AVC et diabète: quoi de neuf ?

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Divulgations

- *Financement de recherche: CIHR, FRQS*
- *Consultant/présentations: Janssen, Novartis Pharmaceuticals Canada, NovoNordisk Canada, HLS Therapeutics, Eli Lilly*
- *Les appellations génériques seront employées pour les médicaments cités et les usages expérimentaux non couramment approuvés par Santé Canada seront mentionnées, le cas échéant.*

Objectifs

Discuter des liens épidémiologiques et physiopathologiques entre diabète et AVC

Examiner les effets des médicaments anti-diabétiques sur la survenue des AVC

Objectifs

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Discuter des liens épidémiologiques et physiopathologiques entre diabète et AVC

Examiner les effets des médicaments anti-diabétiques sur la survenue des AVC

The INTERSTROKE study

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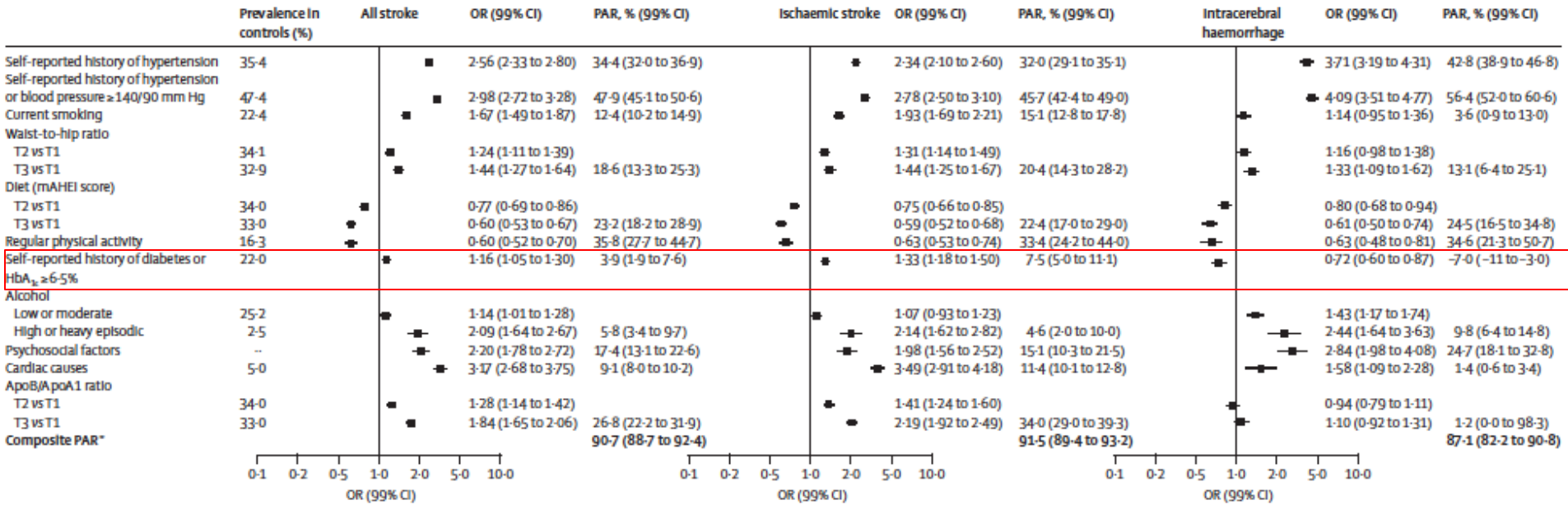
26 919 patients in 32 contries between 2007 and 2015



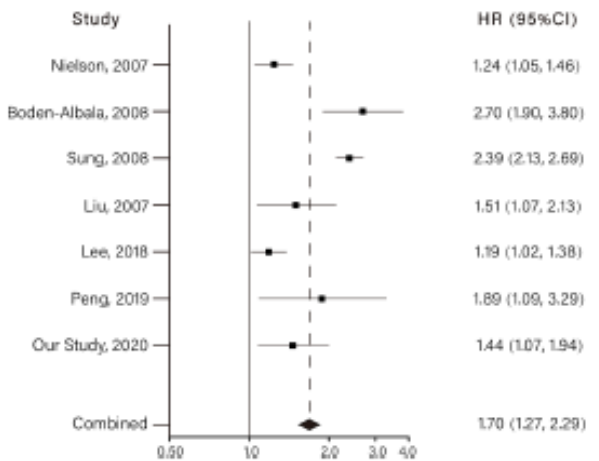
O'Donnell MJ et al. Lancet 2016;388:761-775

Fasting glycemia and strokes

Q1 (<4.87) n=4097 | **Q2 (4.87–5.24) n=4027** | **Q3 (5.24–5.77) n=3979** | **Q4 (>5.77) n=4010**

		Quartile of FBG levels				
		Q1	Q2	Q3	Q4	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	P trend
Men	Cases/N	33/1725	42/1586	53/1599	64/1688	
	Model 1	1 (Ref.)	1.40 (0.89 to 2.20)	1.74 (1.13 to 2.69)	1.99 (1.31 to 3.03)	0.001
	Model 2	1 (Ref.)	1.04 (0.66 to 1.64)	1.16 (0.75 to 1.80)	1.11 (0.73 to 1.71)	0.560
	Model 3	1 (Ref.)	1.05 (0.68 to 1.69)	1.15 (0.74 to 1.78)	1.04 (0.65 to 1.62)	0.741
Women	Cases/N	24/2372	47/2441	57/2380	97/2322	
	Model 1	1 (Ref.)	1.91 (1.21 to 3.29)	2.38 (1.48 to 3.84)	4.19 (2.68 to 6.55)	<0.001
	Model 2	1 (Ref.)	1.45 (0.89 to 2.37)	1.25 (0.78 to 2.03)	1.90 (1.21 to 2.99)	0.006
	Model 3	1 (Ref.)	1.43 (0.87 to 2.33)	1.30 (0.80 to 2.09)	1.92 (1.22 to 3.01)	0.004

Model 1: unadjusted model; model 2: adjusted for age, sex and BMI; model 3: further adjusted for HDL-C, TC, TG, LDL-C, eGFR, hypertension, smoking status, use of statins and family history of stroke.
BMI, body mass index; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.



Zhang Y et al. BMJ Open 2021

Post-reperfusion outcome in DM

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TABLE 4 Post-reperfusion outcomes in patients with diabetes compared to those without

Study	Number of patients	Outcomes	Outcomes that were significantly worse for DM compared to non-DM[a]
Thrombolysis (tPA through IVT or IAT)			
Desilles et al. (2013) (Bichat Clinical Registry)[179]	704	mRS90[b], mortality90, ENI, recanalisation	None
De Silva et al. (2010)[180]	52	Reperfusion, recanalisation, mRS90, NIHSS90, infarct growth	Significantly greater median relative infarct growth
Fang et al. (2020)[170]	1084	END, mortality7, mortality90, mRS90	None
Fuentes et al. (2012)[181]	1475	mRS90, mortality90	None
Fuentes et al. (2014)[182]	261	mRS90, IHM	None
Nikneshan et al. (2013)[183]	1689	mRSdischarge	mRS
Reiter et al. (2014)[184]	2158	mRSdischarge, ENI	mRS
Tang et al. (2016)[185]	419	ENI24[c], ENI7, mRS90, mortality30, recanalisation	mRS, ENI, significantly more incomplete recanalisation
Tsivgoulis et al. (2019)[186]	54,206	mRS90, mortality90	mRS, mortality
Zhang et al. (2019)[187]	135	Recanalisation, mortality150	Significantly more incomplete recanalisation
Thrombectomy			
Borggrefe et al. (2018)[188]	317	Collaterals, mRS90	mRS
Lu et al. (2018)[189]	Number excluding non-diabetic hyperglycaemia not given	mRS90, recanalisation	mRS

Abbreviations: DM, diabetes mellitus; END, early neurological deterioration; ENI, early neurological improvement; IAT, intra-arterial therapy; IHM, in-hospital mortality; IVT, intravenous therapy; mRS, modified Rankin Scale; NIHSS, NIH Stroke Scale/Score; tPA, tissue Plasminogen Activator.

[a]There were no cases in which non-DM had a worse outcome than DM.

[b]A number following an outcome indicates the number of days of follow-up, that is, mRS90 = mRS at 90 days.

[c]ENI at 24 h.

