Prevention of ASCVD in Diabetes *Focus on Strokes*

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Disclosures

- Research payments (to institution): Novo Nordisk, Mylan, Pfizer, Merck, Sanofi
- Consulting/advisory roles: NovoNordisk, Sanofi, Eli Lilly, Zealand Pharma, Boehringer-Ingelheim, Intercept, TARGETPharma, Valeritas, Merck, Medscape, DataRevive, Janssen, Bayer

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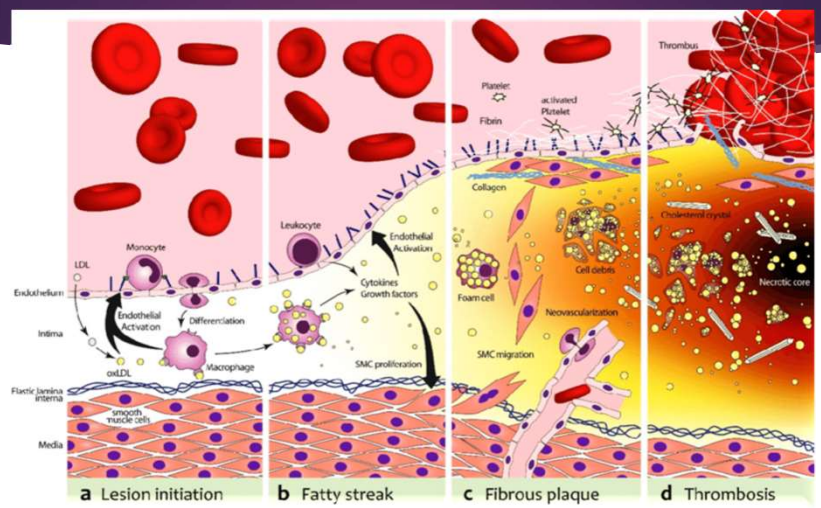
Pathophysiology of Atherosclerosis



Steinl D. Int J Mol Sci 2015.16(5):9749

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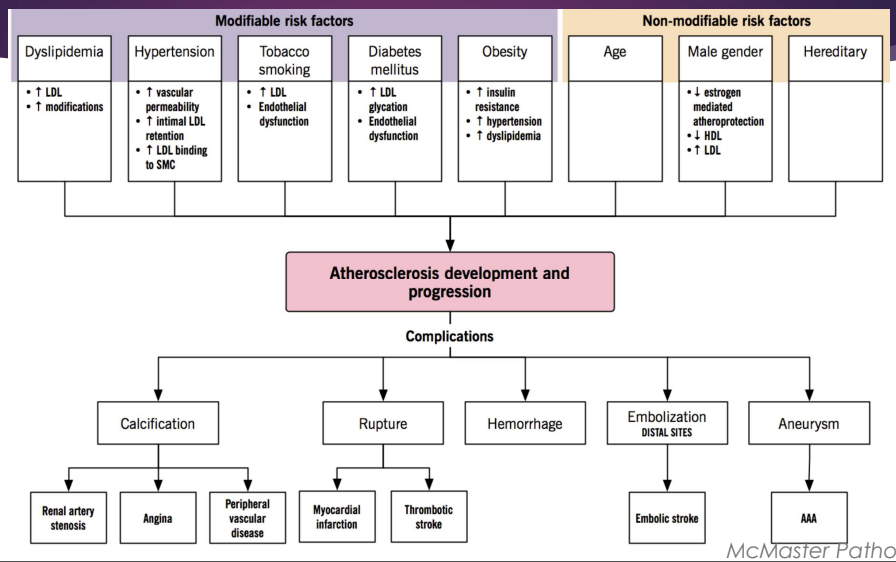
Atherosclerosis Risk Factors & Complications



