NUOVE EVIDENZE E PROPRIE ESPERIENZE SULLA PREVENZIONE…

…dell'Ictus ischemico

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Agenda

- Diabete e stroke
- Farmaci ipoglicemizzanti e prevenzione dello stroke

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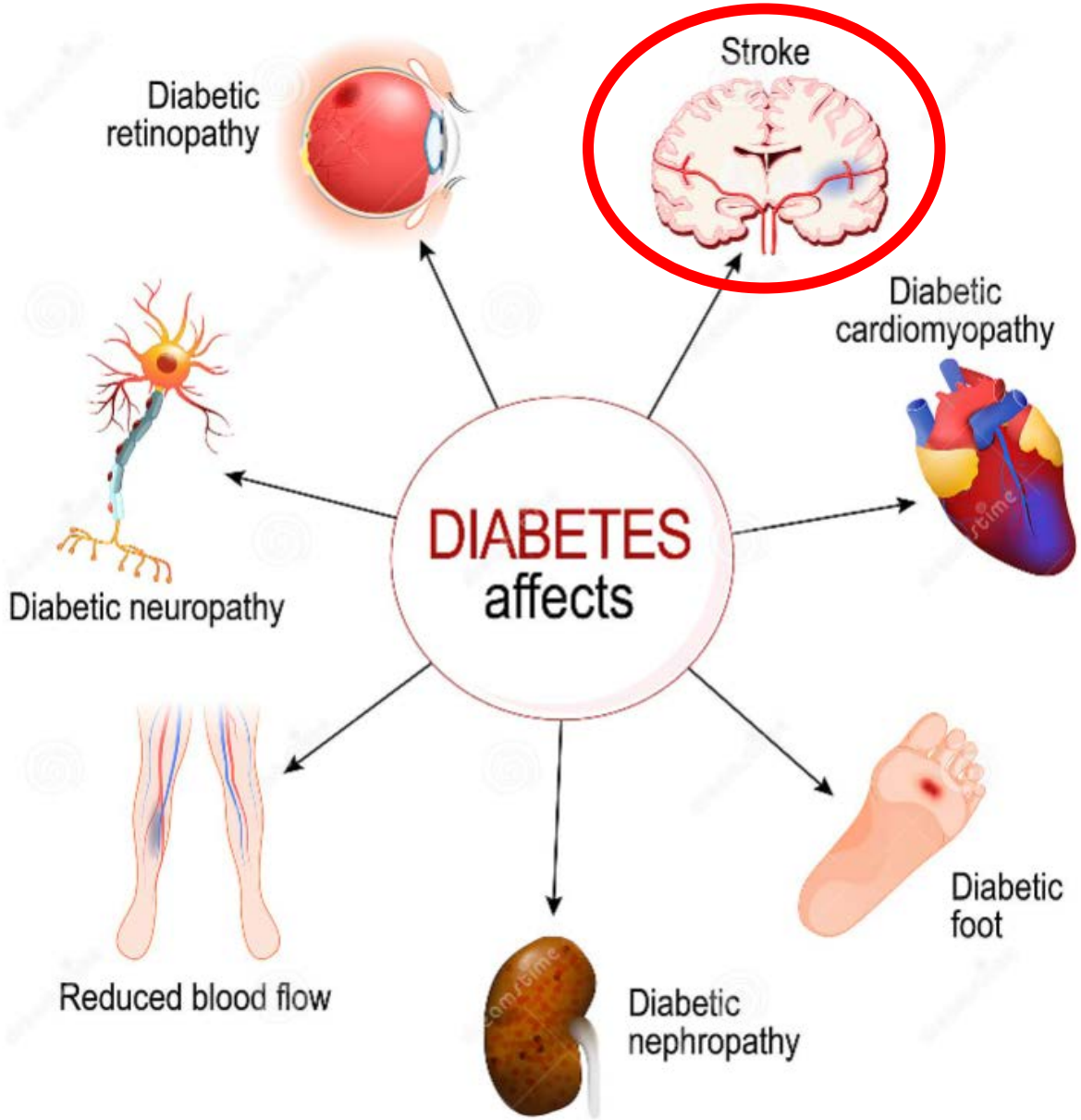


- **Il 65% dei soggetti diabetici di tipo 2 muore a causa di cardiopatia ischemica o di ictus ischemico (Dati ISTAT)**

- **Il 24% dei decessi e attribuibile a ictus cerebri (Verona Study)**

Epidemiology of Ischemic Stroke in Patients With Diabetes

Characteristics of ischemic stroke patients by diabetes and race

	All			Black			White		
	Diabetic	Nondiabetic	*P*	Diabetic	Nondiabetic	*P*	Diabetic	Nondiabetic	*P*
n	856	1,863		259	464		597	1,399	
Age (years)	70 ± 11	72 ± 15	<0.0001	67 ± 11	68 ± 17	0.6	72 ± 11	74 ± 13	<0.0001
History of hypertension	676 (79)	1,061 (57)	<0.0001	219 (84)	289 (62)	<0.0001	457 (76)	772 (55)	<0.0001
History of high cholesterol	135 (16)	177 (10)	<0.0001	35 (14)	51 (11)	0.3	100 (17)	126 (9)	<0.0001
History of myocardial infarction	193 (22)	272 (15)	<0.0001	43 (17)	75 (16)	0.9	150 (25)	197 (14)	<0.0001
History of atrial fibrillation	134 (16)	266 (14)	0.4	19 (7)	45 (10)	0.3	115 (19)	221 (16)	0.1
Current smoking	157 (18)	408 (22)	0.03	63 (24)	140 (30)	0.1	94 (16)	268 (19)	0.1

Data are means ± SD or *n* (%).

Multivariable logistic regression model for ischemic stroke

	African-American patients				Caucasian patients			
	OR	95% CI	PAR	95% CI	OR	95% CI	PAR	95% CI
Age (per year)	1.02	1.01–1.03			1.06	1.05–1.06		
Male	1.2	1.0–1.6			1.4	1.2–1.6		
History of prior stroke	4.7	3.3–7.0	22.3	18.8–25.7	3.6	2.8–4.7	14.8	13.4–16.1
History of both diabetes and hypertension	3.0	2.1–4.3	21.1	18.1–24.0	4.5	3.5–5.8	20.6	19.0–22.1
History of diabetes only	2.7	1.5–5.2	5.6	3.6–7.5	2.1	1.5–3.0	5.2	4.3–6.1
History of hypertension only	1.3	0.9–1.7	9.8	3.7–15.5	1.6	1.4–1.9	16.2	13.8–18.4
Current smoking	1.5	1.1–1.9	10.9	6.5–15.2	1.7	1.4–2.2	12.5	10.7–14.2
History of myocardial infarction	1.1	0.8–1.7	1.4	0–3.6	1.1	0.9–1.4	1.0	0–2.0

*PARs calculated from GCNKSS prevalence data.

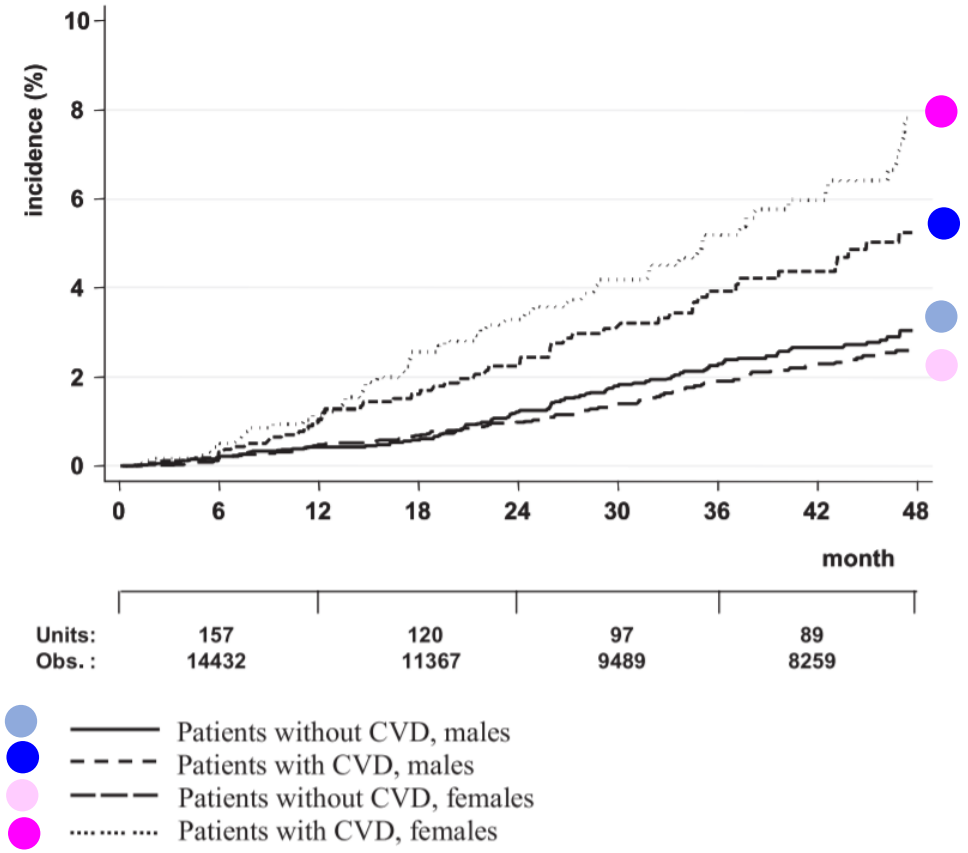
37–42% of all ischemic strokes are attributable to the effects of diabetes alone or in combination with hypertension