Bradley SA et al. Diabetes Metab Res Rev 2021;e3495

Post-reperfusion complications in DM

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TABLE 5 Post-reperfusion therapy complications in patients with diabetes compared to those without

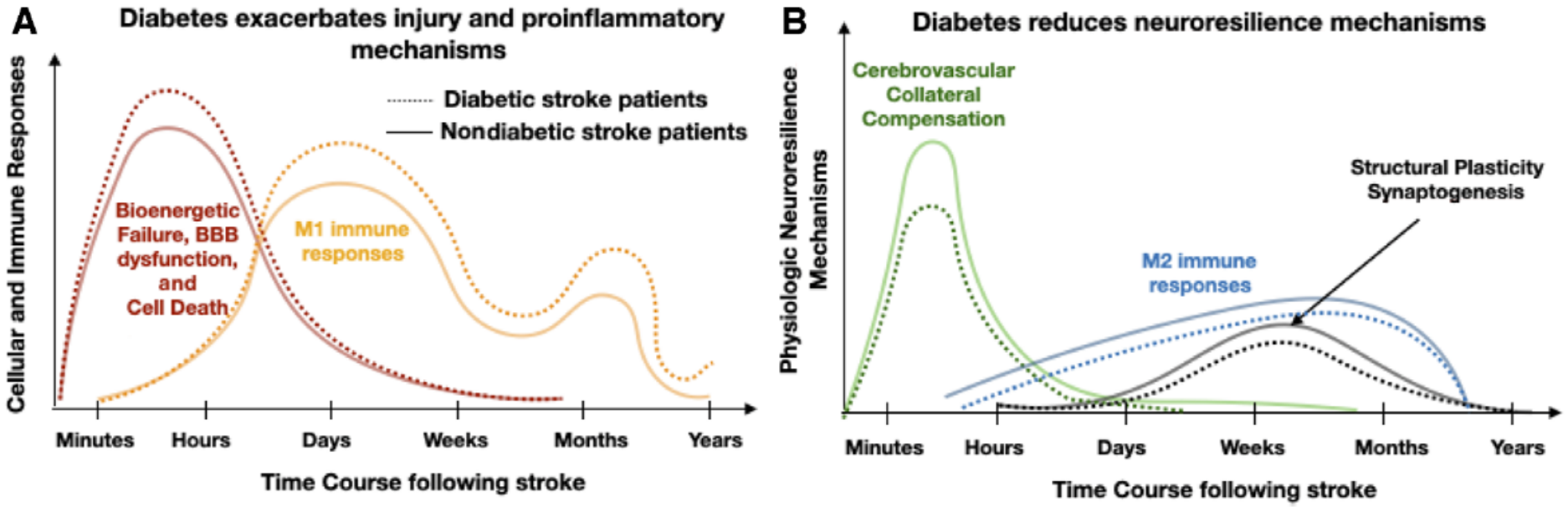
Study	Number of patients	Outcomes	sICH criteria	Key findings
Thrombolysis (tPA through IVT or IAT)				
Desilles et al. (2013) (Bichat clinical registry)[179]	704	sICH and HT	ECASS 2	No significant differences
Fang et al. (2020)[170]	1084	sICH	SITS-MOST	DM had significantly more sICH than non-DM
Fuentes et al. (2012)[181]	1475	sICH	SITS-MOST	No significant differences
Fuentes et al. (2014)[182]	261	HT	-	No significant differences
Nikneshan et al. (2013)[183]	1689	sICH and HT	NINDS	No significant differences
Reiter et al. (2014)[184]	2158	sICH	Undefined	No significant differences
Tang et al. (2016)[185]	419	sICH	Undefined	No significant differences
Tsivgoulis et al. (2019)[186]	54,206	sICH	SITS-MOST	DM had significantly more sICH than non-DM
Zhang et al. (2019)[187]	135	HT	-	No significant differences
Thrombectomy				
Borggrefe et al. (2018)[188]	317	sICH	ECASS 2	DM had significantly more sICH than non-DM
Lu et al. (2018)[189]	Not reported[a]	sICH	Undefined	No significant differences

Abbreviations: DM, diabetes mellitus; ECASS 2, European Co-operative Acute Stroke Study-2; HT, haemorrhagic transformation; IAT, intra-arterial therapy; IVT, intravenous therapy; NINDS, National Institute of Neurological Disorders and Stroke; sICH, symptomatic intracerebral haemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; tPA, tissue Plasminogen Activator.

[a]Number excluding non-diabetic acute hyperglycaemia not given.

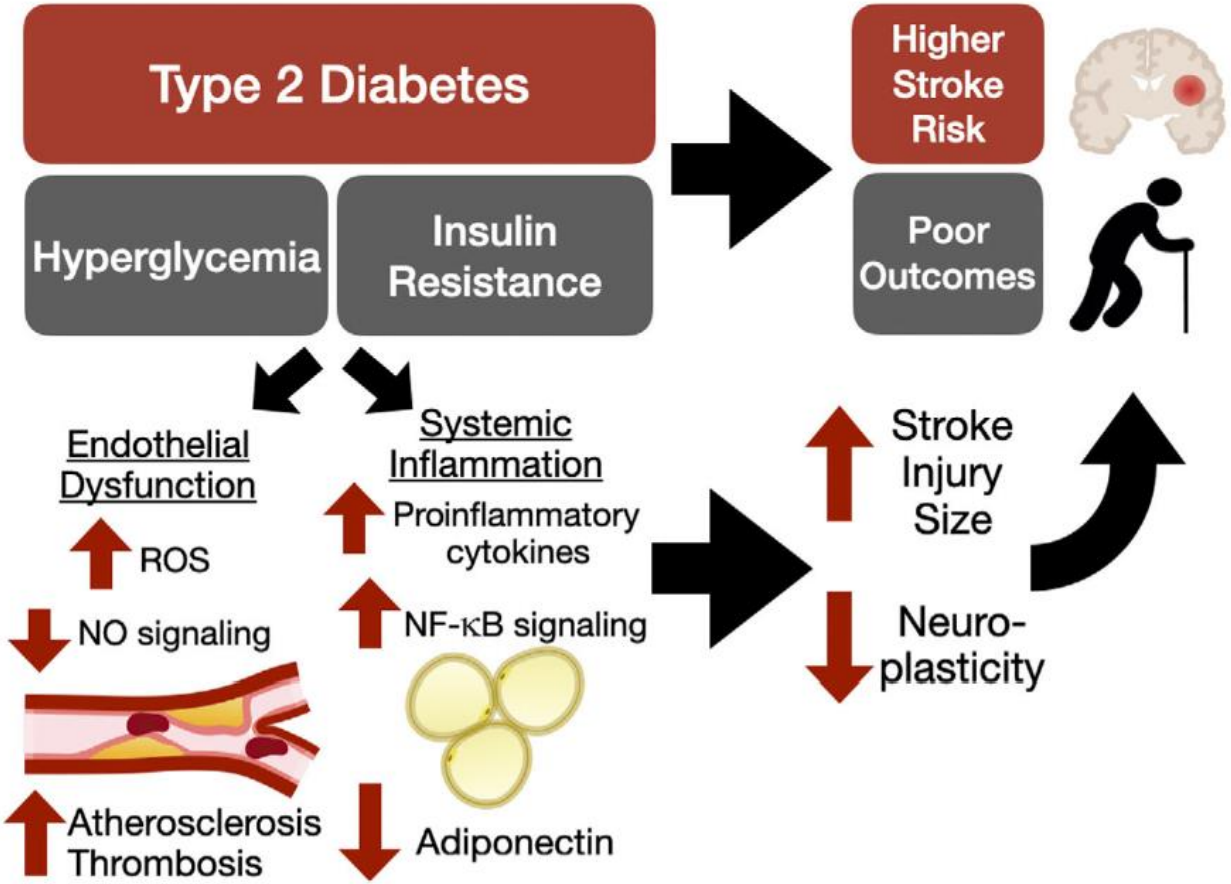
Bradley SA et al. Diabetes Metab Res Rev 2021;e3495