McMaster Pathophysiology Review

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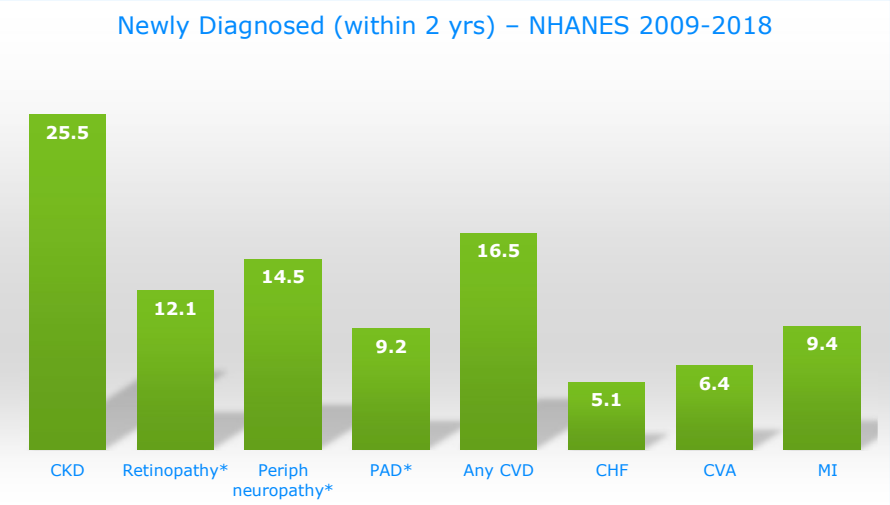
Prevalence of Diabetes-Related Complications in the US



UTSouthwestern Medical Center

*Data from 1999-2008 NHANES

Fang M. Diab Care 2021

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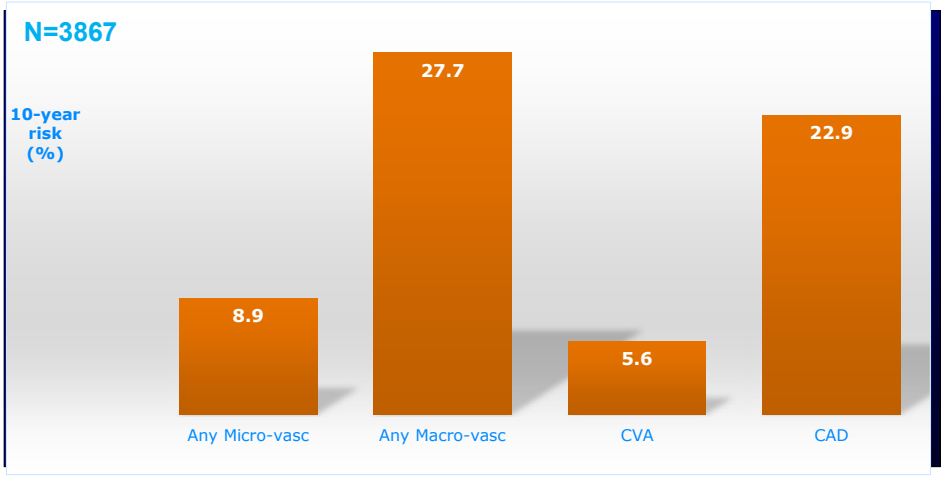
Prevalence of Diabetes Complications in UKPDS



UTSouthwestern Medical Center

UKPDS Investigators. Lancet 1998; 352: 837

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ASCVD Treatment Approach

2019 ACC/AHA Guidelines on Primary Prevention

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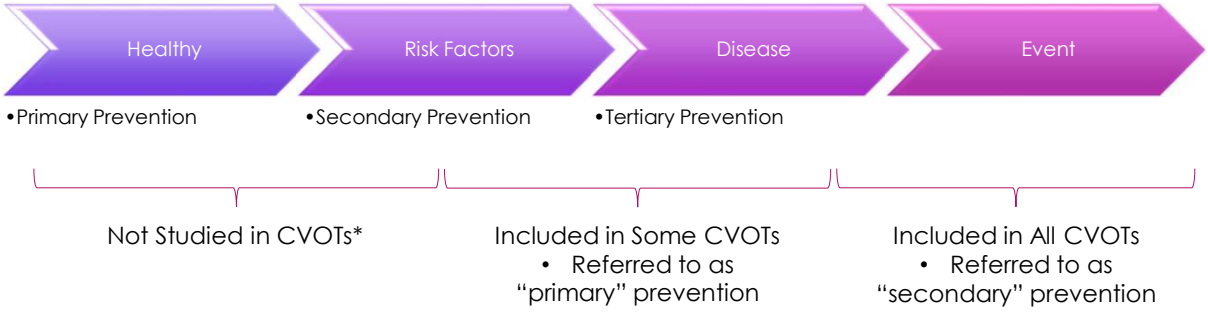
Disease Progression and Prevention



