.41-0.97	.035



Post-Hoc Exploratory Analysis

Erdmann E, et al. *J Am Coll Cardiol.* 2007;49:1772-1780.

PROactive: *Time to Fatal/Nonfatal Stroke in Patients with Previous Stroke*



Wilcox R, et al. *Stroke*. 2007;38:865-873

PROactive
HF Hospitalization and Mortality

N = 5238

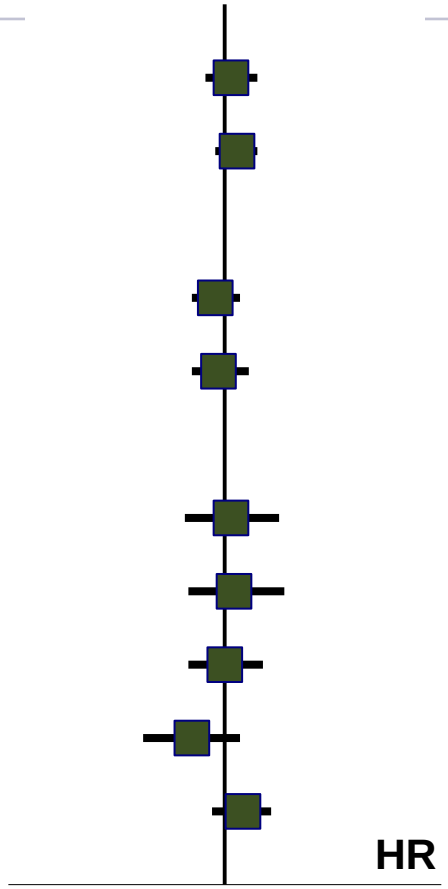
	Pioglitazone, n (%)	Placebo, n (%)	*P*
HF leading to hospital admission*	149 (5.7)	108 (4.1)	.007
Fatal HF	25 (0.96)	22 (0.84)	NS

*Non-adjudicated

Dormandy JA, et al. *Lancet*. 2005;366:1279-1289.

ORIGIN: Composite Outcomes & their Components

	HR (95% CI)	P	Insulin /100 py	Standard /100 py
1st Coprimary	1.02 (0.94, 1.11)	0.63	2.94	2.85
2nd Coprimary	1.04 (0.97, 1.11)	0.27	5.52	5.28
Microvascular	0.97 (0.90, 1.05)	0.43	3.87	3.99
Death	0.98 (0.90, 1.08)	0.70	2.57	2.60
MI	1.02 (0.88, 1.19)	0.75	0.93	0.90
Stroke	1.03 (0.89, 1.21)	0.69	0.91	0.88
CV Death	1.00 (0.89, 1.13)	0.98	1.57	1.55
CHF Hospital	0.90 (0.77, 1.05)	0.16	0.85	0.95
Revascularized	1.06 (0.96, 1.16)	0.24	2.69	2.52



NEJM 2012;367:319

Large CV Outcomes Trials in Diabetes (Non-Insulin)

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	sulfonylurea	placebo
N	16,500	5,400	14,000	6,000	8,300
Results	**2013**	**2013**	**2015**	2017	2017

Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP1-RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide
Comparator	placebo	placebo	placebo	placebo	placebo
N	16,500	14,000	6,000	5,400	8,300
Results	**2016**	**2015**	2016	2018	2019

Study	EMPA-REG	CANVAS	DECLARE	NCT01986881
SGLT-2-i	empaglifozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
N	7300	4300	22,200	3900
Results	**2015**	2017	2019	2020

DPP-4 Inhibitors: SAVOR, EXAMINE, and TECOS *Key Results*

SAVOR[a]	EXAMINE[b]	TECOS[c]
Saxagliptin vs Placebo	**Alogliptin vs Placebo**	**Sitagliptin vs Placebo**
• Median follow-up: 2.1 years • CV outcomes Primary HR: 1.00 (0.89-1.27); *P* = .99 Secondary HR: 1.02 (0.94-1.11); *P* = .66 • Higher incidence of HF hospitalization in saxagliptin group	• Median follow-up: 18 months • CV outcomes Primary HR: 0.96 (≤ 1.16); *P* = .32 Secondary HR: 0.95 (≤ 1.14*); *P* = .26	• Median follow-up: 3.0 years • Noninferior to placebo for CV outcomes Primary HR: 0.98 (0.88-1.09); *P* < .001 Secondary HR: 0.99 (0.89-1.11); *P* < .001

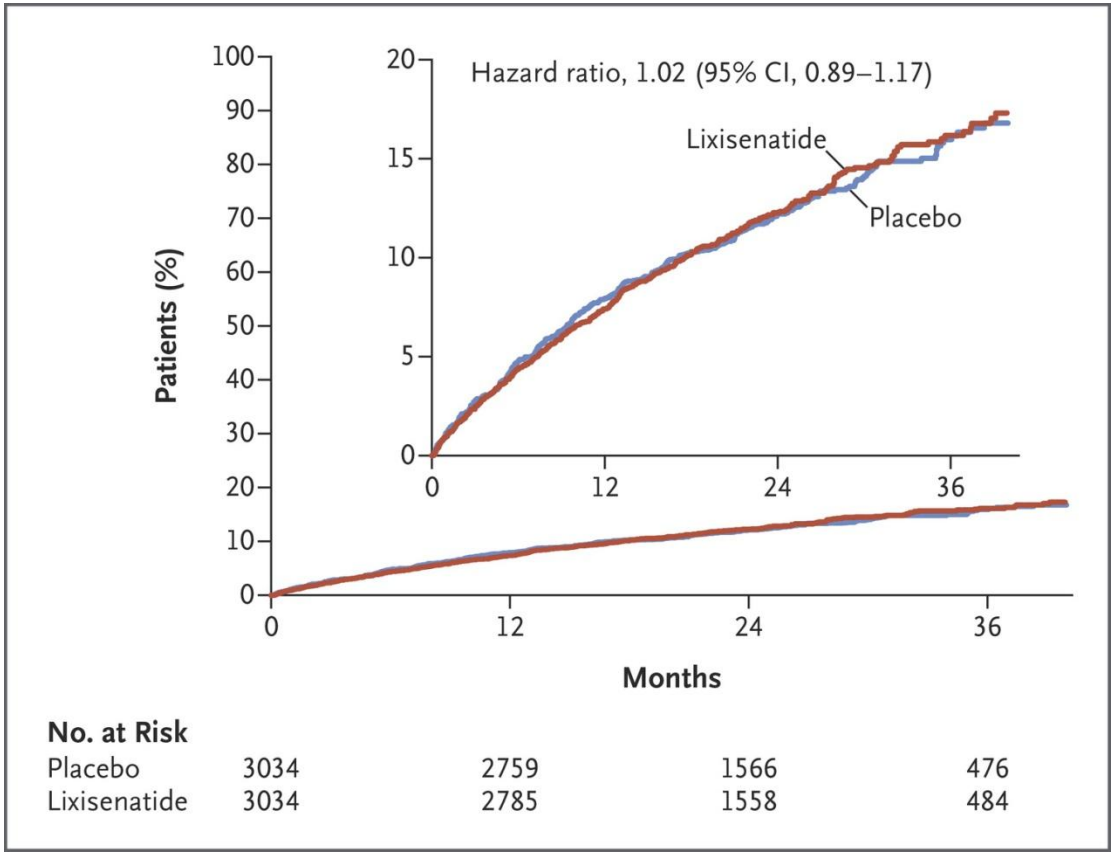
a. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326; b. White WB, et al. *N Engl J Med*. 2013;369:1327-1335; c. Green JB, et al. *N Engl J Med.* 2015;373:232-242.