Diabetes and strokes



Krinock and Singhal. Ann NY Acad Sci 2021

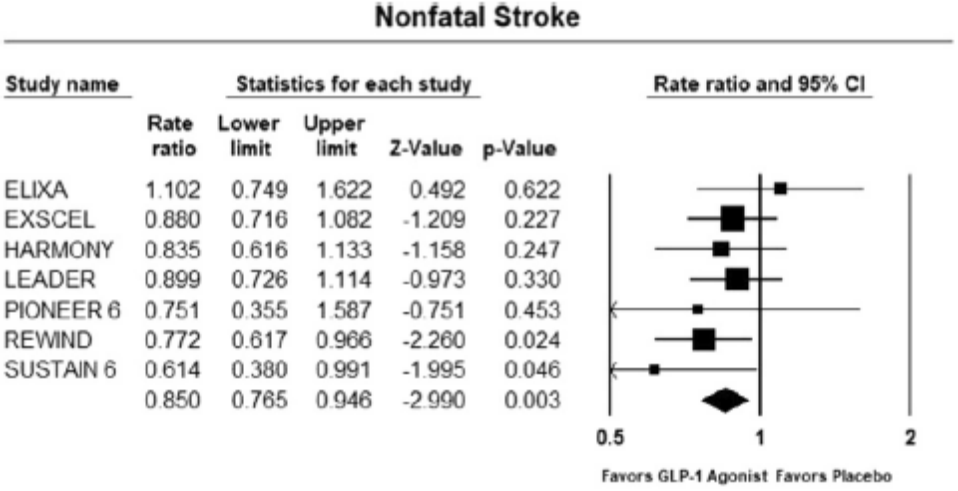
Diabetes and strokes



Krinock and Singhal. Ann NY Acad Sci 2021

aGLP1 and strokes: meta-analysis

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	HARMONY OUTCOMES	REWIND	PIONEER-6
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide
Route	SQ	SQ	SQ	SQ	SQ	SQ	Oral
Dose	20 μg/day	1.8 mg/day	0.5 or 1.0 mg/week	2 mg/week	30 or 50 mg/week	1.5 mg/week	14 mg/day
Mean Age in years	60.3 ± 9.7	64.3 ± 7.2	64.6 ± 7.4	62 (median)	64.2 ± 8.7	66.2 ± 6.5	66 ± 7
Total number of patients	6068	9340	3297	14752	9463	9901	3183
Median follow-up (years)	2.1	3.8	2.1	3.2	1.5	5.4	1.3
Women	30.7%	35.7%	39.3%	38.0%	30.6%	46.3%	31.6%
White	75.4%	77.5%	83.0%	75.8%	69.6%	75.7%	72.3%
Mean BMI (kg/m^2)	30.2 ± 5.7	32.5 ± 6.3	32.8 ± 6.2	N/A	32.3 ± 5.9	32.3 ± 5.7	32.3 ± 6.5
Mean Hb A1C (%)	7.7 ± 1.3	8.7 ± 1.6	8.7 ± 1.5	8.1 ± 1.2	8.7 ± 1.5	7.3 ± 1.1	8.2 ± 1.6



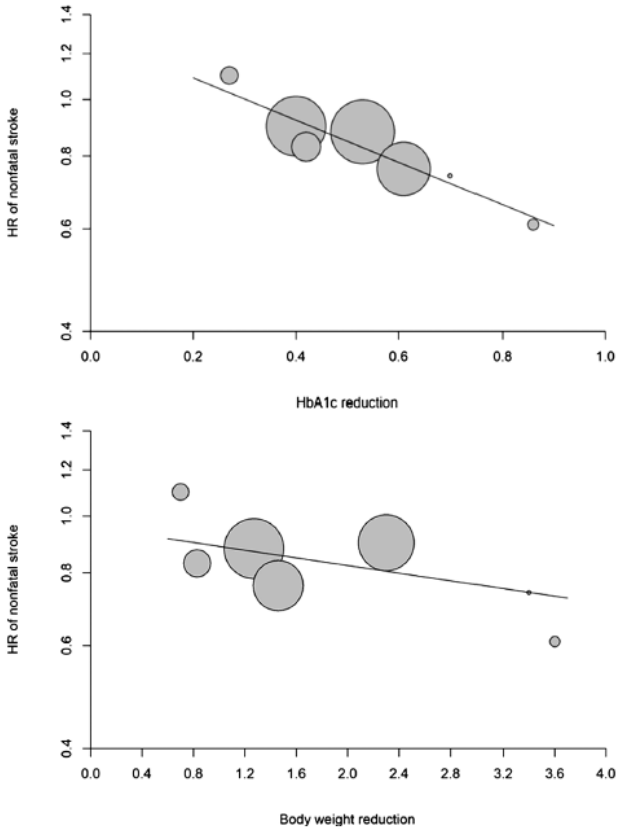
This table shows the heterogeneity for each outcome (major adverse cardiovascular events, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke)

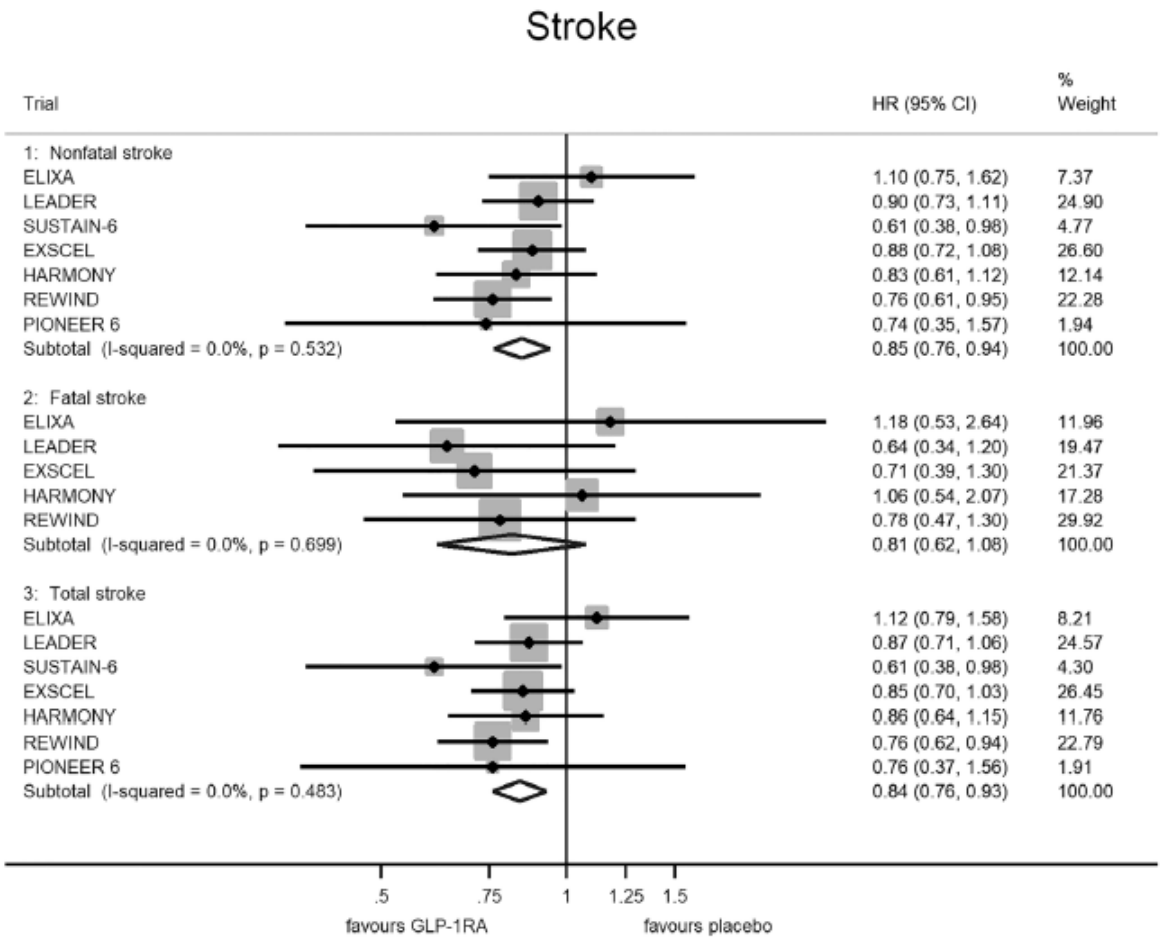
Outcome	Chi^2	P	I^2
MACE	10.34	0.11	42%
CV Death	5.70	0.46	0%
Nonfatal Stroke	4.74	0.58	0%
Nonfatal MI	12.68	0.05	53%

MACE = major adverse cardiovascular events; CV = cardiovascular; MI = myocardial infarction.

Grewal S et al. Am J Cardiol 2021;154:48-53.

aGLP1: Meta-analysis





Bellastella G et al.. Stoke 2020;51:666-669

Network meta-analysis: aGLP1 vs. placebo

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Table 2 | Summary of anticipated absolute differences comparing glucagon-like peptide-1 receptor agonist treatment with placebo treatment per 1000 patients with diabetes type 2 and with very low to very high cardiovascular risk, treated for five years