Not Studied in CVOTs*

Included in Some CVOTs
- Referred to as "primary" prevention

Included in All CVOTs
- Referred to as "secondary" prevention

*Except UKPDS

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GLP1 RAs: 3-point MACE

	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I^2=44·5%, p=0·082)			**0·86 (0·80–0·93)**	**65 (45–130)**	**<0·0001**

Sattar N. Lancet D&E 2021 ePub

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GLP1 RAs: 3-point MACE

Trial	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
LEADER	608/4668 (13%)	694/4672 (15%)	0.87 (0.78, 0.97)		0.01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0.74 (0.58, 0.95)		0.016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0.91 (0.83, 1.00)		0.061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0.78 (0.68, 0.90)		0.0006
REWIND	594/4949 (12%)	663/4952 (13%)	0.88 (0.79, 0.99)		0.026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0.79 (0.57, 1.11)		0.17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0.73 (0.58, 0.92)		0.0069
Subtotal (I-squared = 14.9%, p = 0.316)			0.85 (0.80, 0.90)	61 (46-92)	<0.0001

Sattar N. Lancet D&E 2021 ePub

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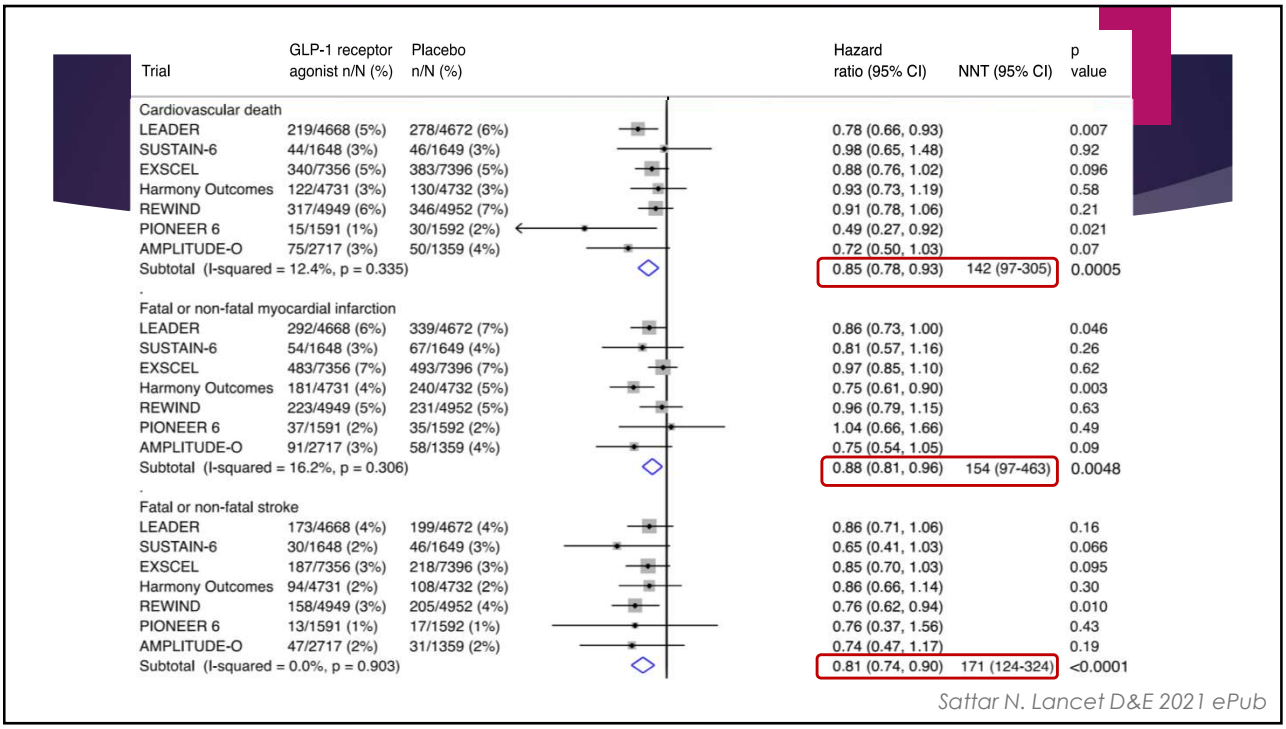