Kissela BM et al, Diab Care, 2005

Characteristic	CVD at Baseline			
	No (11 644)		Yes (2788)	
	Men	Women	Men	Women
	Mean±SD			
Age at visit, y	64±9	66±9	67±8	70±8
Body mass index, kg·m^{-2}	28±4	29±5	28±4	29±5
Waist circumference, cm	100±11	96±13	101±11	97±13
Cholesterol, mg/dL	207±47	220±43	209±45	221±45
HDL cholesterol, mg/dL	48±13	52±14	46±12	51±14
	Median (IQ range)			
Duration of diabetes, y	7 (3–13)	8 (3–14)	9 (4–15)	11 (5–18)
Systolic BP, mm Hg	140 (130–160)	150 (135–160)	140 (130–160)	150 (139–160)
Diastolic BP, mm Hg	80 (80–90)	80 (80–90)	80 (80–90)	80 (80–90)
Plasma glucose, mg/dL	153 (129–186)	158 (130–194)	158 (130–191)	165 (135–203)
Triglycerides, mg/dL	127 (91–180)	134 (99–183)	142 (102–198)	146 (108–201)
	%			
Hypertension†	79.5	86.3	89.6	93.7
HbA1c‡	72.1	77.9	76.4	82.5
Alcohol intake	58.1	20.7	54.1	18.8
Smoking				
Current	21.1	7.4	14.7	5.1
Former	30.9	5.1	45.9	7.3
Microvascular complication	35.0	33.6	46.5	45.4
Relatives with CHD	25.5	30.1	38.1	39.4
Glycemic control				
Diet alone	18.6	14.0	12.8	9.5
Oral agents	67.4	67.1	65.2	60.1
Insulin+oral agents	5.7	9.1	8.0	14.2
Insulin alone	8.3	9.8	14.0	16.1
Antihypertensive treatment	44.2	59.4	71.0	80.6
Lipid-lowering treatment	10.1	17.3	25.1	26.1
Geographic area				
Northern Italy	57.1	49.5	59.1	51.4
Central Italy	10.5	11.0	11.0	8.3
Southern Italy and the islands	32.4	39.6	29.9	40.3
Cardiovascular complication				
AMI	...	...	45.4	22.4
Stroke	...	...	10.9	12.1
CHD	...	...	32.3	57.7
Other*	...	...	11.4	7.8

Incidence and Risk Factors for Stroke in Type 2 Diabetic Patients

The DAI Study



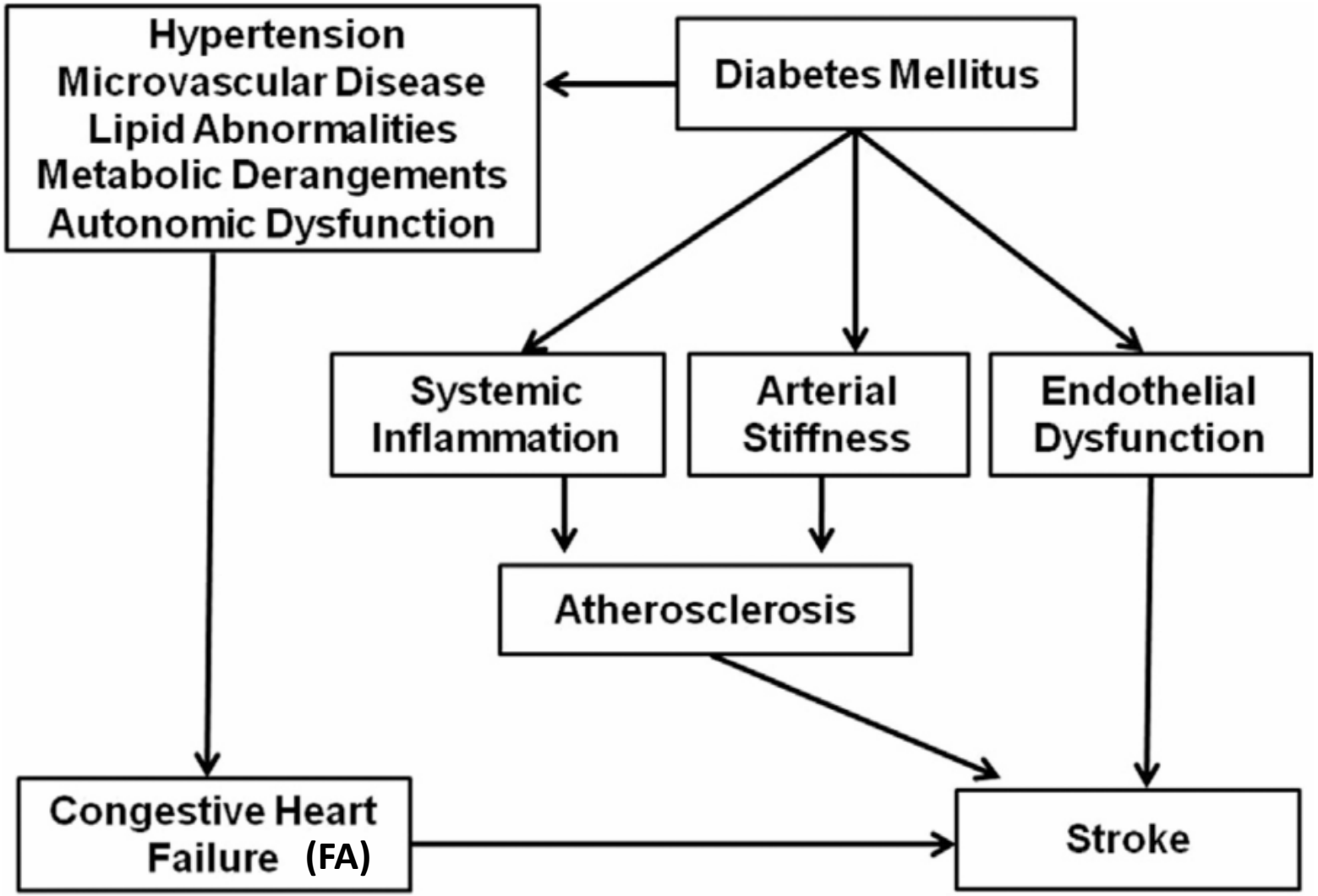
Giorda CB et al, Stroke, 2007

Risk factors for stroke in diabetes mellitus

- Modifiable risk factors for stroke in diabetes mellitus
  - Hypertension
  - Dyslipidemia
  - Smoking
  - Obesity and physical inactivity
  - Hypercoagulability and enhanced platelet aggregation
  - Arrhythmias, especially atrial fibrillation
  - Heart failure or coronary heart disease
  - Dysglycemia
  - Excessive alcohol intake
  - Asymptomatic carotid artery stenosis
- Nonmodifiable risk factors for stroke in diabetes mellitus
  - Age
  - Sex
  - Family history
  - Race/ethnicity

Kurukulasuriya LR et al, Expert Rev Cardiovascular Ther, 2006

Possible mechanisms of stroke in individuals with diabetes



Treatment strategies to reduce stroke

Diet
Exercise
Smoking cessation
Moderation in alcohol

↓
Adiposity
Inflammation
Insulin resistance
Dysglycemia
Endothelial dysfunction

RAAS blockade
Aspirin
Adequate blood pressure control
Glycemic control
Treatment of dyslipidemia

↓
Stoke incidence

Stroke morbidity and mortality

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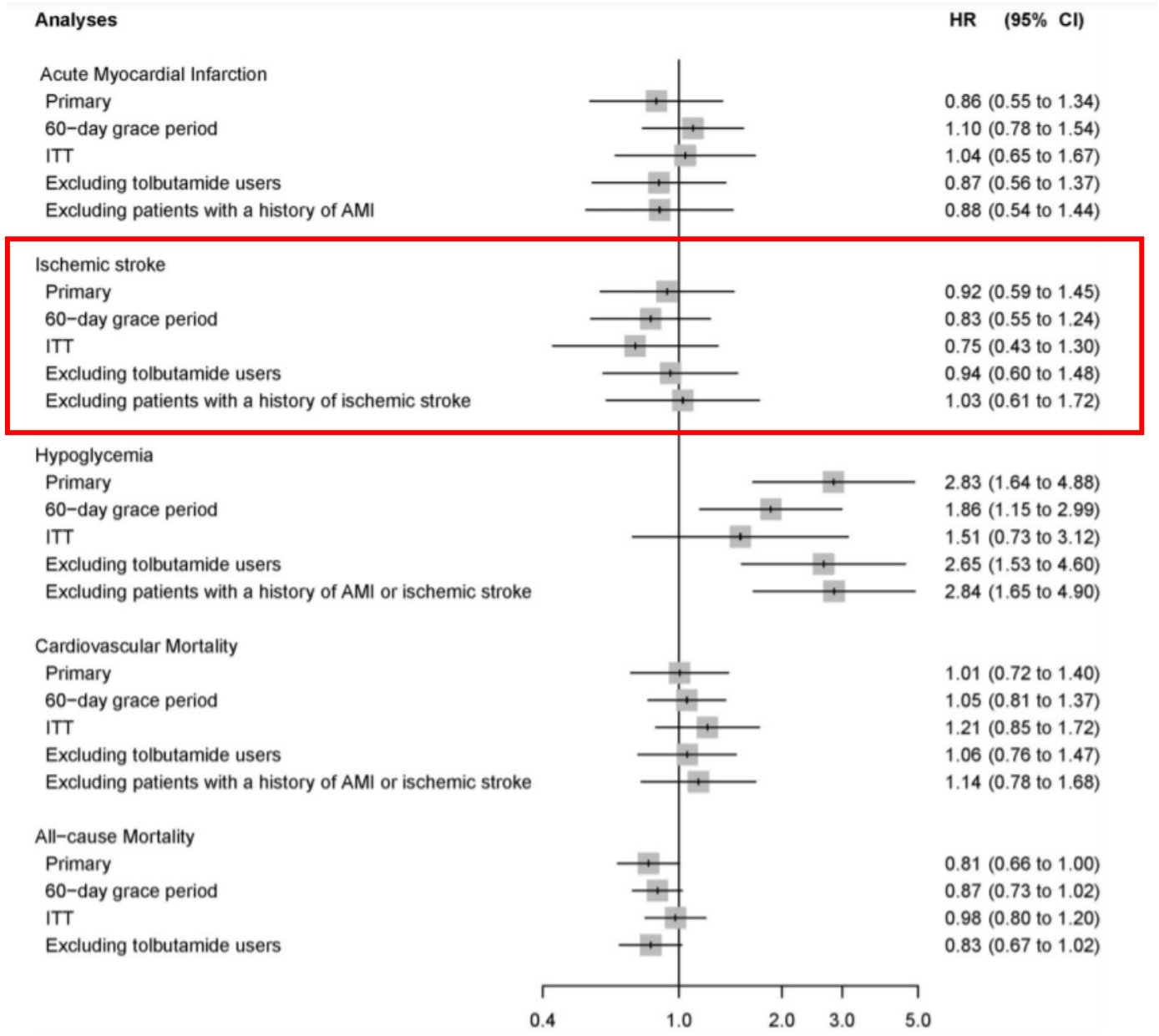
10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Table 2. Aggregate Outcomes for Patients during Follow-up.*