ELIXA: Lixisenatide Outcome Trial

N = 6068, had recent acute coronary syndrome

Follow-up 25 months

4 pt MACE: CV death, MI, stroke or hosp for unstable angina
Events:805



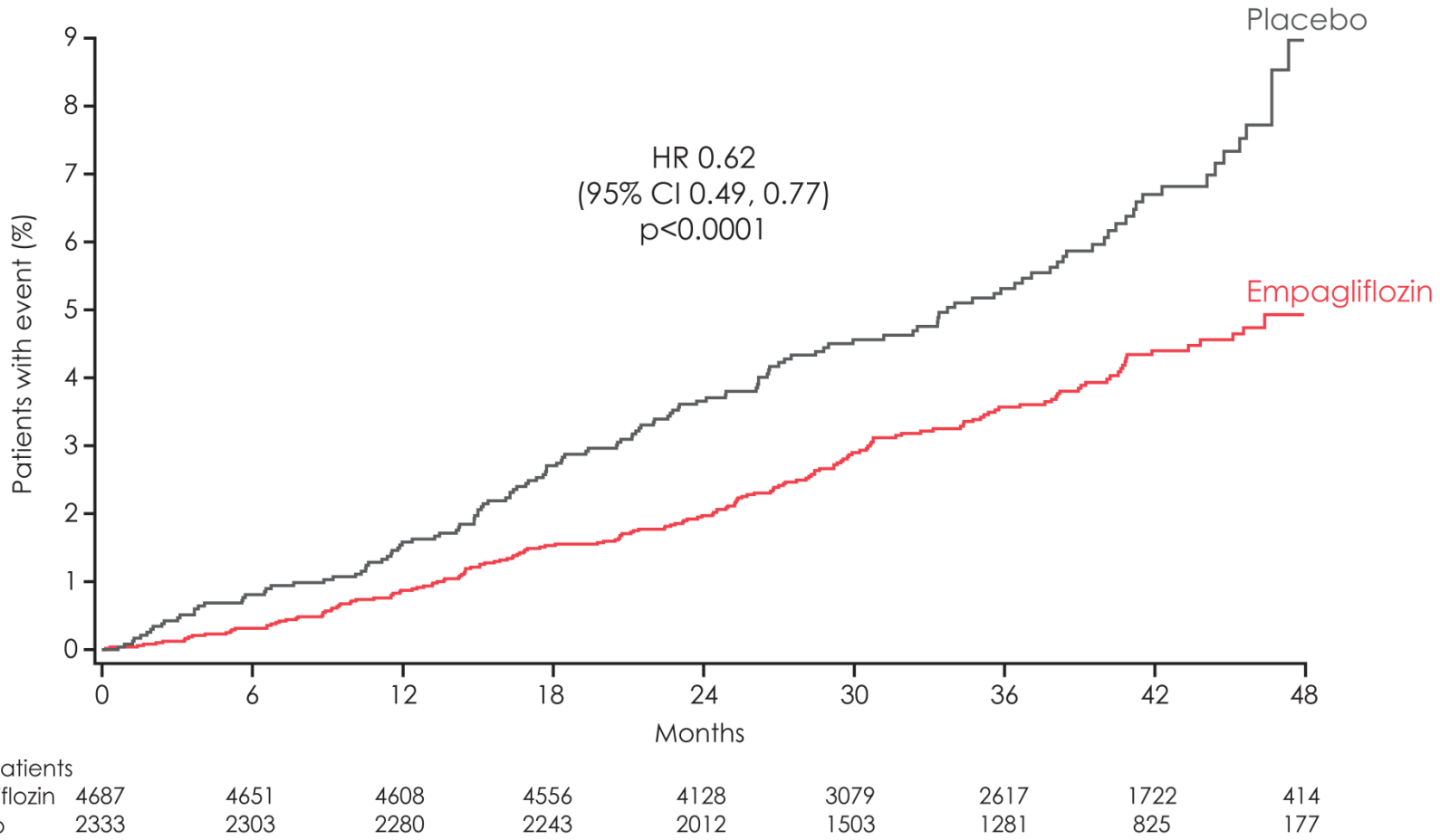
Pfeffer MA et al. N Engl J Med 2015;373:2247-2257

EMPA-REG: Empagliflozin Cardiovascular Outcome Trial

- **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)
- **Primary outcome**
  - **3-point MACE:** Time to first occurrence of CV death, non-fatal MI or non-fatal stroke
- **Key secondary outcome**
  - **4-point MACE:** Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina

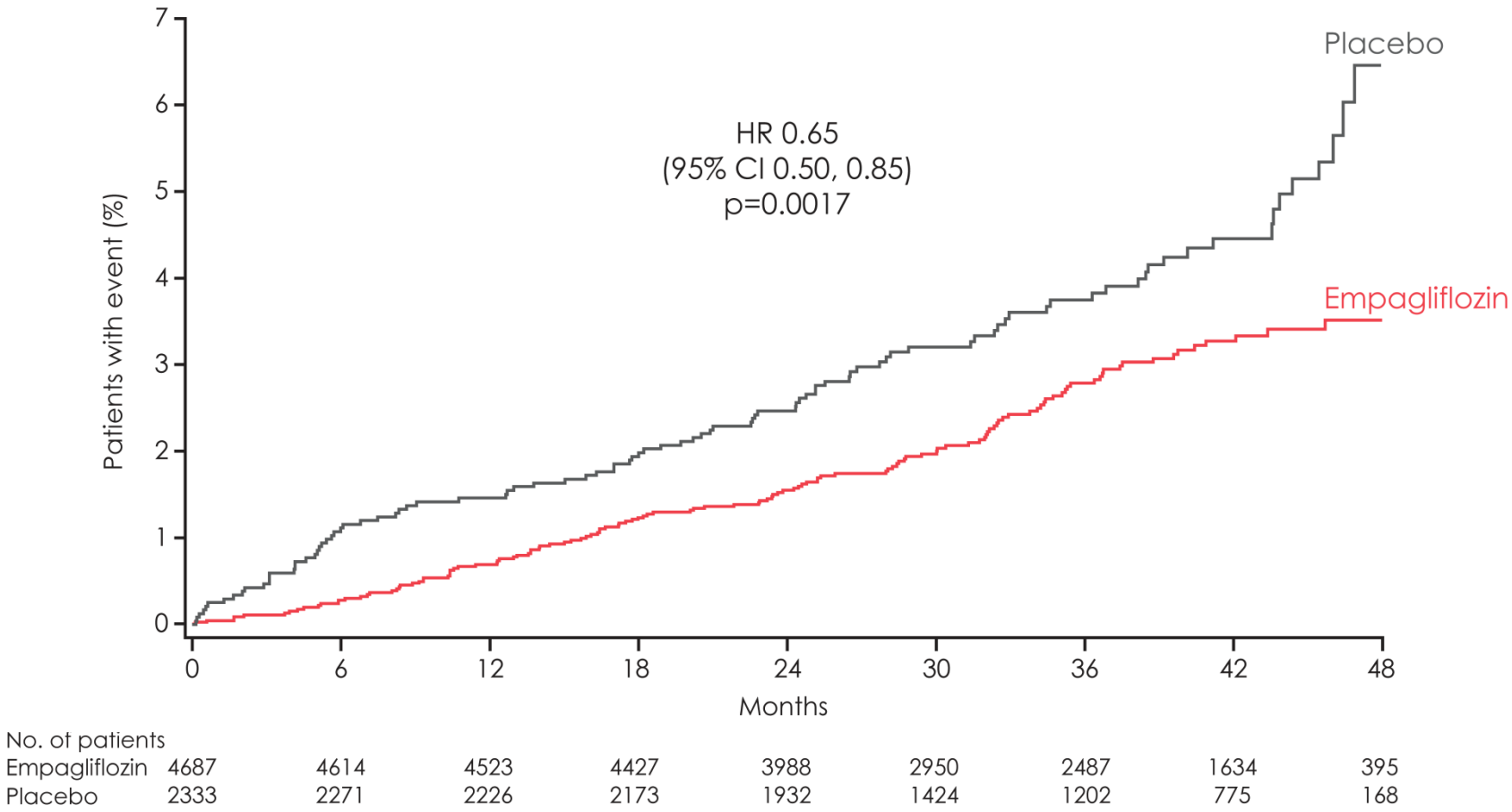
CV, cardiovascular; MI, myocardial infarction; MACE, Major Adverse Cardiovascular Event