Sattar N. Lancet D&E 2021 ePub

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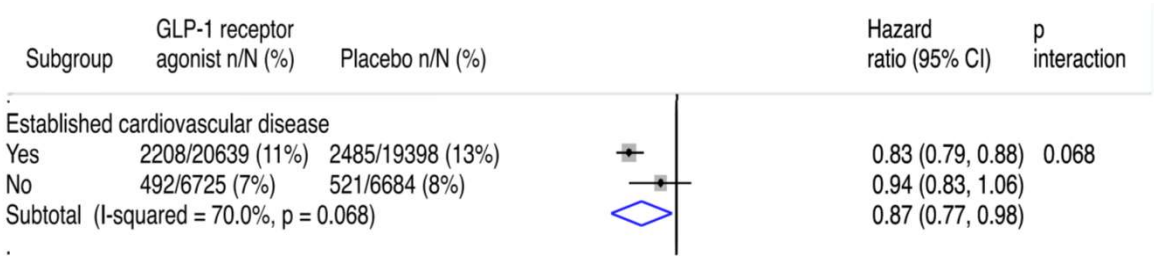
GLP1 RAs: MACE by ASCVD status



Sattar N. Lancet D&E 2021 ePub

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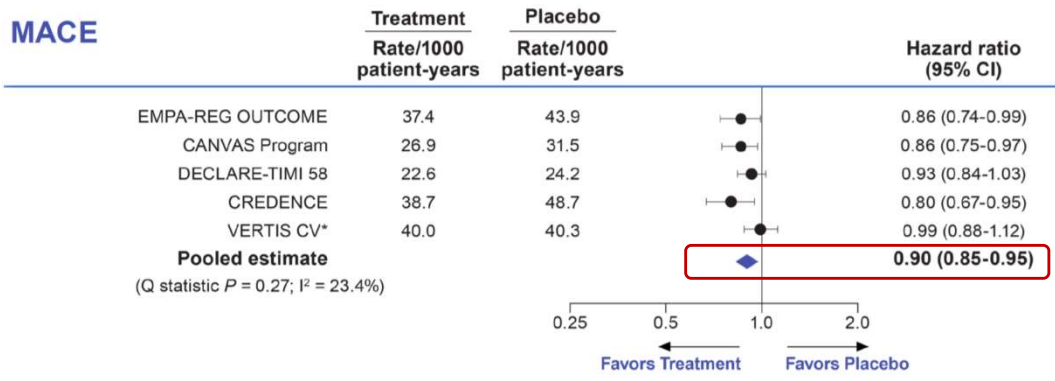
SGLT2 inh: MACE



McGuire DK. JAMA Cardiol. 2021;6(2):148

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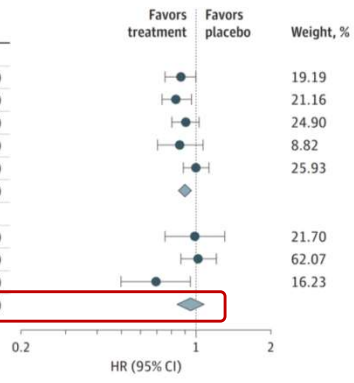
SGLT2 inh: MACE by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 4.53; *df* = 4; *P* = .34; I^2 = 11.8%)					0.89 (0.84-0.95)
Patients without ASCVD					
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)
Fixed-effects model (Q = 4.59; *df* = 2; *P* = .10; I^2 = 56.5%)					0.94 (0.83-1.07)