Risk*	All cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Kidney failure	Hospital admission for heart failure	Severe gastrointestinal events	Body weight
T2D < 3 risk factors	2 fewer (3 fewer to 1 fewer) ⊕⊕⊕	2 fewer (3 fewer to 1 fewer) ⊕⊕⊕	2 fewer (4 fewer to 0) ⊕⊕⊕	5 fewer (7 fewer to 2 fewer) ⊕⊕⊕	0 (1 fewer to 0) ⊕⊕⊕	0 (1 fewer to 0) ⊕⊕⊕		
T2D ≥ 3 risk factors	8 fewer (11 fewer to 4 fewer) ⊕⊕⊕⊕	5 fewer (9 fewer to 2 fewer) ⊕⊕⊕⊕	4 fewer (8 fewer to 1 fewer) ⊕⊕⊕⊕	9 fewer (13 fewer to 4 fewer) ⊕⊕⊕⊕	2 fewer (1 fewer to 3 fewer) ⊕⊕⊕⊕	2 fewer (4 fewer to 1 more) ⊕⊕⊕⊕		
T2D with cardiovascular disease (CVD)	13 fewer (18 fewer to 6 fewer) ⊕⊕⊕⊕	9 fewer (15 fewer to 1 fewer) ⊕⊕⊕⊕	8 fewer (15 fewer to 1 fewer) ⊕⊕⊕⊕	16 fewer (24 fewer to 7 fewer) ⊕⊕⊕⊕	4 fewer (7 fewer to 2 fewer) ⊕⊕⊕⊕	4 fewer (11 fewer to 2 more) ⊕⊕⊕⊕	58 more (9 more to 142 more) ⊕⊕	145 kg lower (1.72 lower to 1.18 lower) over 6 months ⊕⊕
T2D with chronic kidney disease (CKD)	17 fewer (25 fewer to 9 fewer) ⊕⊕⊕⊕	12 fewer (20 fewer to 4 fewer) ⊕⊕⊕⊕	9 fewer (16 fewer to 1 fewer) ⊕⊕⊕⊕	17 fewer (26 fewer to 7 fewer) ⊕⊕⊕⊕	19 fewer (28 fewer to 7 fewer) ⊕⊕⊕⊕	6 fewer (14 fewer to 3 more) ⊕⊕⊕⊕		
T2D with CVD and CKD	24 fewer (35 fewer to 12 fewer) ⊕⊕⊕⊕	18 fewer (30 fewer to 6 fewer) ⊕⊕⊕⊕	13 fewer (24 fewer to 2 fewer) ⊕⊕⊕⊕	25 fewer (39 fewer to 11 fewer) ⊕⊕⊕⊕	29 fewer (44 fewer to 10 fewer) ⊕⊕⊕⊕	11 fewer (28 fewer to 5 more) ⊕⊕⊕⊕		

*Risk categories represent the following patient populations: very low=no or less than three cardiovascular risk factors; low=three or more cardiovascular risk factors; moderate=cardiovascular disease; high=chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); very high=cardiovascular disease and chronic kidney disease.
Certainty of the evidence for each estimate is shown: high certainty ⊕⊕⊕⊕; moderate certainty ⊕⊕⊕; low certainty ⊕⊕; very low certainty ⊕.

Palmer SC et al.. BMJ 2021;372:m4573

iSGLT2 and strokes: Meta-analysis

CENTRE DE RECHERCHE | CHUS

Study name	Subtype	Events / Total		Statistics for each study			
		Favor SGLT2-inh	Favor placebo	Risk ratio	Lower limit	Upper limit	p-Value
CANVAS(2017)	Non-fatal	146 / 5795	128 / 4347	0.856	0.677	1.081	0.192
CREDENCE(2019)	Non-fatal	53 / 2202	66 / 2199	0.802	0.561	1.146	0.225
EMPA-REG(2015)	Non-fatal	150 / 4687	60 / 2333	1.244	0.926	1.672	0.147
VERTIS CV(2020)	Non-fatal	157 / 5499	78 / 2747	1.005	0.769	1.314	0.968
DECLARE-TIMI 58(2019)	Ischemic	235 / 8582	231 / 8578	1.017	0.850	1.216	0.855
Overall (I2=23.3%, P=0.266)				0.981	0.862	1.116	0.767

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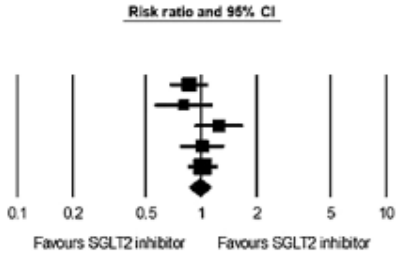

Study name	Subtype	Events / Total		Statistics for each study			
		Favor SGLT2-inh	Favor placebo	Risk ratio	Lower limit	Upper limit	p-Value
CANVAS(2017)	Fatal	20 / 5795	19 / 4347	0.790	0.422	1.478	0.460
CREDENCE(2019)	Fatal	9 / 2202	14 / 2199	0.642	0.278	1.480	0.298
EMPA-REG(2015)	Fatal	16 / 4687	11 / 2333	0.724	0.337	1.558	0.409
VERTIS CV(2020)	Fatal	28 / 5499	9 / 2747	1.554	0.734	3.289	0.249
Overall (I2=29.8%, P=0.223)				0.874	0.602	1.271	0.482

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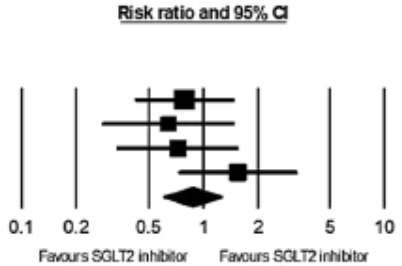

Study name	Subtype	Events / Total		Statistics for each study			
		Favor SGLT2-inh	Favor placebo	Risk ratio	Lower limit	Upper limit	p-Value
CANVAS(2017)	total	166 / 5795	147 / 4347	0.847	0.681	1.054	0.137
CREDENCE(2019)	total	62 / 2202	80 / 2199	0.774	0.558	1.073	0.124
EMPA-REG(2015)	total	165 / 4687	71 / 2333	1.157	0.880	1.521	0.297
VERTIS(2020)	total	185 / 5499	87 / 2747	1.062	0.827	1.365	0.637
Overall (I2=43.7%, P=0150)				0.952	0.799	1.135	0.585

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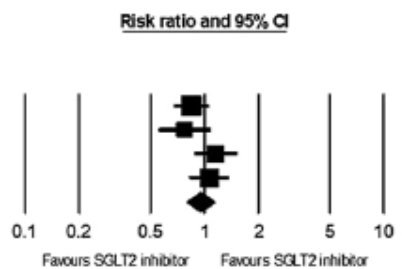

Tsai W-H et al.. Sci Rep 2021;11:15364

iSGLT2 and strokes: Meta-analysis

CENTRE DE RECHERCHE | CHUS

Study name	Subtype	Events / Total		Statistics for each study			
		Favor SGLT2-inh	Favor placebo	Risk ratio	Lower limit	Upper limit	p-Value
CANVAS(2017)	Ischemic	142 / 5795	111 / 4347	0.960	0.751	1.226	0.742
CREDENCE(2019)	Ischemic	52 / 2202	59 / 2199	0.880	0.609	1.272	0.497
DECLARE-TIMI 58(2019)	Ischemic	235 / 8582	231 / 8578	1.017	0.850	1.216	0.855
EMPA-REG(2015)	Ischemic	150 / 4686	63 / 2333	1.185	0.887	1.584	0.250
VERTIS(2020)	Ischemic	69 / 5499	41 / 2747	0.841	0.573	1.234	0.375
Overall (I2=0.0%, P=0.608)				0.996	0.887	1.119	0.952

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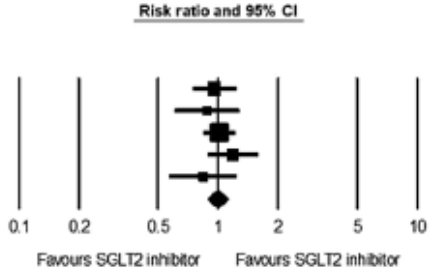

Study name	Subtype	Events / Total		Statistics for each study			
		Favor SGLT2-inh	Favor placebo	Risk ratio	Lower limit	Upper limit	p-Value
EMPA-REG(2015)	Hemorrhagic	9 / 4687	7 / 2333	0.640	0.239	1.716	0.375
CREDENCE(2019)	Hemorrhagic	6 / 2202	12 / 2199	0.499	0.188	1.328	0.164
CANVAS(2017)	Hemorrhagic	11 / 5795	19 / 4347	0.434	0.207	0.912	0.027
Overall (I2=0.0%, P=0.827)				0.499	0.301	0.829	0.007

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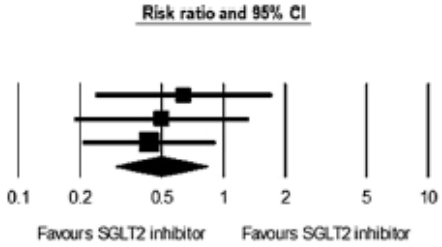

Study name	Subtype	Events / Total		Statistics for each study			
		Favor SGLT2-inh	Favor placebo	Risk ratio	Lower limit	Upper limit	p-Value
EMPA-REG(2015)	TIA	39 / 4687	23 / 2333	0.844	0.505	1.410	0.517
DECLARE-TIMI 58(2019)	TIA	63 / 8582	46 / 8578	1.369	0.937	2.000	0.104
CANVAS(2017)	TIA	202 / 5795	175 / 4347	0.866	0.710	1.056	0.155
Overall (I2=56.9%, P=0098)				0.992	0.731	1.344	0.956