Aggregate Outcome	Patients with Clinical Outcome		Absolute Risk†		P Value‡	Risk Ratio for Intensive-Therapy Regimen (95% CI)
	Intensive Therapy	Conventional Therapy	Intensive Therapy	Conventional Therapy		
	no. of patients					
Sulfonyurea–insulin group	2729	1138				
Any diabetes-related end point	1571	686	48.1	52.2	0.04	0.91 (0.83–0.99)
Diabetes-related death	618	297	14.5	17.0	0.01	0.83 (0.73–0.96)
Death from any cause	1162	537	26.8	30.3	0.007	0.87 (0.79–0.96)
Myocardial infarction	678	319	16.8	19.6	0.01	0.85 (0.74–0.97)
Stroke	260	116	6.3	6.9	0.39	0.91 (0.73–1.13)
Peripheral vascular disease	83	40	2.0	2.4	0.29	0.82 (0.56–1.19)
Microvascular disease	429	222	11.0	14.2	0.001	0.76 (0.64–0.89)
Metformin group	342	411				
Any diabetes-related end point	209	262	45.7	53.9	0.01	0.79 (0.66–0.95)
Diabetes-related death	81	120	14.0	18.7	0.01	0.70 (0.53–0.92)
Death from any cause	152	217	25.9	33.1	0.002	0.73 (0.59–0.89)
Myocardial infarction	81	126	14.8	21.1	0.005	0.67 (0.51–0.89)
Stroke	34	42	6.0	6.8	0.35	0.80 (0.50–1.27)
Peripheral vascular disease	13	21	2.3	3.4	0.19	0.63 (0.32–1.27)
Microvascular disease	66	78	12.4	13.4	0.31	0.84 (0.60–1.17)

Holman RR et al, NEJM, 2008

Pharmacologic Differences of Sulfonylureas and the Risk of Adverse Cardiovascular and Hypoglycemic Events



The nonspecific, long-acting sulfonylureas glyburide and glimepiride do not have an increased risk of cardiovascular adverse events compared with the specific, short-acting sulfonylureas gliclazide, glipizide, and tolbutamide.

Douros A et al, Diabetes Care, 2017

Association of prestroke metformin use, stroke severity, and thrombolysis outcome

Table 3 Comparison of outcome depending on MET treatment before and after matching

Before matching	MET+ (n = 757)	MET− (n = 1,162)	*p* Value
Clinical scores			
NIHSS on admission, mean (SD)	10.0 (6.7)	11.7 (6.5)	<0.001
mRS after 3 months, median [IQR]	2 (1.0–4.0)	3 (1.0–5.0)	<0.001
Complications, n (%)			
Symptomatic ICH (ECASS-II criteria)	39 (5.2)	58 (5.0)	0.96
Mortality within 3 months, n (%)	95 (12.5)	258 (22.2)	<0.001
After matching	**MET+ (n = 757)**	**MET− (n = 757)**	***p* Value**
Clinical scores			
NIHSS on admission, mean (SD)	10.0 (6.7)	11.3 (6.5)	<0.001
mRS after 3 months, median [IQR]	2 (1.0–4.0)	3 (1.0–4.0)	<0.001
Complications, n (%)			
Symptomatic ICH (ECASS-II criteria)	39 (5.2)	39 (5.2)	0.73
Mortality within 3 months, n (%)	95 (12.5)	136 (18)	0.008

Abbreviations: ECASS-II = European Cooperative Acute Stroke Study II; ICH = intracranial hemorrhage; MET = metformin; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.

Secondary outcome:
- Mortality (all causes) within 3 months of stroke
- Symptomatic intracranial hemorrhage (ICH)

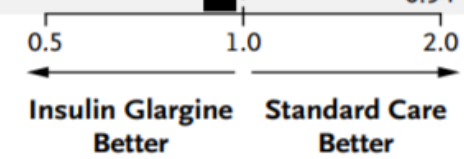
Patients with stroke and diabetes on treatment with MET receiving IV thrombolysis (IVT) had less severe strokes on admission and a better functional outcome at 3 months. The frequency of syntomatic intracerebral hemorrhages did not differ between groups.
This suggests a protective effect of MET resulting in less severe strokes as well as beneficial thrombolysis outcome.

Westphal LP et al, Neurology, 2020

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

Outcome	Insulin Glargine (N=6264)		Standard Care (N=6273)		Hazard Ratio (95% CI)	P Value
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
First coprimary outcome	1041 (16.6)	2.94	1013 (16.1)	2.85	1.02 (0.94–1.11)	0.63
Second coprimary outcome	1792 (28.6)	5.52	1727 (27.5)	5.28	1.04 (0.97–1.11)	0.27
Microvascular outcomes	1323 (21.1)	3.87	1363 (21.7)	3.99	0.97 (0.90–1.05)	0.43
Total mortality	951 (15.2)	2.57	965 (15.4)	2.60	0.98 (0.90–1.08)	0.70
Total myocardial infarctions	336 (5.4)	0.93	326 (5.2)	0.90	1.02 (0.88–1.19)	0.75
Total strokes	331 (5.3)	0.91	319 (5.1)	0.88	1.03 (0.89–1.21)	0.69
Death from cardiovascular causes	580 (9.3)	1.57	576 (9.2)	1.55	1.00 (0.89–1.13)	0.98
Hospitalization for congestive heart failure	310 (4.9)	0.85	343 (5.5)	0.95	0.90 (0.77–1.05)	0.16
Revascularization	908 (14.5)	2.69	860 (13.7)	2.52	1.06 (0.96–1.16)	0.24
Angina	709 (11.3)	2.07	743 (11.8)	2.17	0.95 (0.85–1.05)	0.29
Unstable	238 (3.8)	0.66	261 (4.2)	0.72	0.91 (0.76–1.08)	0.28
New	100 (1.6)	0.27	138 (2.2)	0.38	0.72 (0.56–0.93)	0.01
Worsening	455 (7.3)	1.29	446 (7.1)	1.26	1.02 (0.89–1.16)	0.80
Limb or digit amputation	47 (0.8)	0.13	53 (0.8)	0.14	0.89 (0.60–1.31)	0.55
Cardiovascular hospitalization	2081 (33.2)	6.98	2071 (33.0)	6.91	1.00 (0.94–1.07)	0.90
Noncardiovascular hospitalization	2339 (37.3)	7.90	2349 (37.4)	7.93	0.99 (0.94–1.05)	0.85
Any cancer	476 (7.6)	1.32	477 (7.6)	1.32	1.00 (0.88–1.13)	0.97
Death from cancer	189 (3.0)	0.51	201 (3.2)	0.54	0.94 (0.77–1.15)	0.52