McGuire DK. JAMA Cardiol. 2021;6(2):148

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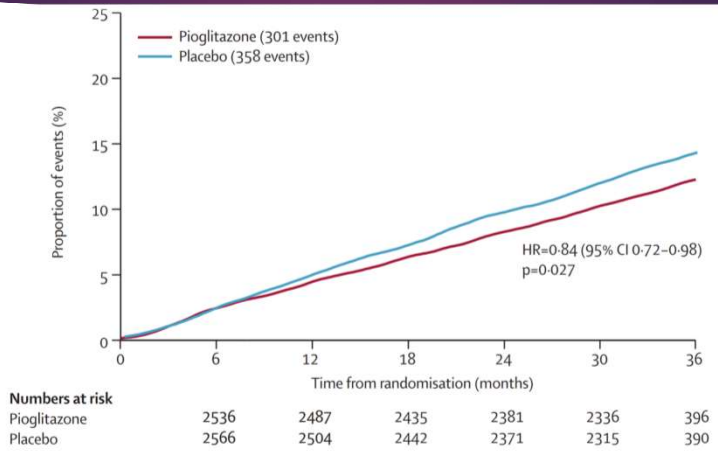
Pioglitazone (PROActive) and MACE



Dormandy JA. Lancet 2005; 366: 1279–89

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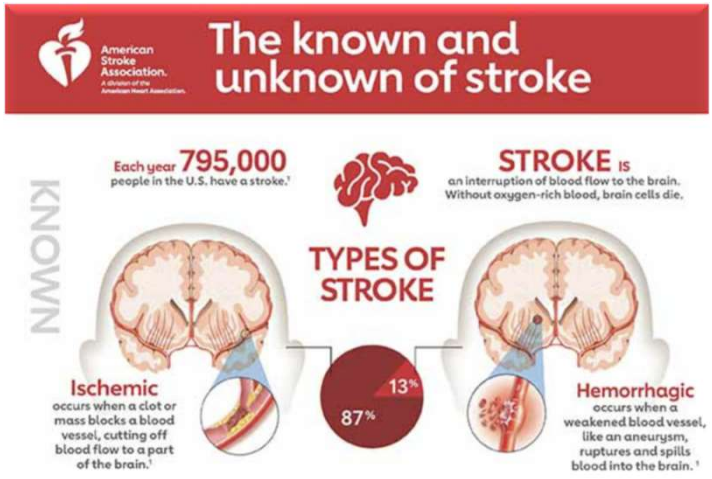

In patients with diabetes the risk of stroke is 2-4 times higher compared to those without diabetes.

Stroke

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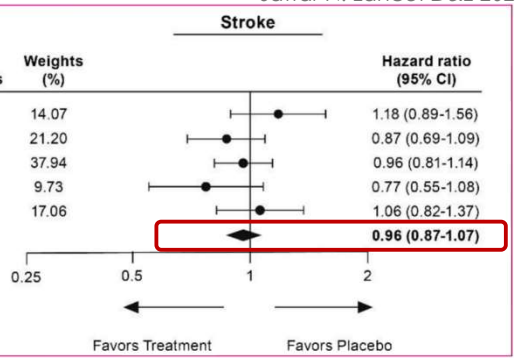
Trial	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Fatal or non-fatal stroke					
LEADER	173/4668 (4%)	199/4672 (4%)	0.86 (0.71, 1.06)		0.16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0.65 (0.41, 1.03)		0.066
EXSCEL	187/7356 (3%)	218/7396 (3%)	0.85 (0.70, 1.03)		0.095
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)	0.86 (0.66, 1.14)		0.30
REWIND	158/4949 (3%)	205/4952 (4%)	0.76 (0.62, 0.94)		0.010
PIONEER 6	13/1591 (1%)	17/1592 (1%)	0.76 (0.37, 1.56)		0.43
AMPLITUDE-O	47/2717 (2%)	31/1359 (2%)	0.74 (0.47, 1.17)		0.19
Subtotal (I-squared = 0.0%, p = 0.903)			0.81 (0.74, 0.90)	171 (124-324)	<0.0001