EMPA–REG: CV death



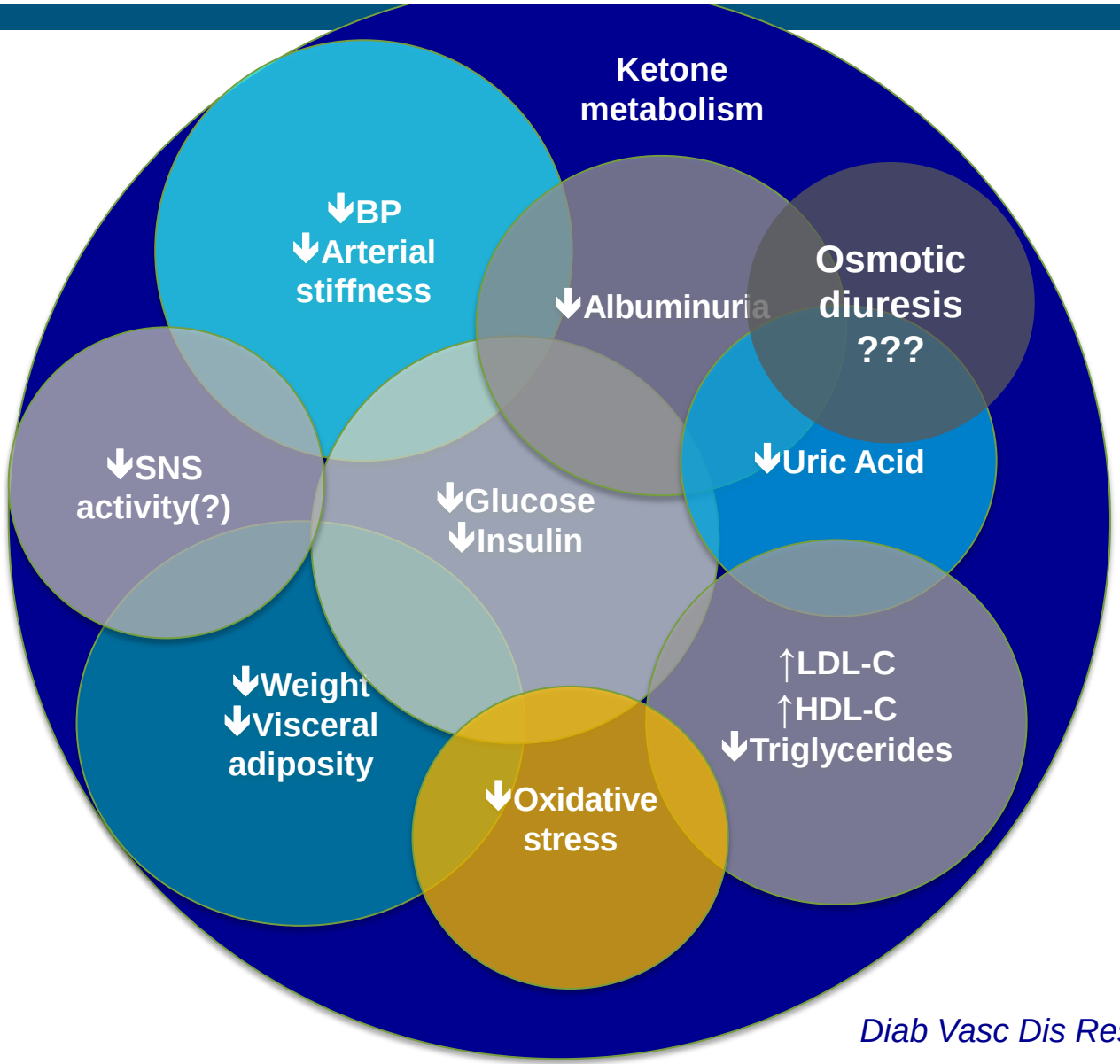
Cumulative incidence function. HR, hazard ratio

EMPA-REG: Hospitalization for HF



Cumulative incidence function. HR, hazard ratio

What was the underlying reason(s) for the dramatic benefit on CV outcomes observed in EMPA-REG?



Inzucchi SE *et al.*
Diab Vasc Dis Res 2015;12:90-100

LEADER: Baseline characteristics

	Liraglutide (N=4668)	Placebo (N=4672)
Male sex, N (%)	3011 (64.5)	2992 (64.0)
Age, years	64.2 ± 7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
HbA_{1c}, %	8.7 ± 1.6	8.7 ± 1.5
BMI, kg/m^2	32.5 ±6.3	32.5 ± 6.3
Body weight, kg	91.9 ±21.2	91.6 ± 20.8
Systolic blood pressure, mmHg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mmHg	77.2 ± 10.3	77.0 ± 10.1
Heart failure*, N (%)	835 (17.9)	832 (17.8)

*Heart failure includes New York Heart Association class I, II and III. BMI: body mass index; HbA_{1c}: glycated hemoglobin.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: Baseline cardiovascular risk profile

	Liraglutide (N=4668)	Placebo (N=4672)
Established CVD/CKD (age ≥50 years)	**3831 (82.1)**	**3767 (80.6)**
Prior myocardial infarction	1464 (31.4)	1400 (30.0)
Prior stroke or prior TIA	730 (15.6)	777 (16.6)
Prior revascularization	1835 (39.3)	1803 (38.6)
>50% stenosis of coronary, carotid, or lower extremity arteries	1188 (25.4)	1191 (25.5)
Documented symptomatic CHD	412 (8.8)	406 (8.7)
Documented asymptomatic cardiac ischemia	1241 (26.6)	1231 (26.3)
Chronic heart failure NYHA II – III	653 (14.0)	652 (14.0)
Chronic kidney disease (eGFR <60 mL/min/1.73m^2)	1185 (25.4)	1122 (24.0)

Data are number of patients (%).
CHD: coronary heart disease; CKD: chronic kidney disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; TIA: transient ischemic attack.

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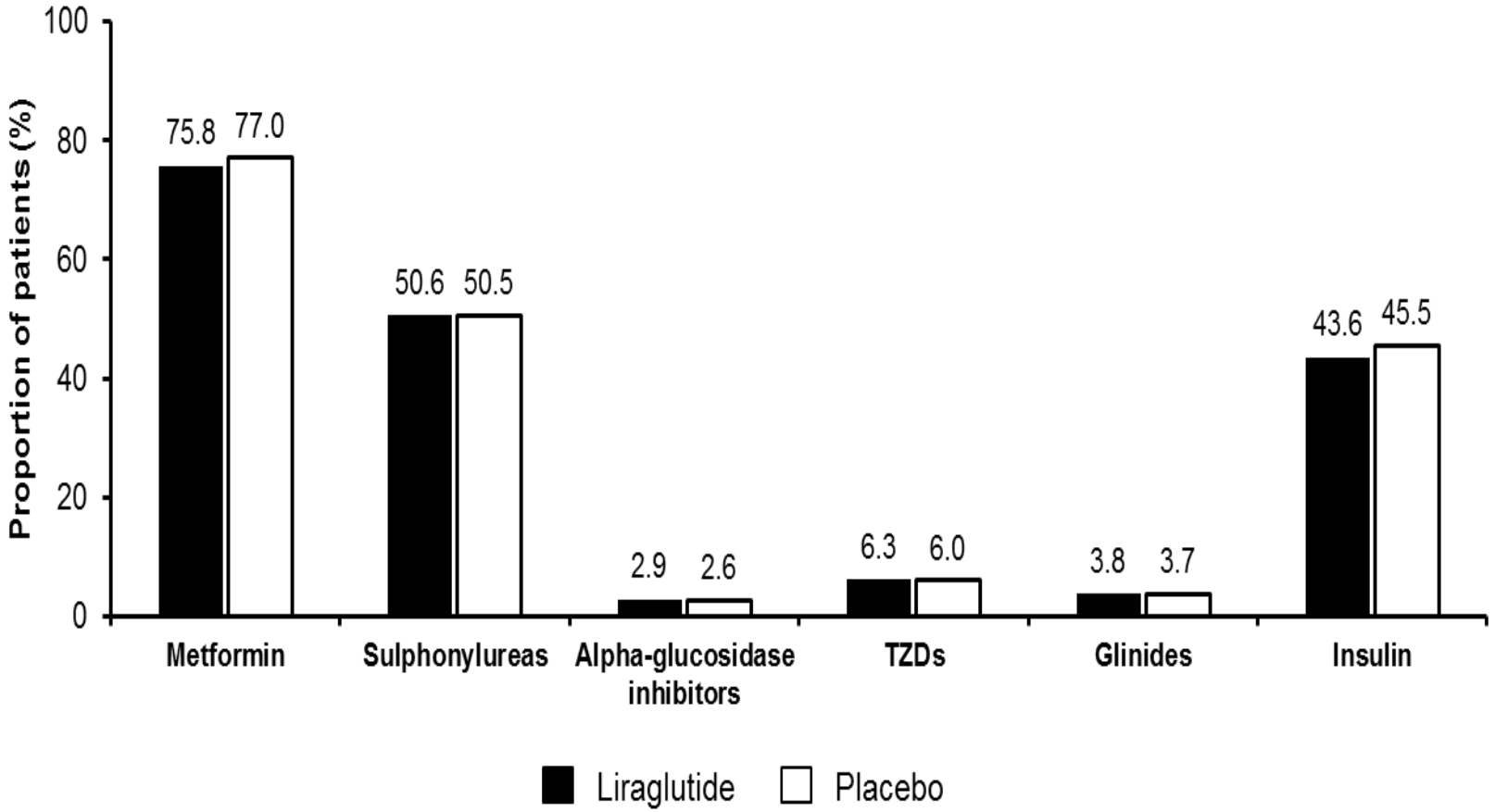
LEADER: Antihyperglycemic medication at baseline