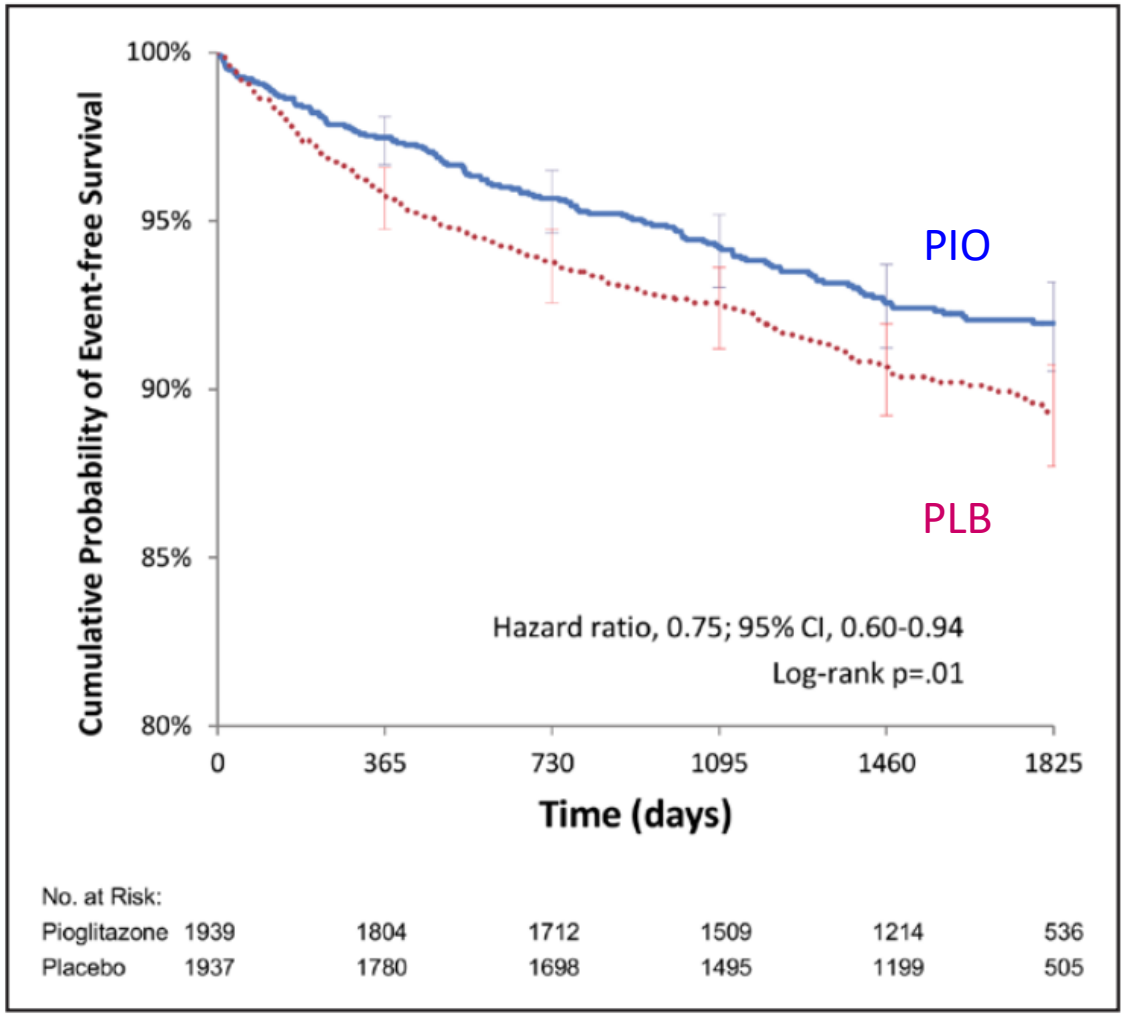


N Engl J Med 2012

Pioglitazone Prevents Stroke in Patients With a Recent Transient Ischemic Attack or Ischemic Stroke

A Planned Secondary Analysis of the IRIS Trial (Insulin Resistance Intervention After Stroke)

Stroke Outcome	Pioglitazone (n=1939)			Placebo (n=1937)			HR (95% CI)‡	P§
	Events	Pts*	Risk,† %	Events	Pts*	Risk,† %		
Any stroke	155	138	8.0	222	181	10.7	0.75 (0.60–0.94)	0.01
Hemorrhagic stroke	17	16	1.0	19	16	1.0	1.00 (0.50–2.00)	1.00
Nonfatal	11	10	0.6	12	9	0.6	1.11 (0.45–2.73)	0.82
Fatal	6	6	0.4	7	7	0.4	0.86 (0.29–2.55)	0.78
Ischemic stroke	137	123	7.1	202	169	9.9	0.72 (0.57–0.91)	0.005
Nonfatal	131	118	6.9	191	161	9.3	0.72 (0.57–0.92)	0.008
Fatal	6	6	0.3	11	11	0.8	0.55 (0.20–1.47)	0.23



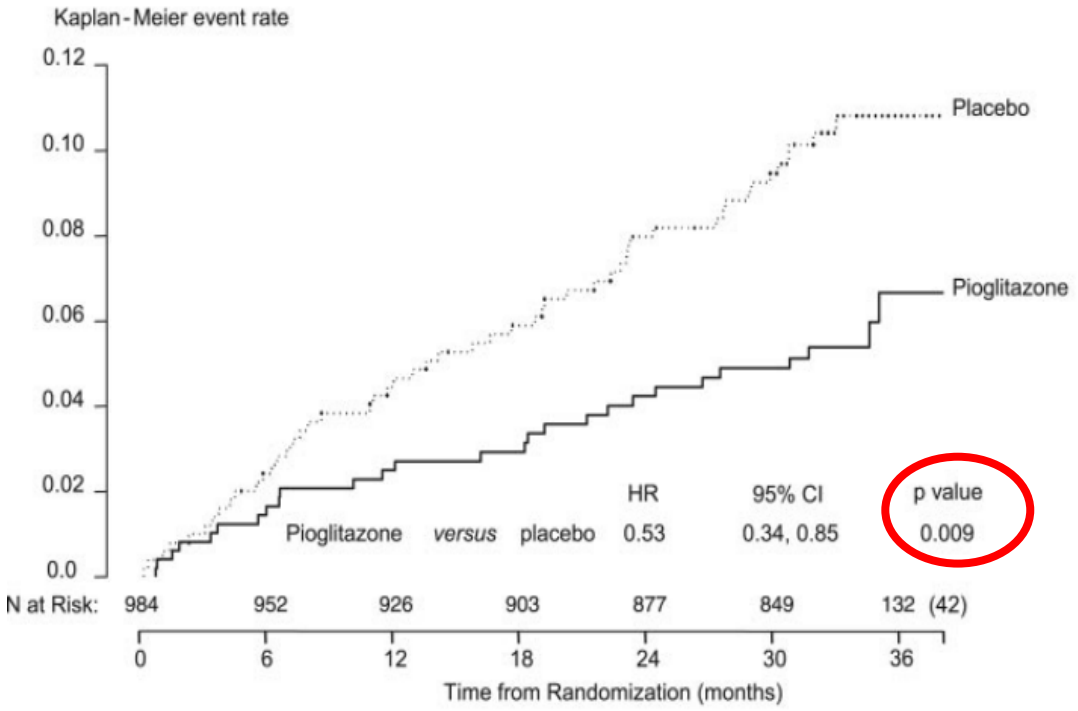
Pioglitazone was effective for secondary prevention of ischemic stroke in nondiabetic patients with insulin resistance

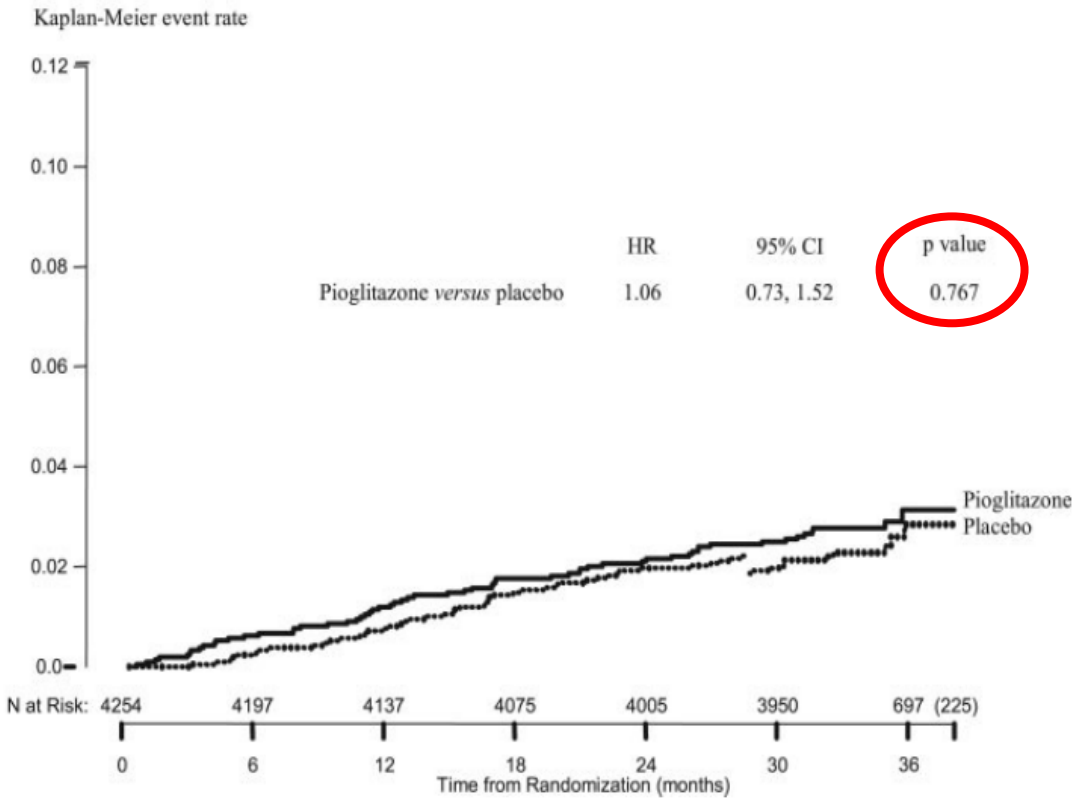
Yaghi S et al, Circulation, 2018

Effects of Pioglitazone in Patients With Type 2 Diabetes With or Without Previous Stroke