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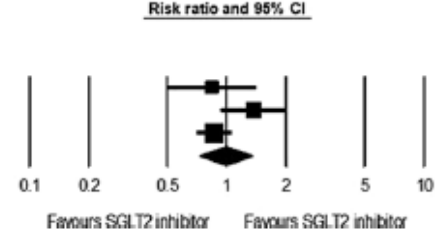

Tsai W-H et al.. Sci Rep 2021;11:15364

Network meta-analysis: iSGLT2 vs. placebo

CENTRE DE RECHERCHE | CHUS

Table 1 | Summary of anticipated absolute differences comparing sodium-glucose cotransporter-2 inhibitor treatment with placebo treatment per 1000 patients with diabetes type 2 and with very low to very high cardiovascular risk, treated for five years

Risk*	All cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Kidney failure	Hospital admission for heart failure	Diabetic ketoacidosis	Genital infection	Body weight
T2D < 3 risk factors	5 fewer (6 fewer to 3 fewer) ⊕⊕⊕	2 fewer (3 fewer to 1 fewer) ⊕⊕⊕	4 fewer (6 fewer to 1 fewer) ⊕⊕⊕	0 more (3 fewer to 4 more) ⊕⊕⊕	1 fewer (1 fewer to 0) ⊕⊕⊕	2 fewer (2 fewer to 1 fewer) ⊕⊕⊕			
T2D ≥ 3 risk factors	15 fewer (19 fewer to 11 fewer) ⊕⊕⊕⊕	7 fewer (11 fewer to 4 fewer) ⊕⊕⊕⊕	7 fewer (12 fewer to 2 fewer) ⊕⊕⊕⊕	1 more (6 fewer to 8 more) ⊕⊕⊕⊕	3 fewer (4 fewer to 1 fewer) ⊕⊕⊕⊕	9 fewer (11 fewer to 7 fewer) ⊕⊕⊕⊕			
T2D with cardiovascular disease (CVD)	25 fewer (32 fewer to 18 fewer) ⊕⊕⊕⊕	12 fewer (18 fewer to 6 fewer) ⊕⊕⊕⊕	13 fewer (21 fewer to 3 fewer) ⊕⊕⊕⊕	1 more (11 fewer to 13 more) ⊕⊕⊕⊕	6 fewer (9 fewer to 2 fewer) ⊕⊕⊕⊕	23 fewer (28 fewer to 17 fewer) ⊕⊕⊕⊕	0 (1 fewer to 2 more) ⊕⊕⊕	143 more (119 more to 170 more) ⊕⊕⊕⊕	1.92 kg lower (2.23 lower to 1.62 lower) over 6 months ⊕⊕
T2D with chronic kidney disease (CKD)	34 fewer (43 fewer to 25 fewer) ⊕⊕⊕⊕	16 fewer (25 fewer to 8 fewer) ⊕⊕⊕⊕	14 fewer (23 fewer to 3 fewer) ⊕⊕⊕⊕	1 more (12 fewer to 15 more) ⊕⊕⊕⊕	25 fewer (37 fewer to 9 fewer) ⊕⊕⊕⊕	29 fewer (36 fewer to 22 fewer) ⊕⊕⊕⊕			
T2D with CVD and CKD	48 fewer (61 fewer to 35 fewer) ⊕⊕⊕⊕	24 fewer (36 fewer to 12 fewer) ⊕⊕⊕⊕	21 fewer (34 fewer to 5 fewer) ⊕⊕⊕⊕	2 more (17 fewer to 21 more) ⊕⊕⊕⊕	38 fewer (58 fewer to 14 fewer) ⊕⊕⊕⊕	58 fewer (73 fewer to 44 fewer) ⊕⊕⊕⊕			

*Risk categories represent the following patient populations: very low=no or less than three cardiovascular risk factors; low=three or more cardiovascular risk factors; moderate=cardiovascular disease; high=chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); very high=cardiovascular disease and chronic kidney disease.
Certainty of the evidence for each estimate is shown: high certainty ⊕⊕⊕⊕; moderate certainty ⊕⊕⊕; low certainty ⊕⊕; very low certainty ⊕.

Palmer SC et al.. BMJ 2021;372:m4573

iSGLT2 and strokes: Meta-analysis

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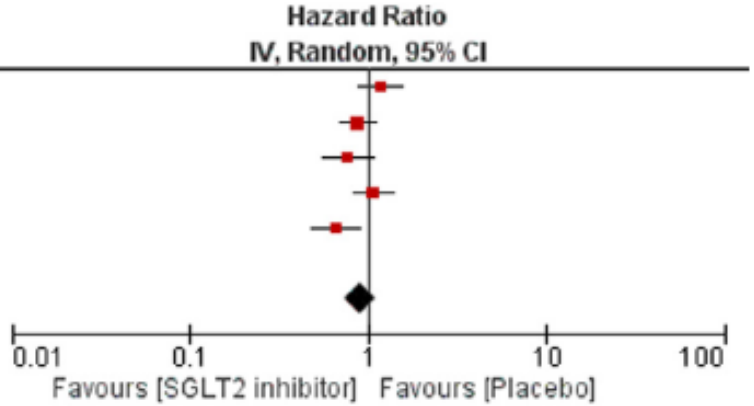
A All patients

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
EMPA-REG OUTCOME	0.1655	0.1439	20.1%	1.18 [0.89, 1.56]	2015
CANVAS	-0.1379	0.119	23.2%	0.87 [0.69, 1.10]	2017
CREDENCE	-0.2614	0.1717	17.1%	0.77 [0.55, 1.08]	2019
VERTIS CV	0.0583	0.131	21.7%	1.06 [0.82, 1.37]	2020
SCORED	-0.4155	0.1625	18.0%	0.66 [0.48, 0.91]	2020
Total (95% CI)			**100.0%**	**0.90 [0.74, 1.09]**	

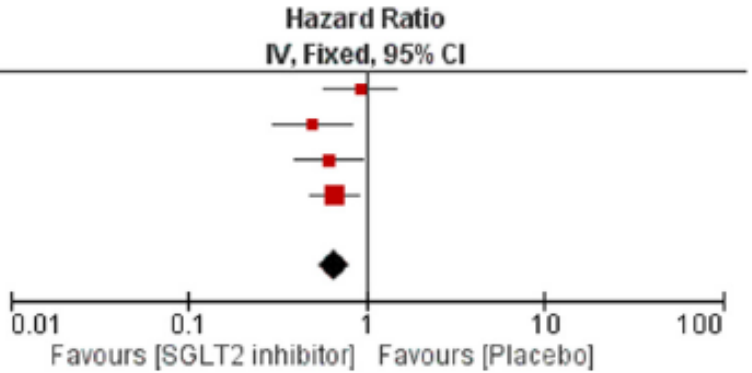
Heterogeneity: Tau² = 0.03; Chi² = 9.60, df = 4 (P = 0.05); I² = 58%
Test for overall effect: Z = 1.06 (P = 0.29)



B eGFR < 60 mL/min/1.73m²

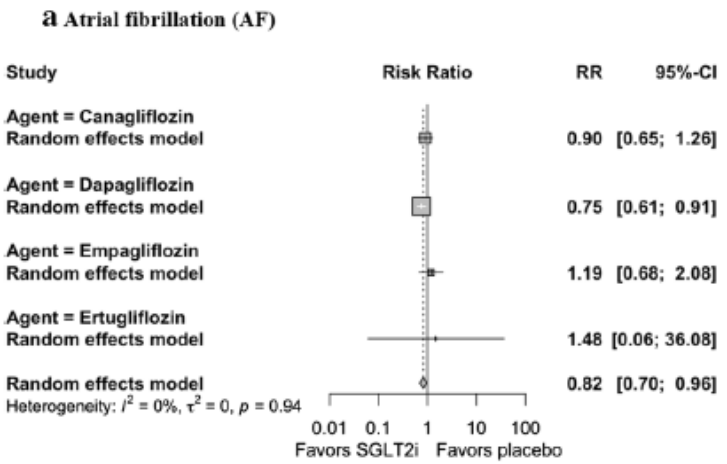
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
EMPA-REG OUTCOME	-0.0763	0.239	19.4%	0.93 [0.58, 1.48]	2015
CANVAS	-0.6952	0.2596	16.4%	0.50 [0.30, 0.83]	2017
CREDENCE	-0.4838	0.2207	22.7%	0.62 [0.40, 0.95]	2019
SCORED	-0.4141	0.1632	41.5%	0.66 [0.48, 0.91]	2020
Total (95% CI)			**100.0%**	**0.66 [0.54, 0.82]**	