TZD: thiazolidinediones.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: Trial follow-up and drug exposure

	Liraglutide	Placebo
Median follow-up (years)	3.84	3.84
Median time of exposure to study medication (years)	3.52	3.52
Mean proportion of time on study drug (%)*	84.0	83.0
Median (IQR) daily dose of liraglutide (mg)†	1.78 (1.54–1.79)	-

*Excluding pre-scheduled 30 day off-treatment follow-up period.
†Including off-treatment periods.
IQR: interquartile range.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: Primary outcome

9,340 patients with T2DM and high risk of CVD randomized to liraglutide 1.8mg or maximally tolerated dose vs placebo

Time to first MACE composed of:

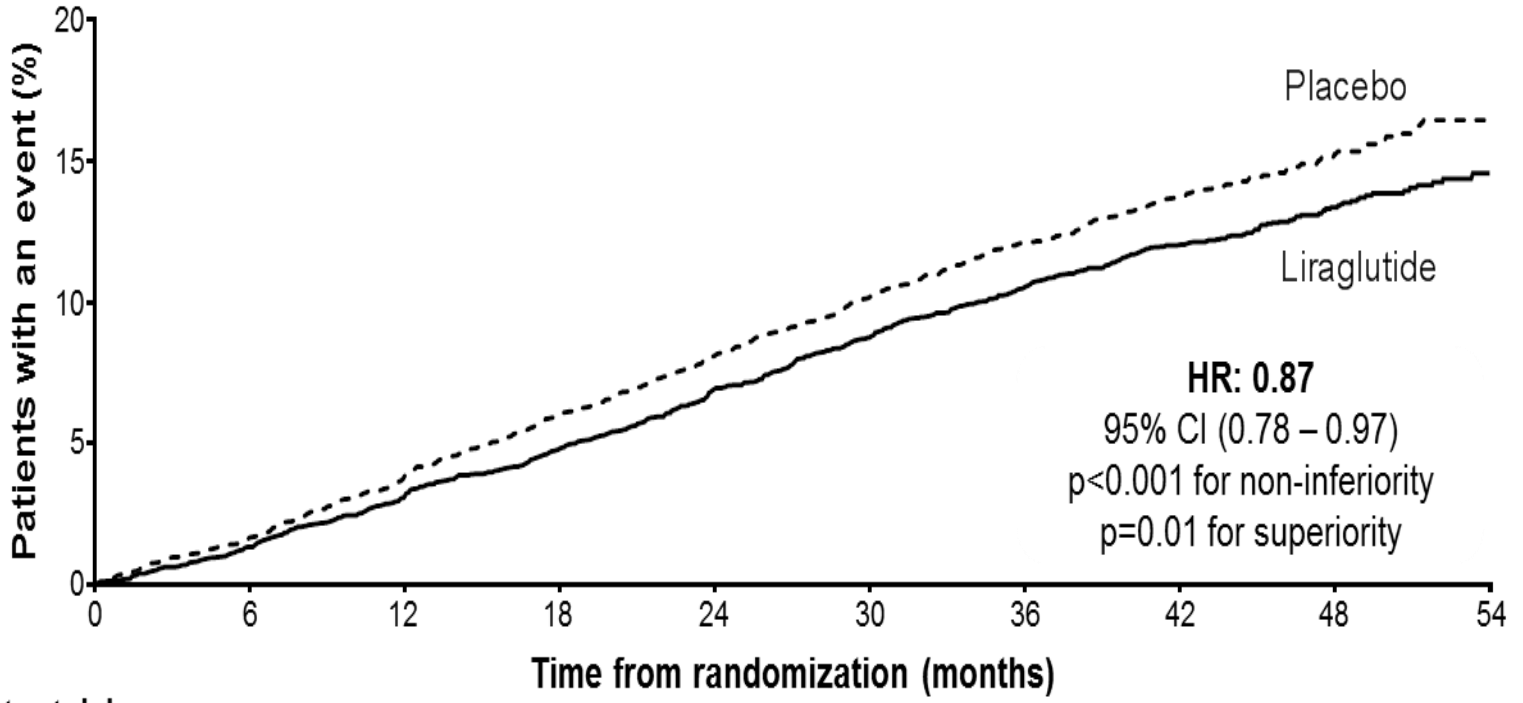
- CV death
- Non-fatal MI
- Non-fatal stroke

CV: cardiovascular; MACE: major adverse cardiovascular event; MI: myocardial infarction.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: Primary outcome

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



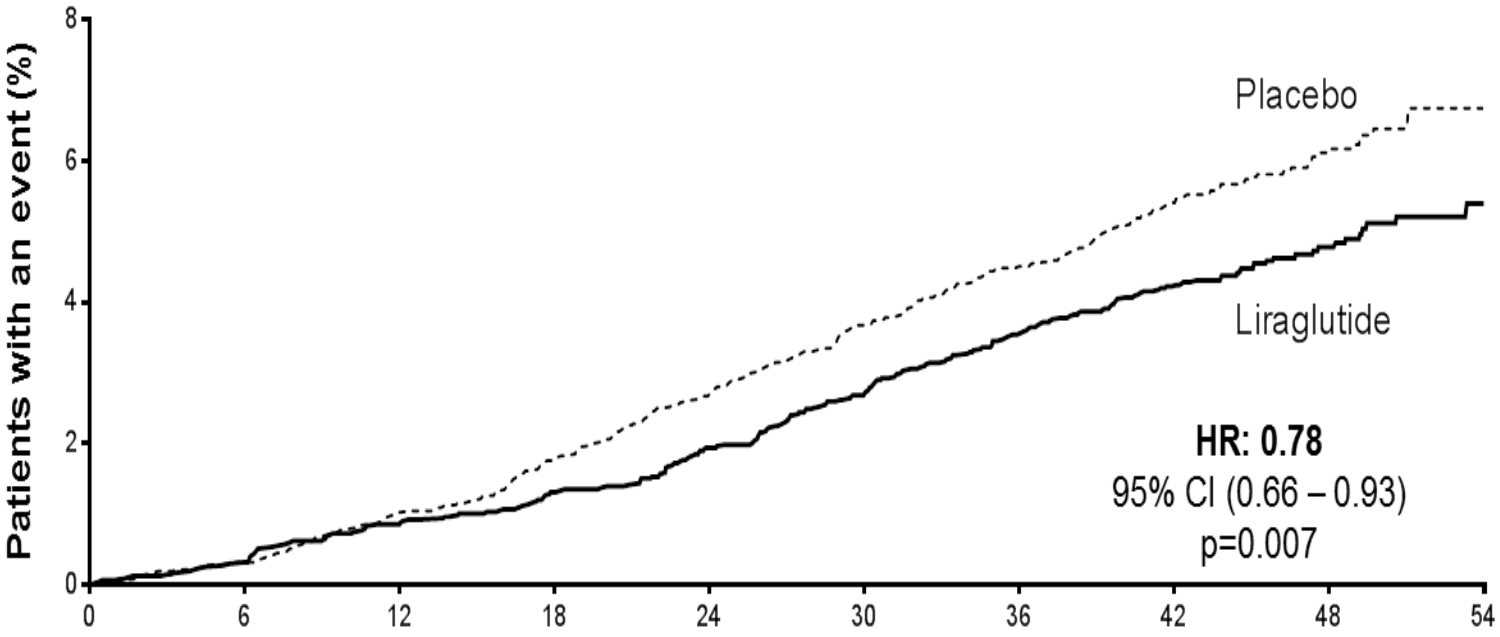
Patients at risk

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

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 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; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: CV death