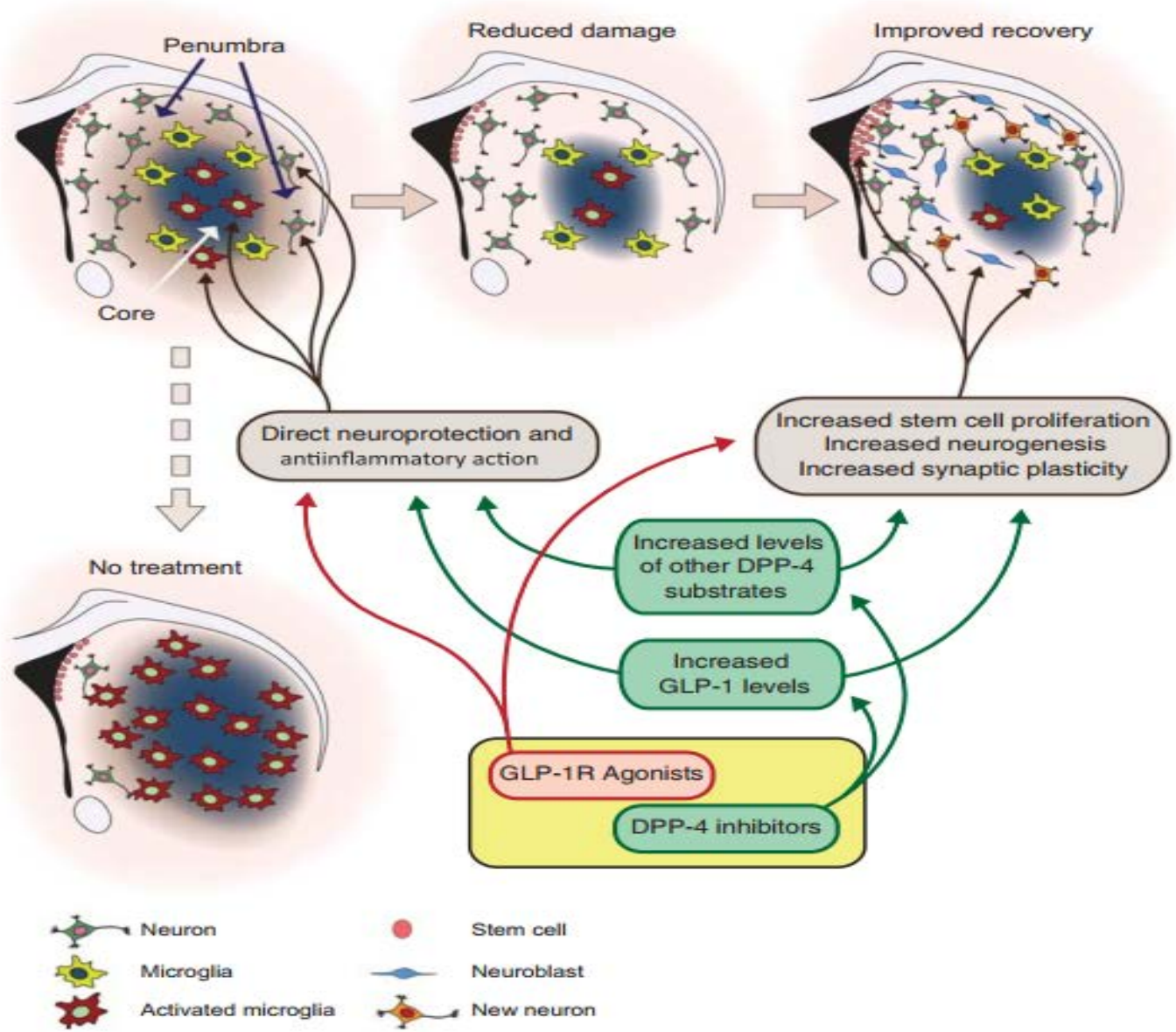
Results From PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04)

Time to stroke (fatal and nonfatal) in patients with and without previous stroke.





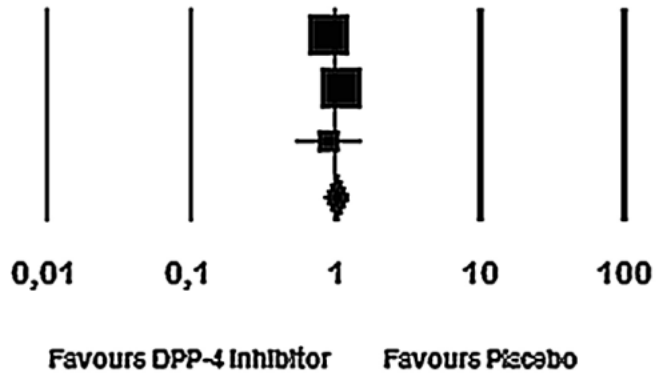
Wilcox R et al, Stroke, 2007



Darsalia V et al, J Cereb Blood Flow Metab. 2015

Incidence of stroke in diabetic subjects treated with DPP-4 inhibitors compared with placebo

Study name	Statistics for each study				Stroke / Total	
	Odds ratio	Lower limit	Upper limit	p-Value	DPP-4	Placebo
TECOS	0,908	0,714	1,155	0,432	129 / 7257	142 / 7266
SAVOR-TIMI 53	1,106	0,879	1,392	0,388	157 / 8280	141 / 8212
EXAMINE	0,898	0,542	1,488	0,676	29 / 2701	32 / 2679
Overall	0,966	0,850	1,166	0,958		



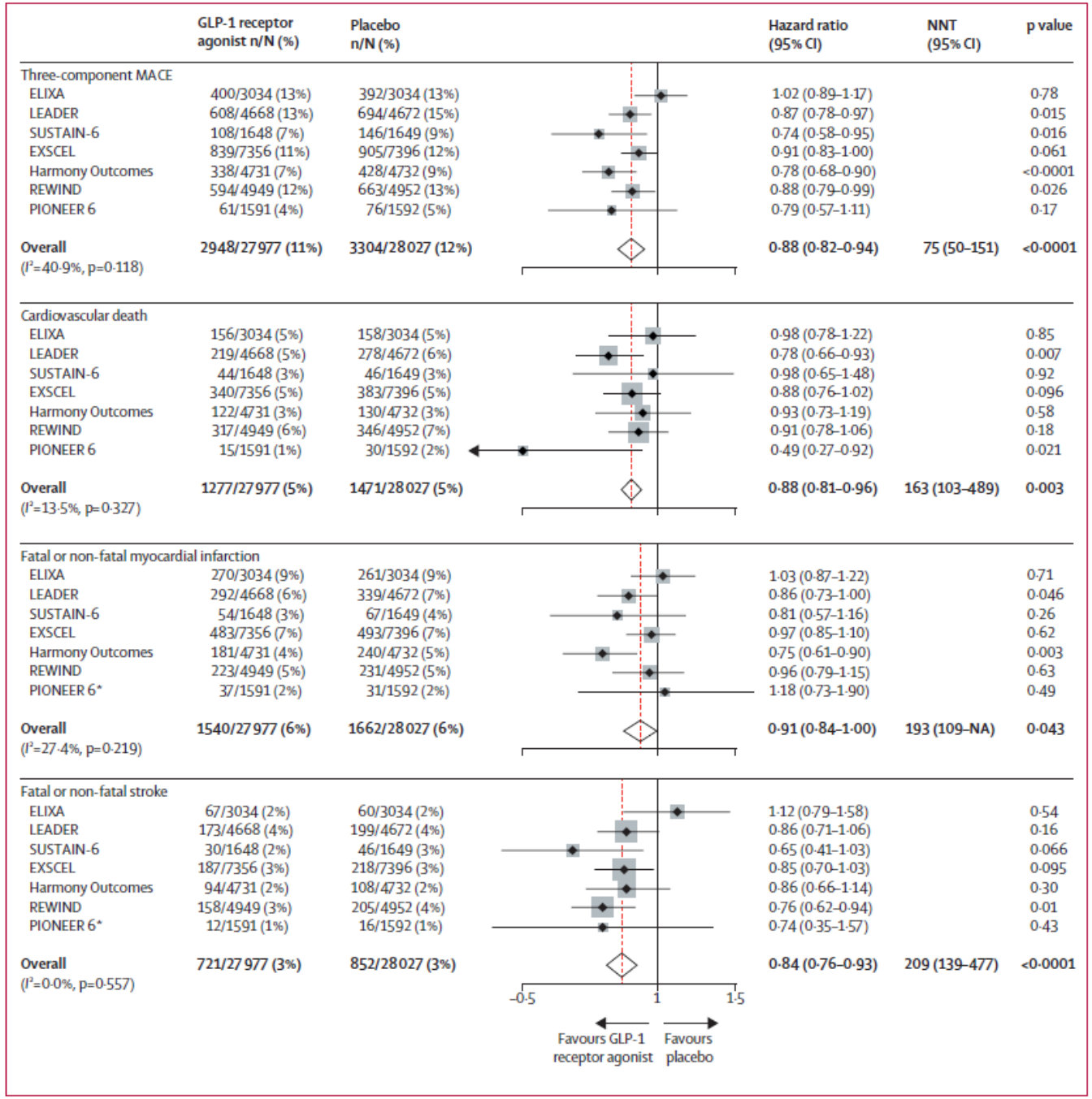
Barkas F, et al. Diabetes Metab, 2017

Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk The CARMELINA Randomized Clinical Trial