Sattar N. Lancet D&E 2021 ePub

	Treatment n/N	Treatment Rate/1000 patient-years	Placebo n/N	Placebo Rate/1000 patient-years	Weights (%)	Hazard ratio (95% CI)
EMPA-REG OUTCOME	164/4687	12.3	69/2333	10.5	14.07	1.18 (0.89-1.56)
CANVAS Program	NA/5795	7.9	NA/4347	9.6	21.20	0.87 (0.69-1.09)
DECLARE-TIMI 58	NA/8582	7.5	NA/8578	7.8	37.94	0.96 (0.81-1.14)
CREDENCE	62/2202	10.9	80/2199	14.2	9.73	0.77 (0.55-1.08)
VERTIS CV	185/5499	9.8	87/2747	9.3	17.06	1.06 (0.82-1.37)
Fixed Effects Model	(Q = 5.01, df = 4, *P* = .29; I^2 = 20.1%)					**0.96 (0.87-1.07)**



McGuire DK. JAMA Cardiol. 2021;6(2):148

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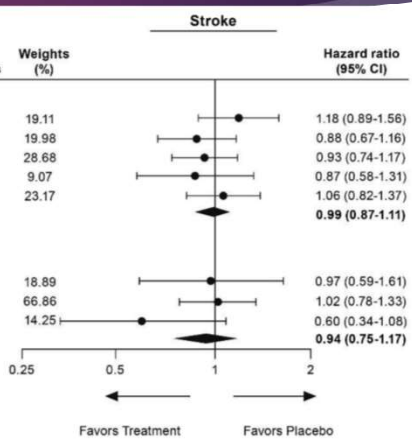
Stroke by ASCVD Status

	Treatment n/N	Treatment Rate/1000 patient-years	Placebo n/N	Placebo Rate/1000 patient-years	Weights (%)	Hazard ratio (95% CI)
Patients with ASCVD						
EMPA-REG OUTCOME	164/4687	12.3	69/2333	10.5	19.11	1.18 (0.89-1.56)
CANVAS Program	NA/3756	8.8	NA/2900	10.4	19.98	0.88 (0.67-1.16)
DECLARE-TIMI 58	NA/3474	10.9	NA/3500	11.7	28.68	0.93 (0.74-1.17)
CREDENCE	44/1113	15.4	50/1107	17.7	9.07	0.87 (0.58-1.31)
VERTIS CV	185/5499	9.8	87/2747	9.3	23.17	1.06 (0.82-1.37)
Fixed Effects Model	(Q = 3.16, df = 4, *P* = .53; I^2 = 0.0%)					**0.99 (0.87-1.11)**
Patients without ASCVD						
CANVAS Program	NA/2039	4.5	NA/1447	5.0	18.89	0.97 (0.59-1.61)
DECLARE-TIMI 58	NA/5108	5.2	NA/5078	5.1	66.86	1.02 (0.78-1.33)
CREDENCE	18/1089	6.3	30/1092	10.7	14.25	0.60 (0.34-1.08)
Fixed Effects Model	(Q = 2.69, df = 2, *P* = .26; I^2 = 25.7%)					**0.94 (0.75-1.17)**