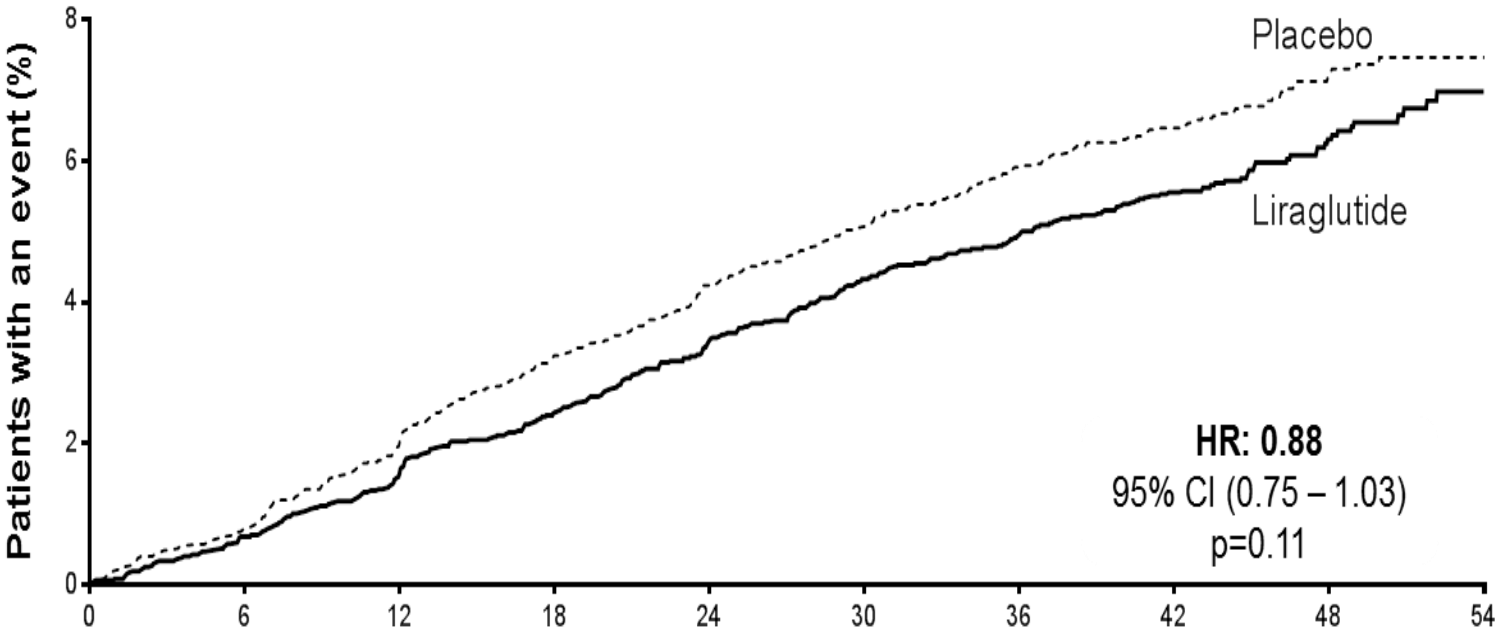


Patients at risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

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; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: Time to non-fatal myocardial infarction

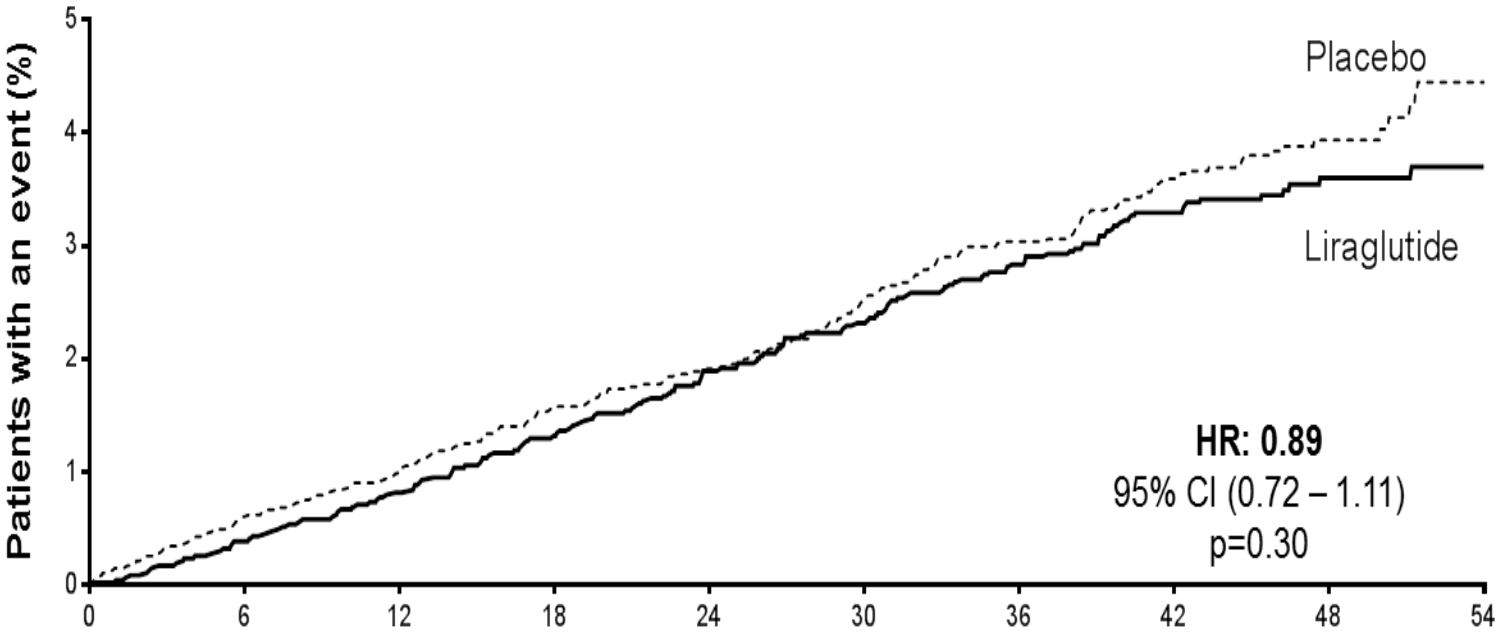


Patients at risk										
Liraglutide	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Placebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

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 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

LEADER: Time to non-fatal stroke



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

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.