Outcomes	Linagliptin (n = 3494)[a]		Placebo (n = 3485)[a]		Incidence Rate Difference, Linagliptin – Placebo (95% CI)	Hazard Ratio (95% CI)[b]	*P* Value
	No. (%)	Rate per 100 Patient-Years	No. (%)	Rate per 100 Patient-Years			
Primary Outcome (3-Point MACE)							
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	434 (12.4)	5.77	420 (12.1)	5.63	0.13 (−0.63 to 0.90)	1.02 (0.89-1.17)	<.001[c]; .74[d]
Cardiovascular death[e]	221 (6.3)		225 (6.5)				
Nonfatal myocardial infarction[e]	154 (4.4)		132 (3.8)				
Nonfatal stroke[e]	59 (1.7)		63 (1.8)				
Secondary Kidney Composite Outcome							
Sustained ESRD, death due to kidney failure, or sustained decrease of ≥40% in eGFR from baseline	327 (9.4)	4.89	306 (8.8)	4.66	0.22 (−0.52 to 0.97)	1.04 (0.89-1.22)	.62
ESRD[e]	63 (1.8)		64 (1.8)				
Death due to renal failure[e]	1 (0.03)		1 (0.03)				
Sustained decrease of ≥40% in eGFR[e]	263 (7.5)		241 (6.9)				
Exploratory Cardiovascular and Death Outcomes							
All-cause death	367 (10.5)	4.69	373 (10.7)	4.80	−0.11 (−0.79 to 0.58)	0.98 (0.84-1.13)	.74
Cardiovascular death	255 (7.3)	3.26	264 (7.6)	3.40	−0.14 (−0.71 to 0.44).	0.96 (0.81-1.14)	.63
Noncardiovascular death	112 (3.2)	1.43	109 (3.1)	1.40	0.03 (−0.34 to 0.40)	1.02 (0.78-1.33)	.89
Fatal myocardial infarction	11 (0.3)	0.14	14 (0.4)	0.18	−0.04 (−0.17 to 0.09)	0.78 (0.36-1.72)	.54
Nonfatal myocardial infarction	156 (4.5)	2.06	135 (3.9)	1.80	0.27 (−0.18 to 0.71)	1.15 (0.91-1.45)	.23
Fatal or nonfatal myocardial infarction	165 (4.7)	2.18	146 (4.2)	1.94	0.24 (−0.22 to 0.70)	1.12 (0.90-1.40)	.30
Fatal stroke	17 (0.5)	0.22	16 (0.5)	0.21	0.01 (−0.13 to 0.16)	1.05 (0.53-2.09)	.88
Nonfatal stroke	65 (1.9)	0.85	73 (2.1)	0.96	−0.12 (−0.42 to 0.19)	0.88 (0.63-1.23)	.45
Fatal or nonfatal stroke	81 (2.3)	1.06	88 (2.5)	1.16	−0.11 (−0.44 to 0.23)	0.91 (0.67-1.23)	.53
4-point MACE (3-point MACE plus hospitalization for unstable angina)	463 (13.3)	6.20	459 (13.2)	6.21	−0.02 (−0.82 to 0.79)	1.00 (0.88-1.13)	.96
Hospitalization for unstable angina	42 (1.2)	0.55	48 (1.4)	0.63	−0.09 (−0.33 to 0.16)	0.87 (0.57-1.31)	.50
Coronary revascularization procedure	160 (4.6)	2.12	149 (4.3)	1.99	0.13 (−0.33 to 0.59)	1.07 (0.85-1.33)	.57
Hospitalization for heart failure	209 (6.0)	2.77	226 (6.5)	3.04	−0.27 (−0.82 to 0.28)	0.90 (0.74-1.08)	.26

Rosenstock J et al, JAMA, 2018

GLP 1 RA: Risk of MACE and each of its components



Kristensen SL et al, Lancet Diabetes Endocrinol 2019

GLP-1 receptor agonists in diabetes for stroke prevention: a systematic review and meta-analysis

Overview of cerebrovascular outcomes among patients treated with GLP-1R agonists

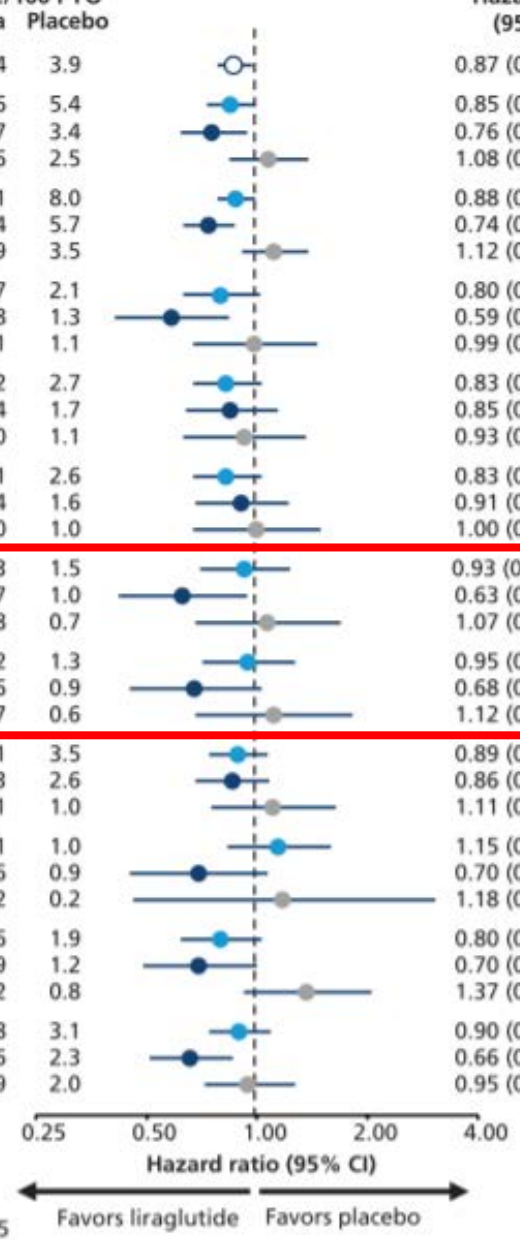
Clinical outcome	Number of RCTs	OR (95% CI)	*p*	Heterogeneity (I^2, *p* for Cochran *Q*)
Nonfatal strokes	7	0.84 (0.76–0.94)	**0.002**	0%, 0.61
Fatal strokes	5	0.82 (0.62–1.09)	0.17	0%, 0.71
All strokes	5	0.84 (0.75–0.93)	**0.001**	0%, 0.92
Cardiovascular mortality	8	0.88 (0.81–0.95)	**0.002**	0%, 0.44
All-cause mortality	7	0.88 (0.82–0.95)	**<0.001**	15%, 0.31
MACE	7	0.87 (0.81–0.94)	**<0.001**	42%, 0.11

Malhotra K et al, J Neurol, 2020

Effects of Liraglutide on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus With or Without History of Myocardial Infarction or Stroke

Post Hoc Analysis From the LEADER Trial

Outcome	Prior MI/stroke	n (%) Lira	n (%) Placebo	Rate/100 PYO Lira	Rate/100 PYO Placebo	Hazard ratio (95% CI)	Interaction *P*-value
Primary endpoint	Overall population	608 (13.0)	694 (14.9)	3.4	3.9	0.87 (0.78; 0.97)	
Primary endpoint	Prior MI/stroke	322 (17.3)	372 (20.4)	4.6	5.4	0.85 (0.73; 0.99)	
	CVD without MI/stroke	158 (10.3)	199 (12.9)	2.7	3.4	0.76 (0.62; 0.94)	0.11
	CV risk factors	128 (10.1)	123 (9.5)	2.6	2.5	1.08 (0.84; 1.38)	
Expanded MACE	Prior MI/stroke	500 (26.8)	552 (30.2)	7.1	8.0	0.88 (0.78; 0.99)	
	CVD without MI/stroke	261 (17.0)	336 (21.7)	4.4	5.7	0.74 (0.63; 0.87)	0.01
	CV risk factors	187 (14.8)	174 (13.4)	3.9	3.5	1.12 (0.91; 1.38)	
CV death	Prior MI/stroke	120 (6.4)	147 (8.0)	1.7	2.1	0.80 (0.63; 1.02)	
	CVD without MI/stroke	48 (3.1)	78 (5.0)	0.8	1.3	0.59 (0.41; 0.84)	0.14
	CV risk factors	51 (4.0)	53 (4.1)	1.1	1.1	0.99 (0.67; 1.46)	
All MIs*	Prior MI/stroke	157 (8.4)	185 (10.1)	2.2	2.7	0.83 (0.67; 1.03)	
	CVD without MI/stroke	85 (5.5)	98 (6.3)	1.4	1.7	0.85 (0.64; 1.14)	0.89
	CV risk factors	50 (4.0)	56 (4.3)	1.0	1.1	0.93 (0.63; 1.36)	
Non-fatal MI	Prior MI/stroke	150 (8.0)	177 (9.7)	2.1	2.6	0.83 (0.67; 1.03)	
	CVD without MI/stroke	84 (5.5)	91 (5.9)	1.4	1.6	0.91 (0.68; 1.22)	0.71
	CV risk factors	47 (3.7)	49 (3.8)	1.0	1.0	1.00 (0.67; 1.49)	
All strokes*	Prior MI/stroke	95 (5.1)	101 (5.5)	1.3	1.5	0.93 (0.70; 1.23)	
	CVD without MI/stroke	39 (2.5)	61 (3.9)	0.7	1.0	0.63 (0.42; 0.94)	0.17
	CV risk factors	39 (3.1)	37 (2.8)	0.8	0.7	1.07 (0.68; 1.69)	
Non-fatal stroke	Prior MI/stroke	87 (4.7)	91 (5.0)	1.2	1.3	0.95 (0.71; 1.27)	
	CVD without MI/stroke	38 (2.5)	55 (3.6)	0.6	0.9	0.68 (0.45; 1.03)	0.28
	CV risk factors	34 (2.7)	31 (2.4)	0.7	0.6	1.12 (0.68; 1.82)	
Coronary revascularization	Prior MI/stroke	219 (11.7)	239 (13.1)	3.1	3.5	0.89 (0.74; 1.07)	
	CVD without MI/stroke	134 (8.7)	153 (9.9)	2.3	2.6	0.86 (0.68; 1.08)	0.51
	CV risk factors	52 (4.1)	49 (3.8)	1.1	1.0	1.11 (0.75; 1.64)	
Hospitalization for unstable angina	Prior MI/stroke	78 (4.2)	66 (3.6)	1.1	1.0	1.15 (0.83; 1.59)	
	CVD without MI/stroke	35 (2.3)	50 (3.2)	0.6	0.9	0.70 (0.45; 1.07)	0.18
	CV risk factors	9 (0.7)	8 (0.6)	0.2	0.2	1.18 (0.46; 3.06)	
Hospitalization for heart failure	Prior MI/stroke	110 (5.9)	134 (7.3)	1.6	1.9	0.80 (0.62; 1.03)	
	CVD without MI/stroke	52 (3.4)	72 (4.7)	0.9	1.2	0.70 (0.49; 1.00)	0.03
	CV risk factors	56 (4.4)	42 (3.2)	1.2	0.8	1.37 (0.92; 2.05)	
All-cause death	Prior MI/stroke	196 (10.5)	212 (11.6)	2.8	3.1	0.90 (0.74; 1.09)	
	CVD without MI/stroke	93 (6.0)	135 (8.7)	1.6	2.3	0.66 (0.51; 0.86)	0.12
	CV risk factors	92 (7.3)	100 (7.7)	1.9	2.0	0.95 (0.72; 1.27)	