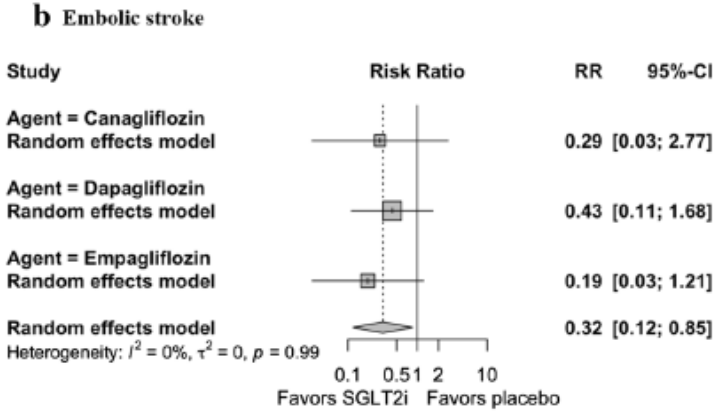
Heterogeneity: Chi² = 3.27, df = 3 (P = 0.35); I² = 8%
Test for overall effect: Z = 3.90 (P < 0.0001)

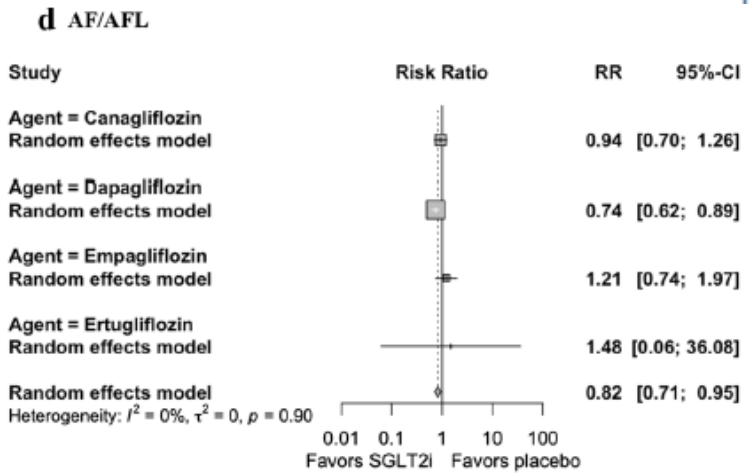


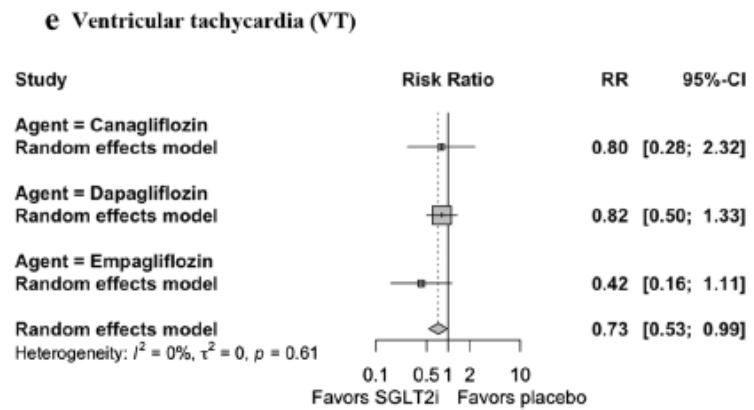
Barkas F et al.. J Stroke Cereb Dis 2021;30:105708

Meta-analysis: iSGLT2, arrhythmias and strokes









Li H-L et al. Cardiovasc Diabetol 2021

TZD: PROACTIVE study

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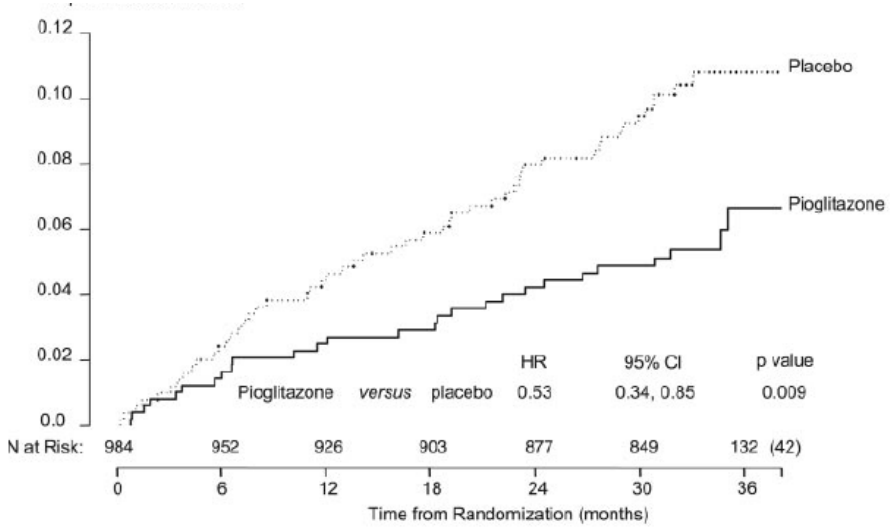
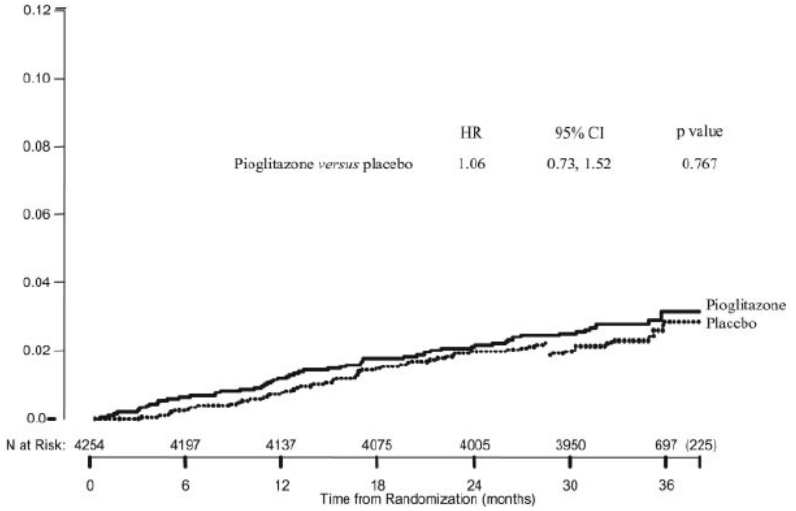
With previous stroke



Without previous stroke



Wilcox R et al. Stoke 2007;38:865-873

TZD: IRIS study

CENTRE DE RECHERCHE | CHUS

Characteristic	Pioglitazone (N=1939)	Placebo (N=1937)
Demographic feature		
Age — yr	63.5±10.6	63.5±10.7
Male sex — no. (%)	1293 (66.7)	1245 (64.3)
Black race — no./total no. (%)†	218/1906 (11.4)	225/1904 (11.8)
Hispanic ethnic group — no./total no. (%)†	75/1927 (3.9)	72/1929 (3.7)
Clinical history		
Stroke — no./total no. (%)		
At entry	1693/1928 (87.8)	1682/1930 (87.2)
Previous	246/1938 (12.7)	242/1935 (12.5)
Hypertension — no./total no. (%)	1380/1938 (71.2)	1390/1936 (71.8)
Coronary artery disease — no./total no. (%)	241/1938 (12.4)	221/1936 (11.4)
Atrial fibrillation — no./total no. (%)	134/1914 (7.0)	130/1912 (6.8)
Physical and cognitive examination‡		
Body-mass index	29.9±5.6	30.0±5.3
Blood pressure — mm Hg		
Systolic	133.2±17.7	133.0±17.3
Diastolic	79.4±10.7	79.0±10.5
Score on Modified Mini–Mental State Examination — median (IQR)	96 (92–99)	97 (92–99)
Score on NIH Stroke Scale — median (IQR)	0 (0–2)	0 (0–1)
Score on Modified Rankin Scale — median (IQR)	1 (0–2)	1 (0–1)
Laboratory data		
Fasting glucose — mg/dl	98.3±10.0	98.2±9.9
Median fasting insulin (IQR) — μU per milliliter	19 (16–26)	19 (16–25)
HOMA-IR index — median (IQR)	4.7 (3.8–6.2)	4.6 (3.7–6.2)
Glycated hemoglobin — %	5.8±0.4	5.8±0.4

3876 patients with ischemic stroke or TIA < 6 months prior to randomization

Not T2D
HOMA-IR > 3

Kernan WN et al. NEJM 2016;374:1321-1331

TZD: IRIS study

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Table 2. Primary and Secondary Outcomes.