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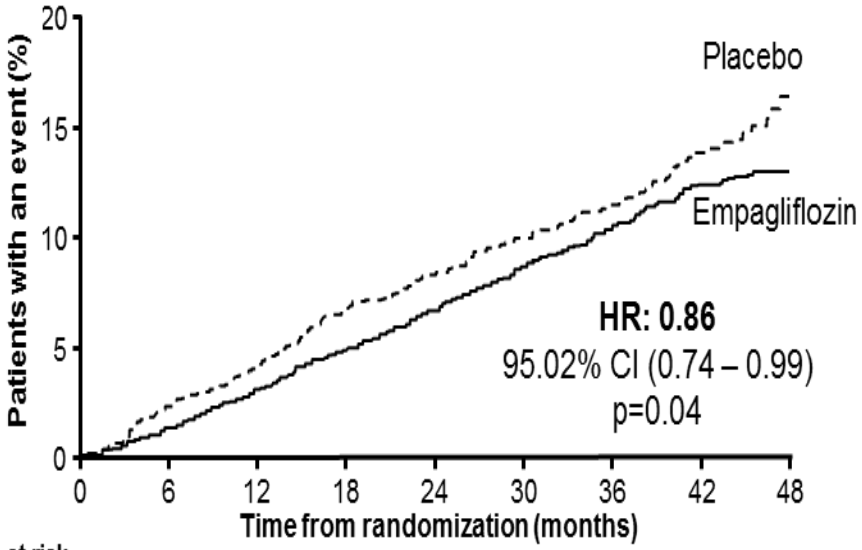
Empagliflozin and Liraglutide

EMPA-REG OUTCOME

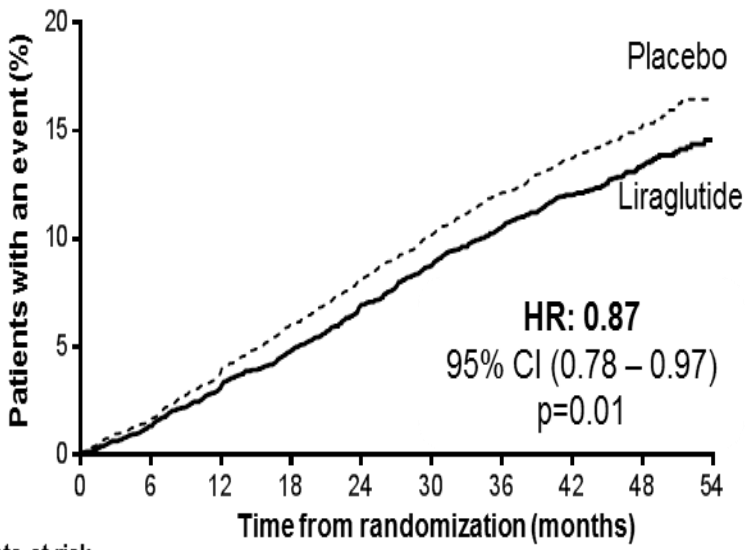
CV death, non-fatal MI, or non-fatal stroke



Patients at risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

LEADER

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



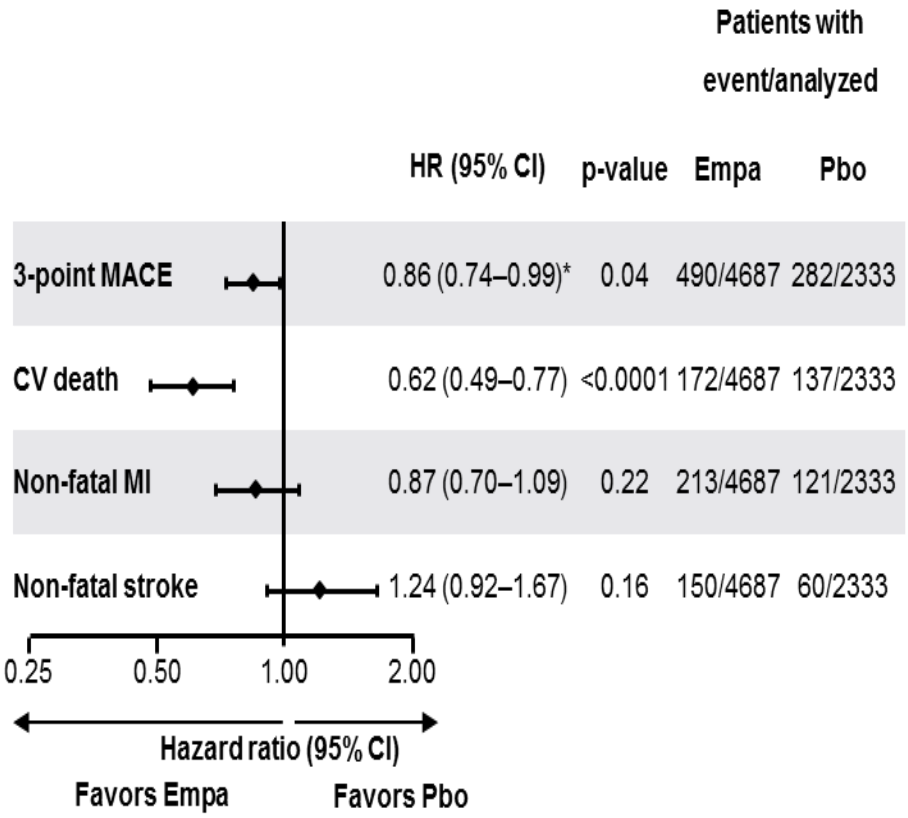
Patients at risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction.
Zinman B et al. *N Engl J Med* 2015;373:2117-2128.

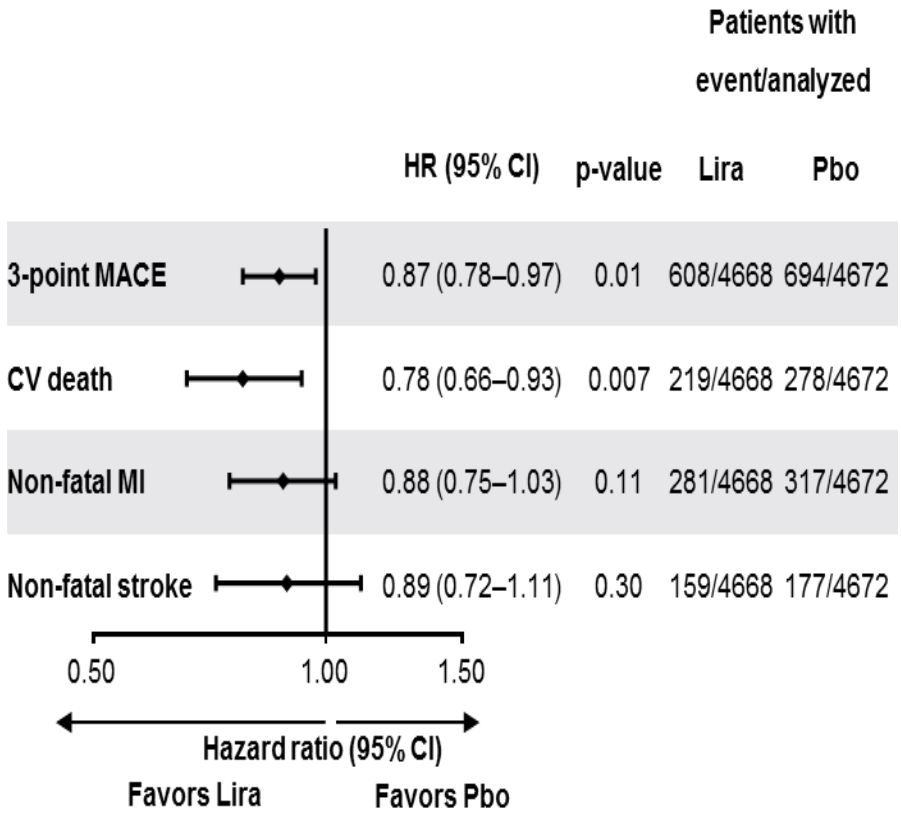
Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Individual components of the primary endpoint

EMPA-REG OUTCOME



LEADER



*95.02% CI.
CV: cardiovascular; Empa: empaglifloin; Lira: liraglutide; MACE: major adverse cardiovascular event; MI: myocardial infarction; Pbo: placebo.
Zinman B et al. Presented at European Association for the Study of Diabetes 2015, Stockholm, Sweden.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Drug Safety

- **Liraglutide**
  - Gastrointestinal
  - Risk of AKI
  - Pancreatitis
  - Medullary Thyroid CA
- **Empagliflozin**
  - Genital mycotic infections
  - Volume Depletion
  - Urinary Frequency
  - DKA
  - Not to be used with GFR < 45.