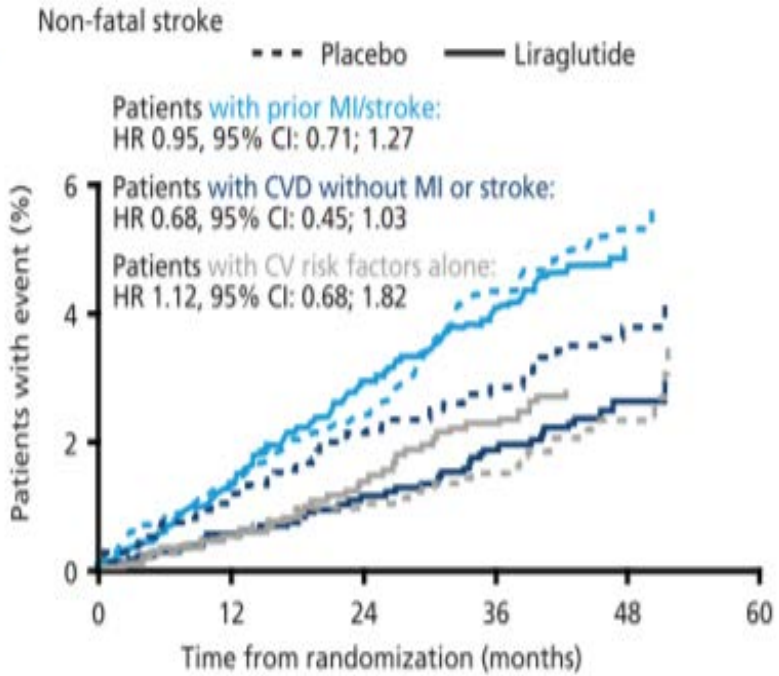


Overall population
Liraglutide n=4668
Placebo n=4672

With prior MI/stroke
Liraglutide n=1865
Placebo n=1827

With CVD without MI/stroke
Liraglutide n=1538
Placebo n=1545

With CV risk factors alone
Liraglutide n=1265
Placebo n=1300



Liraglutide exerts a consistent benefit in patients with established atherosclerotic cardiovascular disease with and without a history of MI/stroke; however, it appears to be neutral in patients with cardiovascular risk factors alone.

Verma S et al, Circulation, 2016

The effect of dulaglutide on stroke: an exploratory analysis of the REWIND trial

	Dulaglutide (n=4949)	Placebo (n=4952)	HR (95% CI)	p value
Stroke	158 (3·2%); 0·61	205 (4·1%); 0·81	0·76 (0·62–0·94)	0·010
Non-fatal stroke*	135 (2·7%); 0·52	175 (3·5%); 0·69	0·76 (0·61–0·95)	0·017
Fatal stroke	26 (0·5%); 0·10	33 (0·7%); 0·13	0·78 (0·47–1·30)	0·34
Disabling stroke†	82 (1·7%); 0·32	109 (2·2%); 0·43	0·74 (0·56–0·99)	0·042
Ischaemic stroke	129 (2·6%); 0·50	171 (3·4%); 0·67	0·75 (0·59–0·94)	0·012
Haemorrhagic stroke	19 (0·4%); 0·07	18 (0·4%); 0·07	1·05 (0·55–1·99)	0·89
Stroke of unknown type	14 (0·3%); 0·05	17 (0·3%); 0·07	0·82 (0·40–1·66)	0·58
Transient ischaemic attack	39 (0·8%); 0·15	49 (1·0%); 0·19	0·79 (0·52–1·20)	0·27
Non-fatal stroke or all-cause death	643 (13·0%); 2·50	722 (14·6%); 2·84	0·88 (0·79–0·98)	0·017
All-cause death	536 (10·8%); 2·06	592 (12·0%); 2·29	0·90 (0·80–1·01)	0·067

Data are n (%); number of events per 100 person-years, unless otherwise indicated. All HRs are from Cox models and p values are two-sided. HR=hazard ratio. * After adjusting for the competing risk of death HR 0·77 (95% CI 0·61–0·96; p=0·02). †Any stroke with a modified Rankin score ≥3.

Table 2: **Effect of treatment allocation on stroke outcomes**

In conclusion, given the frequency of stroke in people with diabetes, the severity of its associated morbidity, and the paucity of preventive therapies, the findings of this study suggest that GLP-1 receptor agonists should be considered when developing future stroke prevention guidelines for people with diabetes. Furthermore, our study strongly supports the need for further research on the effect of these drugs on stroke.

Gerstein HC et al, Lancet Diabetes Endocrinol, 2020

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

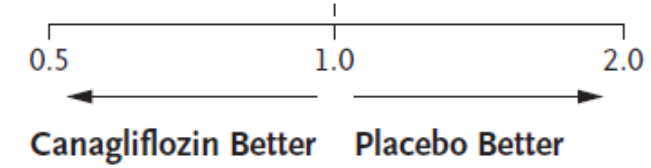
Table 1. Primary and Secondary Cardiovascular Outcomes.

Outcome	Placebo (N=2333)		Empagliflozin (N=4687)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74–0.99)	
Noninferiority						<0.001†
Superiority						0.04†
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*	333 (14.3)	52.5	599 (12.8)	46.4	0.89 (0.78–1.01)	
Noninferiority						<0.001†
Superiority						0.08†
Death						
From any cause	194 (8.3)	28.6	269 (5.7)	19.4	0.68 (0.57–0.82)	<0.001
From cardiovascular causes	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70–2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

Zinman B et al, NEJM, 2015

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

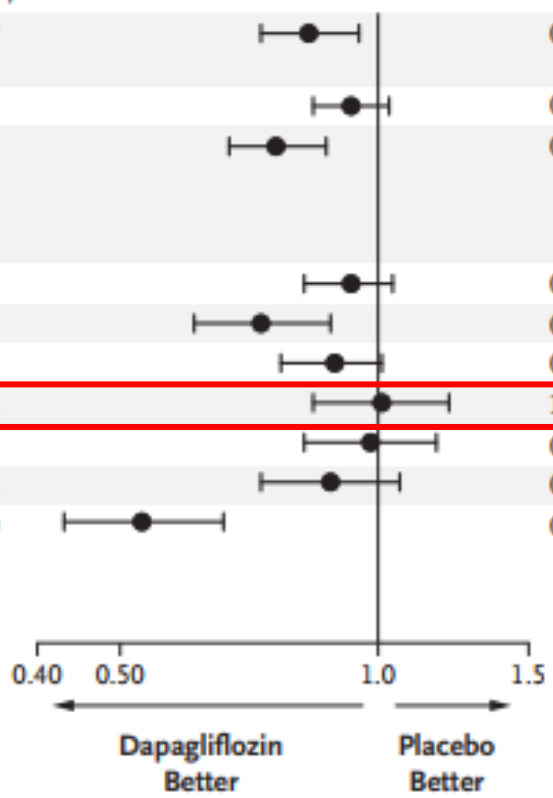
Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



Neal B et al, NEJM, 2017

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	



Wiviott SD et al, NEJM, 2018

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

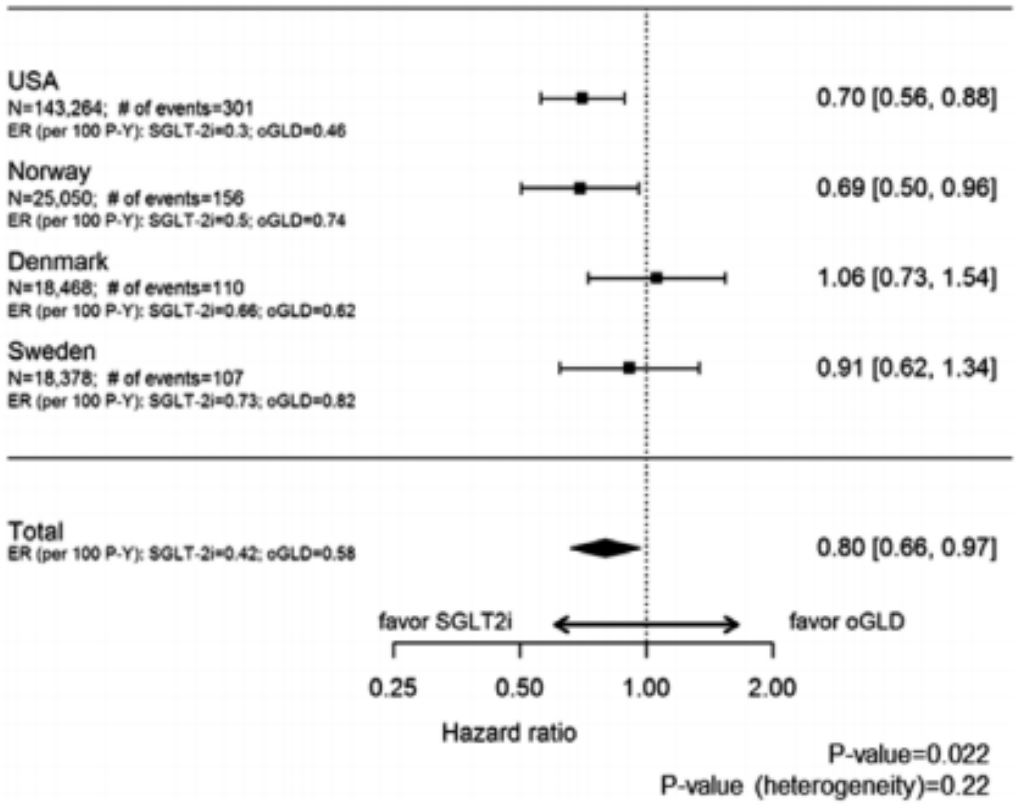
Table 2. Primary and Secondary Outcomes.*