McGuire DK. JAMA Cardiol. 2021;6(2):148

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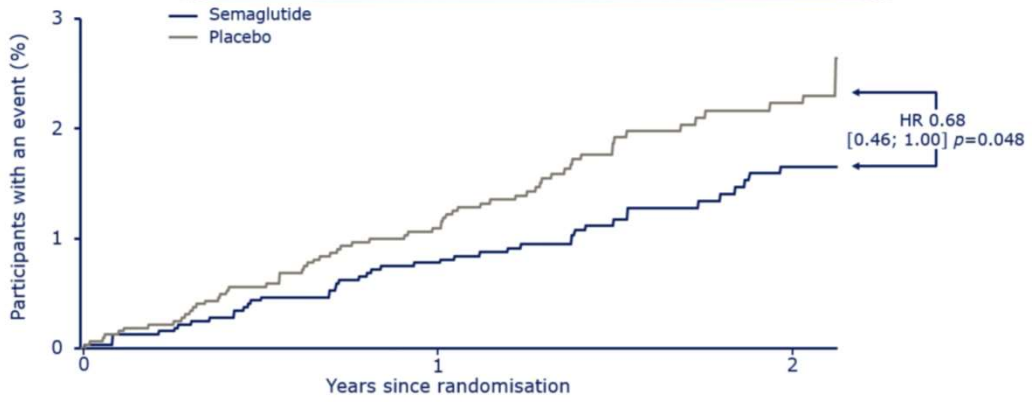
Semaglutide and stroke

Patient level pooled analysis of SUSTAIN 6 and PIONEER 6



GLP-1, glucagon-like peptide 1; HR, hazard ratio

Presented at the 56th Annual Meeting of the European Association for the Study of Diabetes (EASD), 21–25 September 2020

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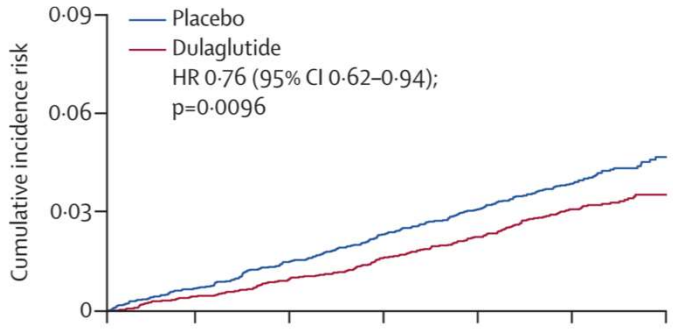
Dulaglutide and Stroke



Number at risk

Placebo	4952	4826	4692	4534	4396	3710	777
Dulaglutide	4949	4847	4736	4606	4476	3796	776

Gerstein H. Lancet D&E 2020;8:106

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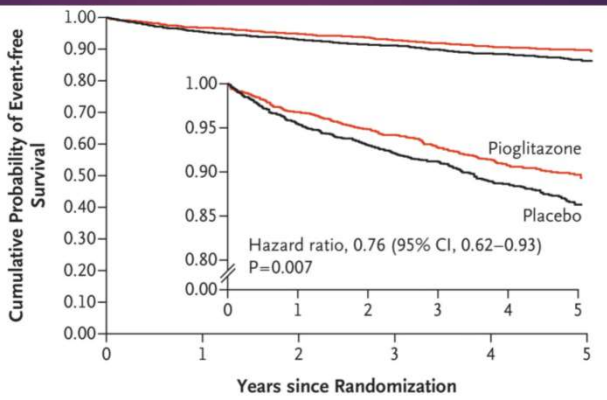
Pioglitazone in stroke & insulin resistance



No. at Risk						
Pioglitazone	1939	1793	1701	1491	1196	481
Placebo	1937	1778	1690	1476	1182	459

Kernan WA. N Engl J Med 2016; 374:1321

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Conclusions: Treatment of ASCVD in T2DM

Healthy → Risk Factors → Disease → Event

- Healthy Lifestyle (weight management, healthy diet, regular exercise, smoking cessation)
- Manage risk factors (BP, LDL, glucose, weight)
- Statin therapy if ASCVD Risk>20%
- Antithrombotic
- GLP1-RA
- SGLT2 inh
- Pioglitazone*

*based on secondary endpoint in PROActive and IRIS trial

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