Ongoing Outcomes Trials of AHA

Class	Participants	Drugs	Est. N
DPP4i	Diabetes	linagliptin, omarigliptin	15,000
GLP1a	Diabetes	exenatide. dulaglutide, semaglutide, albiglutide, ITCA	50,000
SGLT2i	Diabetes	canagliflozin, dapagliflozin, ertugliflozin	23,000
Insulin	Diabetes	Degludec	7,500
Biguanide	A1c 5.5-6.49	Metformin	12,000
AGI	IGT	Acarbose	7,500
			120,000

CVDREAL

ACC.17

Study Objectives

Primary

- Compare risk of HHF in patients with Type 2 diabetes newly initiated on SGLT-2 inhibitors versus other glucose-lowering drugs (GLDs)

Secondary

- Compare risk of all-cause death between the two treatment groups
- Compare risk of HHF or all-cause death between the two treatment groups

CVDREAL

ACC.17

Data Sources: Health Records Across Six Countries

- Truven MarketScan Claims & Encounters and linked Medicare
- National full-population registries
- National full-population registries
- National full-population registries
- Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN)
- Diabetes Patienten Verlaufsdokumentation (DPV) initiative

Cohort 1
HHF

Cohort 2
All-cause death and composite HHF/all-cause death

CVDREAL

ACC.17

Inclusion/Exclusion Criteria

Inclusion

- New users receiving SGLT-2 inhibitors or other GLDs
  - Established Type 2 diabetes on or prior to the index date
  - ≥18 years old
  - >1 year* historical data available prior to the index date

Exclusion

- Patients with Type 1 diabetes
- Patients with gestational diabetes

*In Germany, >6 months

CVDREAL

ACC.17

Baseline Characteristics for Propensity Match Cohort

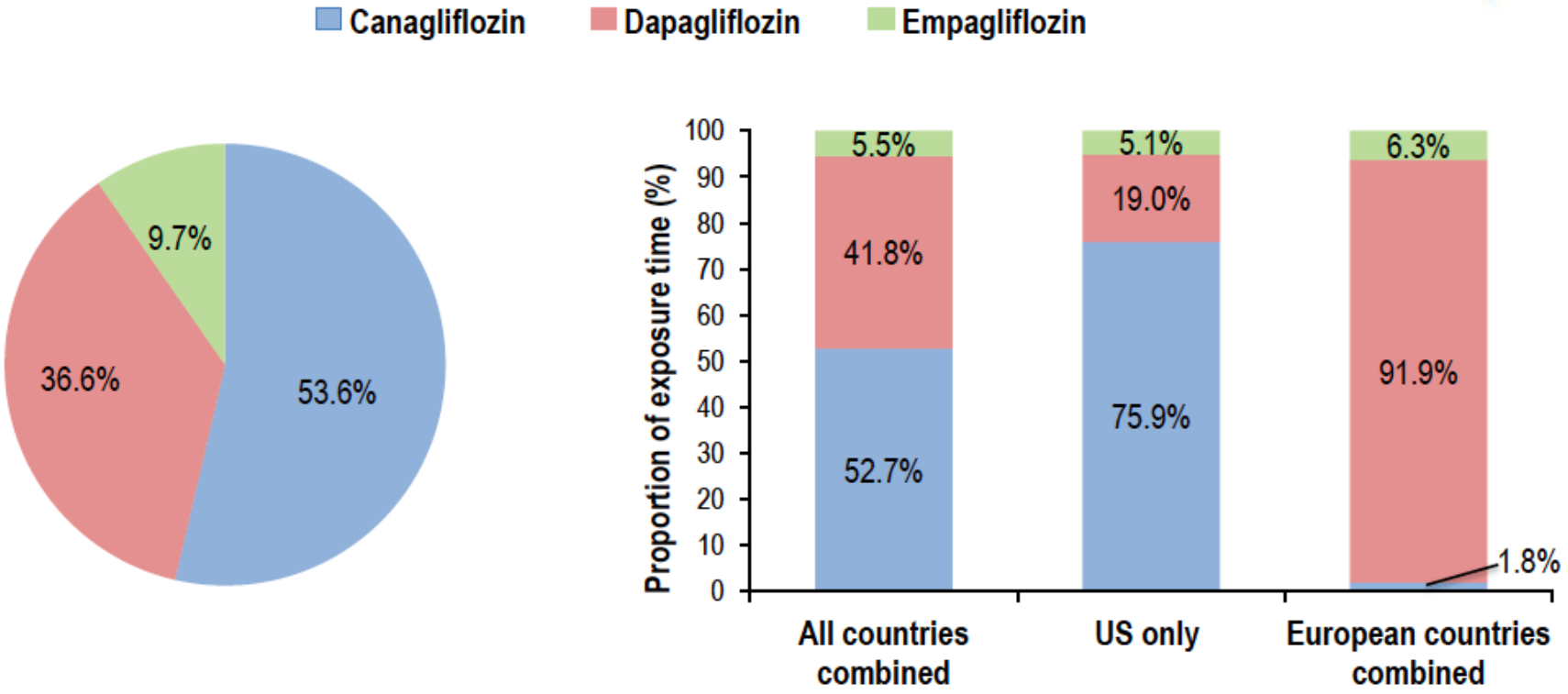
	SGLT-2 inhibitor* N=154,523	Other GLD* N=154,523
Age, years, mean (SD)	57.0 (9.9)	57.0 (10.1)
Women	68,419 (44.3)	68,770 (44.5)
Established cardiovascular disease†	20,043 (13.0)	20,302 (13.1)
Acute myocardial infarction	3792 (2.5)	3882 (2.5)
Unstable angina	2529 (1.6)	2568 (1.7)
Heart failure	4714 (3.1)	4759 (3.1)
Atrial fibrillation	5632 (3.6)	5698 (3.7)
Stroke	6347 (4.1)	6394 (4.1)
Peripheral arterial disease	5239 (3.4)	5229 (3.4)
Microvascular disease	42,214 (27.3)	42,221 (27.3)
Chronic kidney disease	3920 (2.5)	4170 (2.7)

*Data are n (%) unless otherwise stated; †Myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization or occlusive peripheral artery disease

CVDREAL

Contribution of SGLT-2 inhibitor Class as a Proportion of Exposure Time in Propensity-Match Cohorts

Cohort 1: HHF Analysis (N=309,046)



CVDREAL

HHF Primary Analysis

ACC.17

Database	N	# of events	HR (95% CI)
US	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)

P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.169

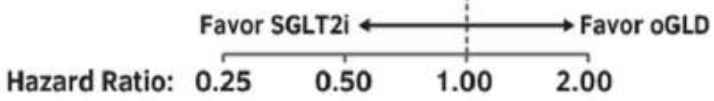
Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

CVDREAL

All-Cause Death Primary Analysis

ACC.17

Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1334	0.49 (0.41, 0.57)



P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.089

Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

Large CV Outcomes Trials in Diabetes (Non-Insulin)