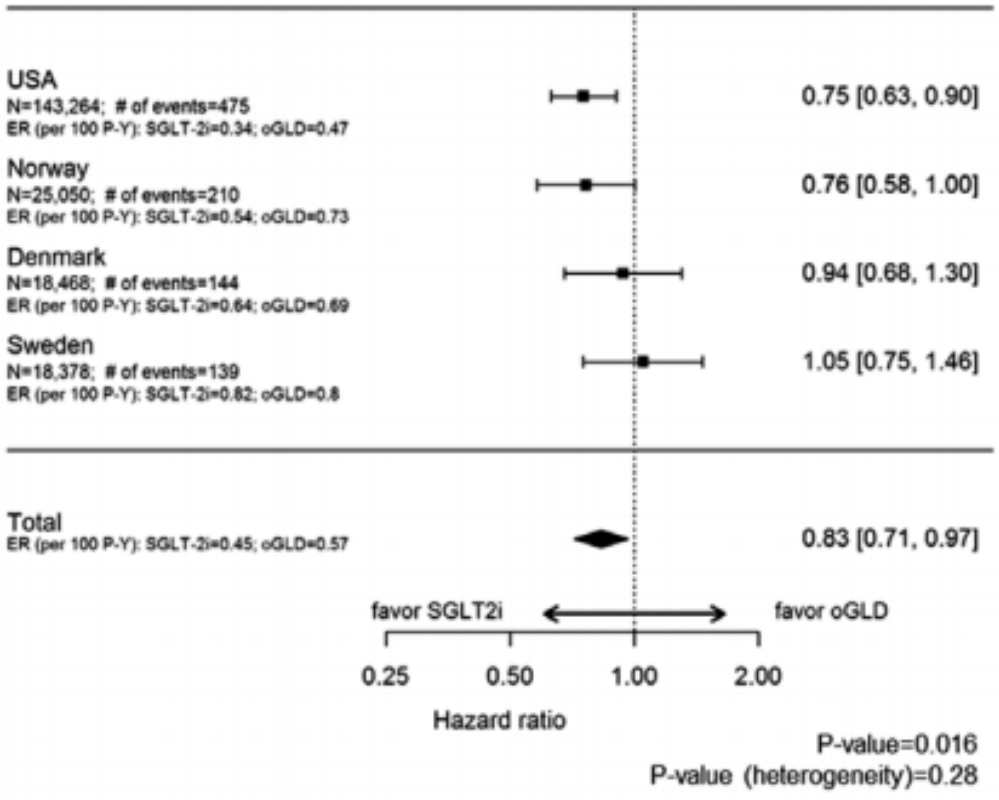
Outcome	Ertugliflozin†		Placebo		Hazard Ratio (CI)‡	P Value§
	no. of patients/ total no. (%)	*no. of events/ 100 patient-yr*	*no. of patients/ total no. (%)*	*no. of events/ 100 patient-yr*		
Primary outcome						
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	653/5493 (11.9)	3.9	327/2745 (11.9)	4.0	0.97 (0.85–1.11)	<0.001
Key secondary outcomes						
Death from cardiovascular causes or hospitalization for heart failure	444/5499 (8.1)	2.3	250/2747 (9.1)	2.7	0.88 (0.75–1.03)	0.11
Death from cardiovascular causes	341/5499 (6.2)	1.8	184/2747 (6.7)	1.9	0.92 (0.77–1.11)	
Death from renal causes, renal replacement therapy, or doubling of the serum creatinine level	175/5499 (3.2)	0.9	108/2747 (3.9)	1.2	0.81 (0.63–1.04)	
Death from renal causes	0/5499	NA	0/2747	NA	NA	
Renal replacement therapy	7/5499 (0.1)	NA	3/2747 (0.1)	NA	NA	
Doubling of serum creatinine level	168/5499 (3.1)	NA	105/2747 (3.8)	NA	NA	
Other secondary outcomes						
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina	823/5499 (15.0)	4.5	439/2747 (16.0)	4.9	0.92 (0.82–1.04)	
Fatal or nonfatal myocardial infarction	330/5499 (6.0)	1.8	158/2747 (5.8)	1.7	1.04 (0.86–1.26)	
Fatal or nonfatal stroke	185/5499 (3.4)	1.0	87/2747 (3.2)	0.9	1.06 (0.82–1.37)	
Hospitalization for heart failure	139/5499 (2.5)	0.7	99/2747 (3.6)	1.1	0.70 (0.54–0.90)	
Nonfatal myocardial infarction	310/5499 (5.6)	1.7	148/2747 (5.4)	1.6	1.04 (0.86–1. 27)	
Nonfatal stroke	157/5499 (2.9)	0.8	78/2747 (2.8)	0.8	1.00 (0.76–1.32)	
Death from any cause	473/5499 (8.6)	2.4	254/2747 (9.2)	2.6	0.93 (0.80–1.08)	

Cannon CP et al, NEJM, 2020

Rates of myocardial infarction and stroke in patients initiating treatment with SGLT2-inhibitors versus other glucose-lowering agents in real-world clinical practice: Results from the CVD-REAL study

Event rates, unadjusted hazard ratios and 95% CIs for stroke in the on-treatment population and in the ITT population





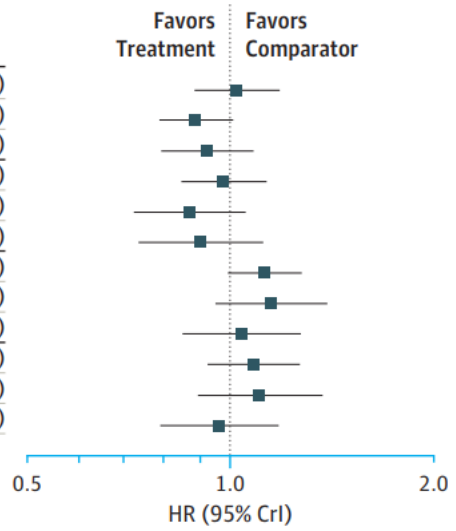
Kosiborod M et a, Diabetes Obes Metab, 2018

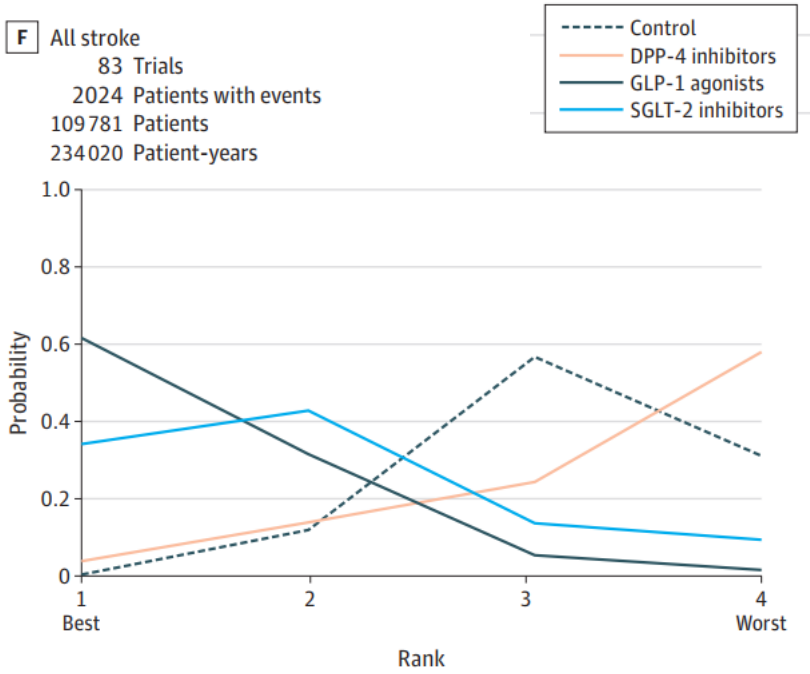
Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes

A Systematic Review and Meta-analysis

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.0 (-0.2 to 0.4)	1.02 (0.88 to 1.18)
GLP-1 agonist		-0.2 (-0.5 to 0.0)	0.89 (0.78 to 1.01)
SGLT-2 inhibitor		-0.2 (-0.4 to 0.2)	0.92 (0.79 to 1.08)
Control	vs DPP-4 inhibitor	0.0 (-0.2 to 0.2)	0.98 (0.85 to 1.13)
GLP-1 agonist		-0.2 (-0.4 to 0.1)	0.87 (0.72 to 1.05)
SGLT-2 inhibitor		-0.1 (-0.4 to 0.2)	0.90 (0.73 to 1.12)
Control	vs GLP-1 agonist	0.2 (0.0 to 0.5)	1.12 (0.99 to 1.27)
DPP-4 inhibitor		0.3 (-0.1 to 0.8)	1.15 (0.95 to 1.39)
SGLT-2 inhibitor		0.1 (-0.3 to 0.5)	1.04 (0.85 to 1.27)
Control	vs SGLT-2 inhibitor	0.1 (-0.1 to 0.4)	1.08 (0.92 to 1.27)
DPP-4 inhibitor		0.2 (-0.2 to 0.6)	1.11 (0.89 to 1.37)
GLP-1 agonist		-0.1 (-0.3 to 0.3)	0.96 (0.79 to 1.18)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	75	955 (2.1)	46012
DPP-4 inhibitor	39	371 (1.5)	25106
GLP-1 agonist	28	455 (2.0)	23330
SGLT-2 inhibitor	30	243 (1.6)	15333





In this network meta-analysis, the use of SGLT-2 inhibitors or GLP-1 agonists was associated with lower mortality than DPP-4 inhibitors or placebo or no treatment. Use of DPP-4 inhibitors was not associated with lower mortality than placebo or no treatment.

There was no associated difference between drug classes for nonfatal stroke

Zheng SL et al, JAMA, 2018

Grazie per l'attenzione