Outcome	Pioglitazone (N=1939)	Placebo (N=1937)	Hazard Ratio (95% CI)*	Adjusted P Value†
	no. of patients (%)			
Primary outcome				
Stroke or myocardial infarction‡	175 (9.0)	228 (11.8)	0.76 (0.62– 0.93)	0.007
Stroke	123 (6.3)	150 (7.7)		
Fatal	9 (0.5)	13 (0.7)		
Nonfatal	114 (5.9)	137 (7.1)		
Myocardial infarction	52 (2.7)	78 (4.0)		
Fatal	7 (0.4)	14 (0.7)		
Nonfatal	45 (2.3)	64 (3.3)		
Secondary outcome§				
Stroke	127 (6.5)	154 (8.0)	0.82 (0.61–1.10)	0.19
Acute coronary syndrome: myocardial infarction or unstable angina	96 (5.0)	128 (6.6)	0.75 (0.52–1.07)	0.11
Stroke, myocardial infarction, or serious heart failure¶	206 (10.6)	249 (12.9)	0.82 (0.65–1.05)	0.11
Diabetes mellitus	73 (3.8)	149 (7.7)	0.48 (0.33–0.69)	<0.001
Death from any cause	136 (7.0)	146 (7.5)	0.93 (0.73–1.17)	0.52

More weight gain, oedema and bone fractures

Median FU = 4.8 years

NNT MACE = 28
NNT new-onset DM = 19

NNA bone fracture = 59
NNA >10% weight gain = 7
NNA leg oedema = 8

Kernan WN et al. NEJM 2016;374:1321-1331

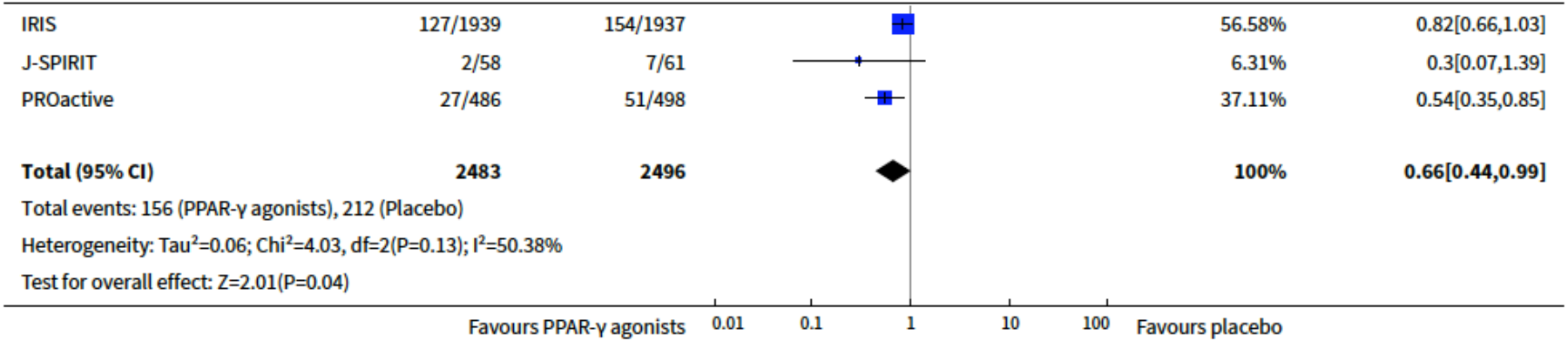
Spence JD et al. JAMA Neurol 2019;76:526-535

Cochrane: TZD and strokes

CENTRE DE RECHERCHE | CHUS

Analysis 1.1. Comparison 1 Peroxisome proliferator-activated receptor gamma agonists agonists versus placebo, Outcome 1 Recurrence of stroke.

Study or subgroup	PPAR-γ agonists n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
IRIS	127/1939	154/1937		56.58%	0.82[0.66,1.03]
J-SPIRIT	2/58	7/61		6.31%	0.3[0.07,1.39]
PROactive	27/486	51/498		37.11%	0.54[0.35,0.85]
Total (95% CI)	**2483**	**2496**		**100%**	**0.66[0.44,0.99]**
Total events: 156 (PPAR-γ agonists), 212 (Placebo)					
Heterogeneity: Tau^2=0.06; Chi^2=4.03, df=2(P=0.13); I^2=50.38%					
Test for overall effect: Z=2.01(P=0.04)					



Liu J and Wang LN. Cochrane Database Syst Rev 2019

Intensive insulin therapy post-stroke

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TABLE 6 Insulin and intensive insulin treatment post-stroke

Study	Study design	Number of patients	Findings
Laird et al. (2013)[176]	Systematic review	1257	Insulin significantly lowers glucose levels when compared with controls but monitoring and treatment adherence is limited by the challenge it poses on nurses in the stroke unit
Kreisel et al. (2008)[208]	RCT	40	IIT protocol effectively lowers blood glucose levels with an increased risk of manageable hypoglycaemic events. However, feasibility outside of speciality care settings was limited
Rosso et al. (2012)[209]	RCT	180	IIT regimen improved glucose control in the first 24 h of stroke but was associated with larger infarct growth
Ntaois et al. (2014)[210]	Meta-analysis of RCTs	1491	The use of IV insulin compared to controls in hyperglycaemic stroke patients gave no significant improvement in mortality or functional outcome. It also increased the risk of hypoglycaemia

Abbreviations: IIT, intensive insulin treatment; IV, intravenous; RCT, randomised control trial.

Bradley SA et al. Diabetes Metab Res Rev 2021;e3495

Conclusions

Les aGLP1 réduisent le risque d'AVC chez les patients à risque souffrant de DM2

Les iSGLT2 ne réduisent par le risque d'AVC chez les patients diabétiques mais pourraient réduire le risque de FA et d'AVC embolique chez les patients avec maladie rénale

La pioglitazone réduit le risque cardiovasculaire chez les sujets pré-diabétiques, mais augmente le risque de fracture, de gain de poids et d'oedème