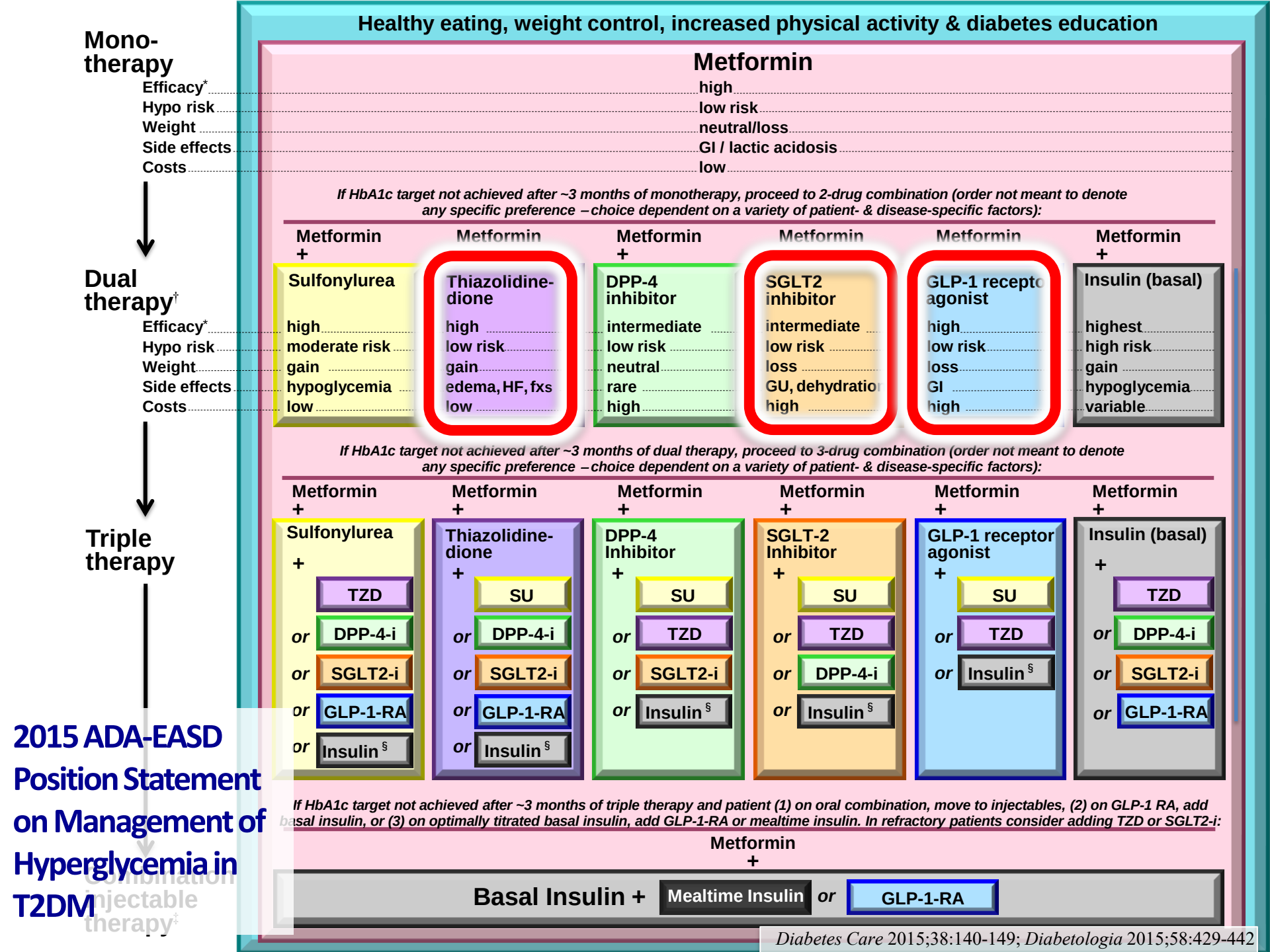
Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	pl	pl	pla	sulfonylurea	placebo
N	,500	,400	,000	6,000	8,300
Results	2013	2013	2015	2017	2017

NEUTRAL

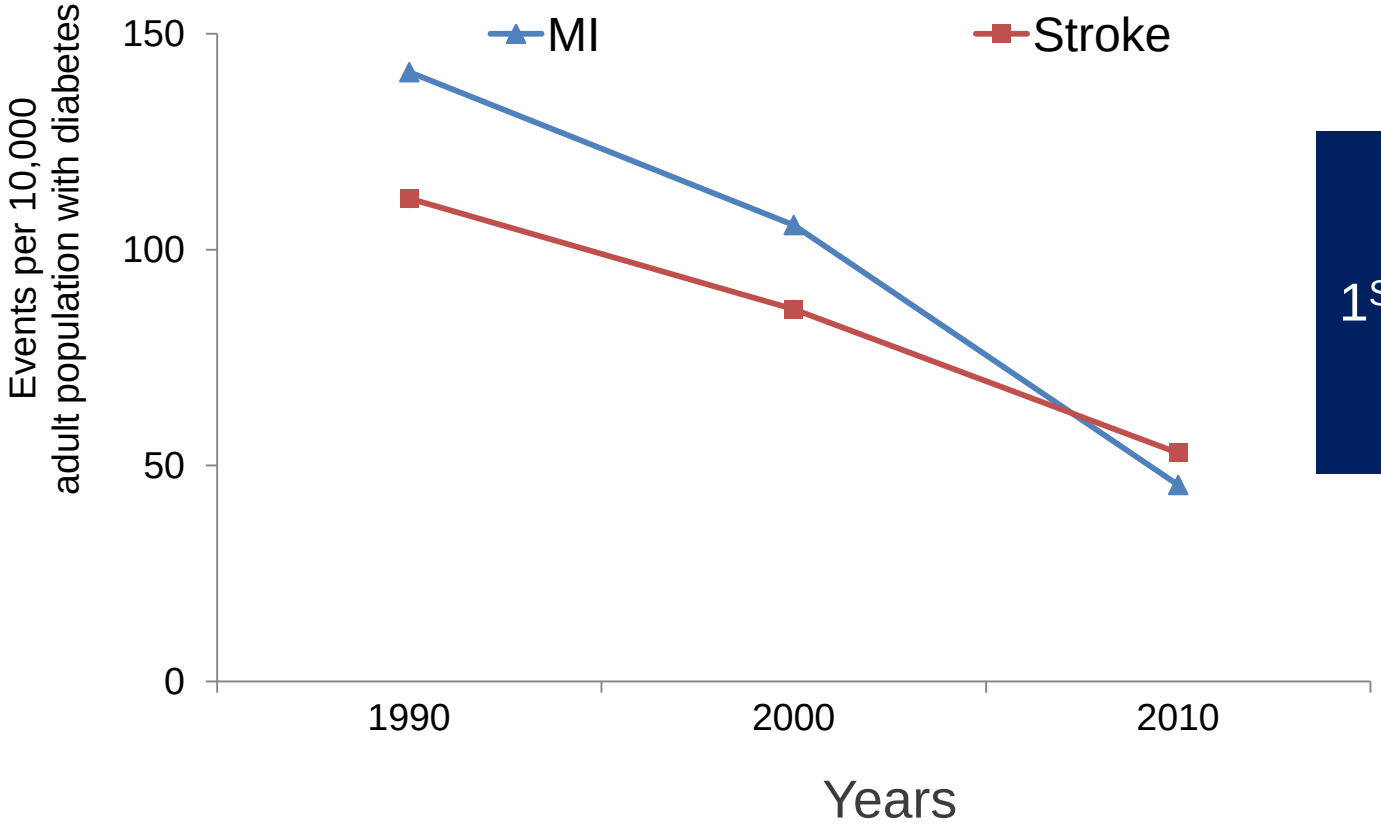
Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP1-RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide
Comparator	placebo	pla	placebo	placebo	placebo
N	16,500	,00	6,000	5,400	8,300
Results	2016	2015	2016	2018	2019

NEUTRAL

Study	EMPA-REG	CANVAS	DECLARE	NCT01986881
SGLT-2-i	empaglifozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
N	7300	4300	22,200	3900
Results	2015	2017	2019	2020


Healthy eating, weight control, increased physical activity & diabetes education
Mono-therapy
Dual therapy†
Triple therapy
Combination injectable therapy‡
Metformin
Efficacy* high
Hypo risk low risk
Weight neutral/loss
Side effects GI / lactic acidosis
Costs low
If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):
Metformin + Sulfonylurea
high
moderate risk
gain
hypoglycemia
low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydratio
high
Metformin + GLP-1 recepto agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin §
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin §
Metformin + DPP-4 Inhibitor + SU or TZD or SGLT2-i or Insulin §
Metformin + SGLT-2 Inhibitor + SU or TZD or DPP-4-i or Insulin §
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin §
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Metformin +
Basal Insulin + Mealtime Insulin or GLP-1-RA
2015 ADA-EASD Position Statement on Management of Hyperglycemia in T2DM
Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442

Diabetes-related CV complications have declined with improved care



PAD, CHF, commonest 1ST CVD events in DM Shah et al (2015) Lancet D/E

Adapted Gregg E et al.*N Engl J Med.* 2014.

Summary: Risk for CVD events in Diabetes is Lower

- Clear evidence ⇓ CVD /mortality in T2DM over several decades, but there remains a large gap over the risk for patients without diabetes
  - Better management CVD risk factors big part, but many sub-optimally treated
    - BP and LDL-C reduction > glucose reduction
    - Smoking reduction
- Data from cardiovascular outcome trials support role of SGLT-2 inhibitors and long-acting GLP-1 receptor agonists for reduction of CVD deaths in patients with established CVD
- Keeping in mind the limitations of the study, CVD Real suggests that CVD benefit with SGLT-2 inhibitors may be a class effect