Conclusions

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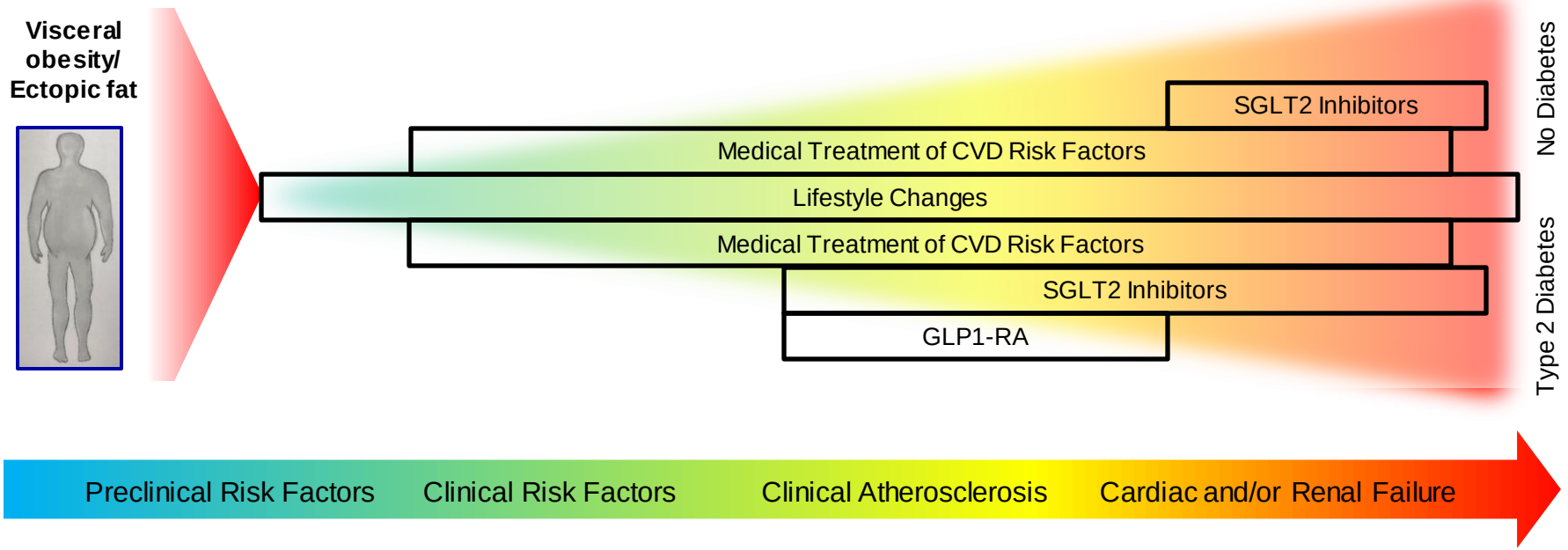
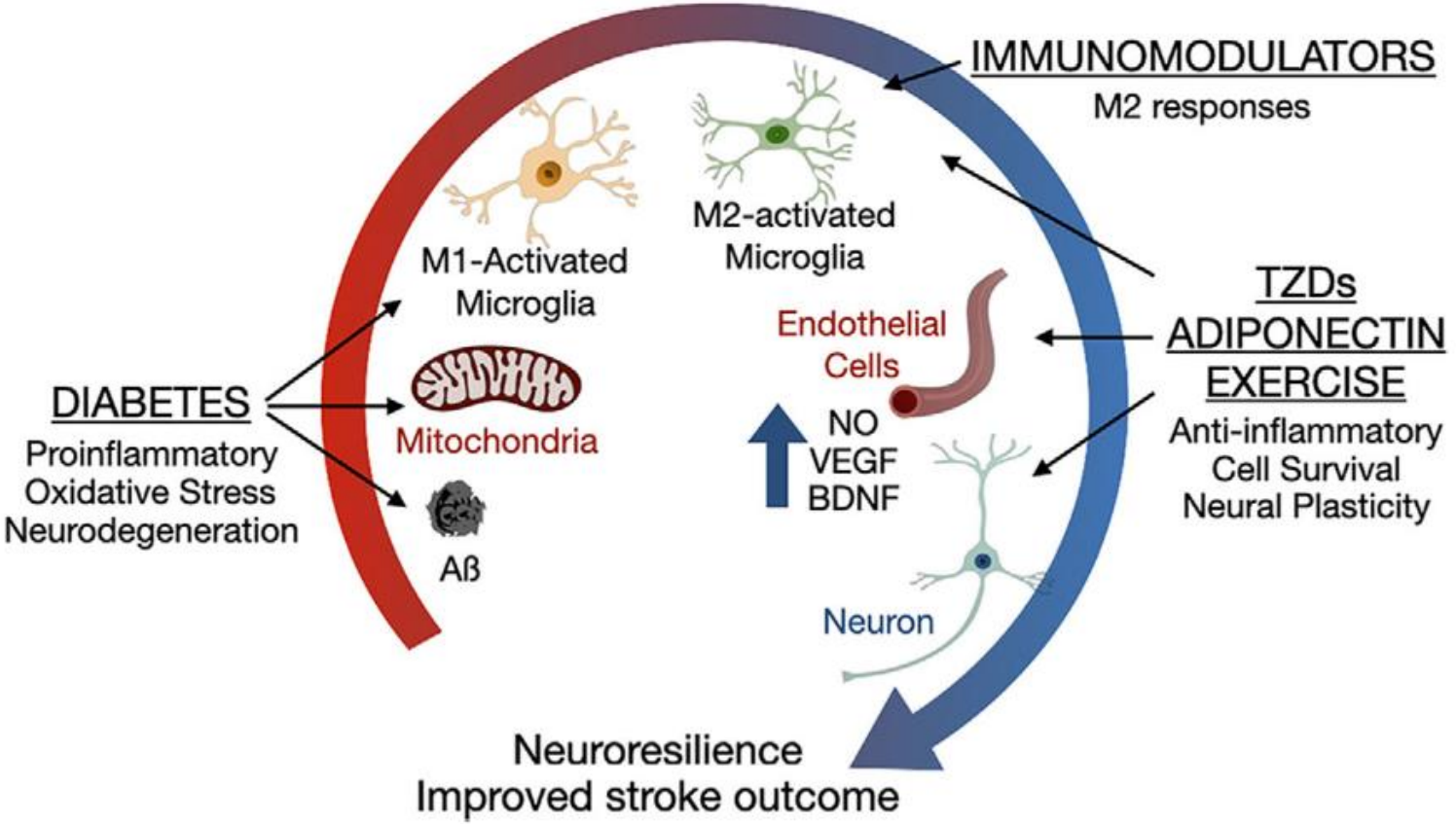
Emploi élargi des Rx anti-diabétiques



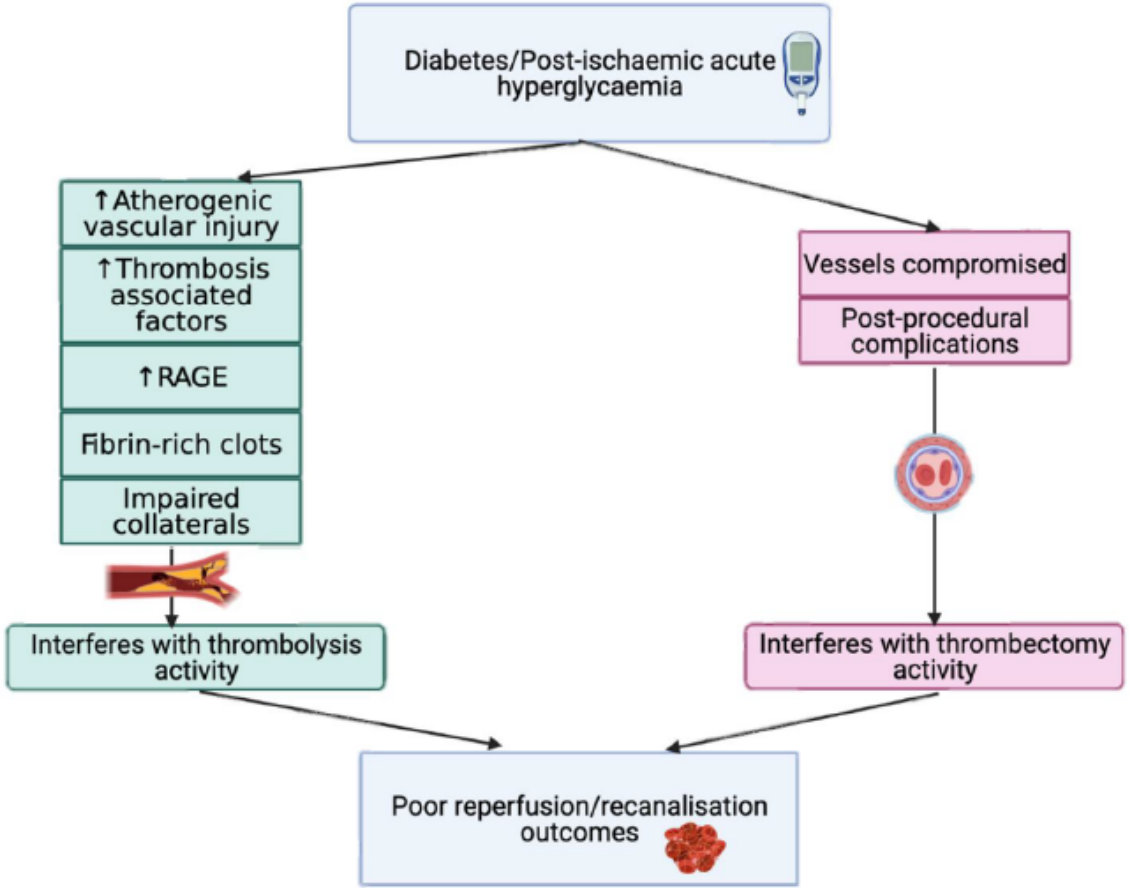
Adapted from Després JP, Carpentier AC, Poirier P, Tchernof A, Neeland I. JACC 2021

Activating neuroresilience



Krinock and Singhal. Ann NY Acad Sci 2021

Diabetes and strokes



Bradley SA et al. Diabetes Metab Res Rev 2021;e3495

TZD: PROACTIVE study

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TABLE 3. Effects of Add-On Pioglitazone Therapy vs Placebo on Cardiovascular Events

	Previous Stroke, No. of Events (%)			No Previous Stroke, No. of Events (%)		
End Points	Pioglitazone (n=486)	Placebo (n=498)	HR*; 95% CI; *P*	Pioglitazone (n=2119)	Placebo (n=2135)	HR*, 95% CI, *P*
Primary‡	98 (20.2%)	126 (25.3%)	0.78; 0.60–1.02; *P*=0.067	416 (19.6%)	446 (20.9%)	0.94; 0.82–1.07; *P*=0.350
Main secondary§	76 (15.6%)	98 (19.7%)	0.78; 0.58–1.06; *P*=0.110	225 (10.6%)	260 (12.2%)	0.86; 0.72–1.03; *P*=0.109
Total stroke	27 (5.6%)	51 (10.2%)	0.53; 0.34–0.85; *P*=0.009	59 (2.8%)	56 (2.6%)	1.06; 0.73–1.52; *P*=0.767
Cardiovascular death, nonfatal stroke, or nonfatal MI†	63 (13.0%)	88 (17.7%)	0.72; 0.53–1.00; *P*=0.047	194 (9.2%)	225 (10.5%)	0.86; 0.71–1.04; *P*=0.129
All-cause mortality	46 (9.5%)	49 (9.8%)	0.96; 0.64–1.44; *P*=0.843	131 (6.2%)	137 (6.4%)	0.96; 0.75–1.22; *P*=0.725

*Pioglitazone vs placebo, from a Cox proportional-hazards model (with treatment as the only covariate).

†Excluding silent MI.

‡All-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, ACS, cardiac intervention (including CABG or PCI), leg revascularization, or major leg amputation (above the ankle).

§All-cause mortality, nonfatal MI, or nonfatal stroke.

Wilcox R et al. Stoke 2007;38:865-873