Regards croisés sur AVC et Diabète
Point de vue du diabétologue

Pr Gaëtan Prévost

Service Endocrinologie, Diabète et Maladies Métaboliques

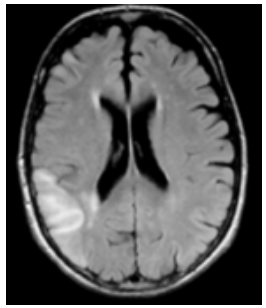
Liens d'intérêts

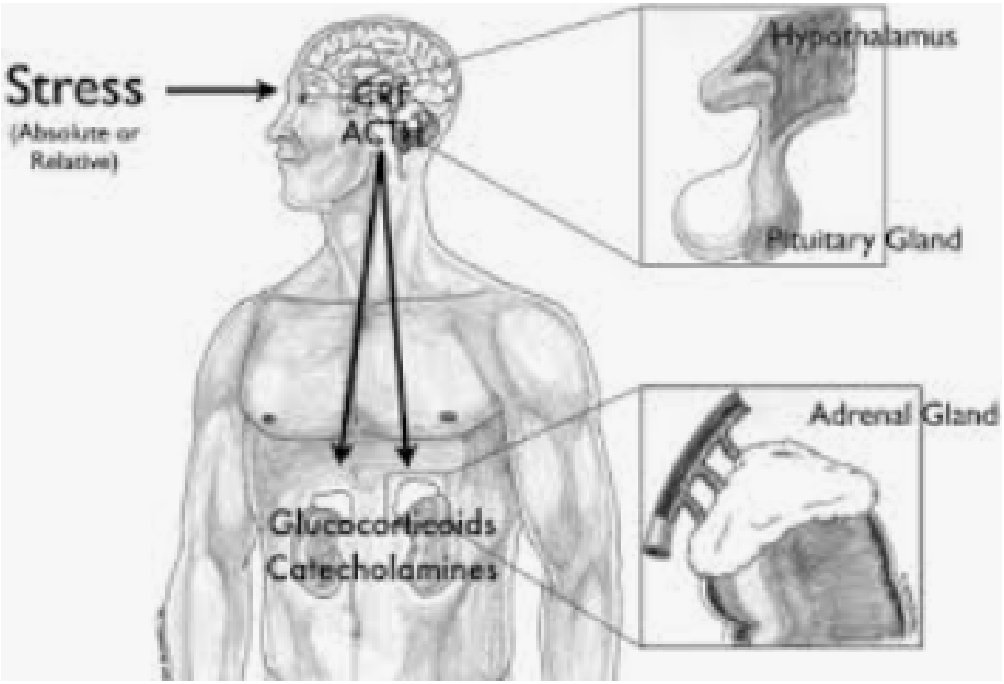
Le Pr Gaëtan Prévost

- déclare avoir les liens d'intérêts suivants à ce jour dans le cadre de cette présentation

Nature	Financeur (s)
-Essais cliniques :	Lilly, Sanofi, NovoNordisk, Jansen
Consultant :	BMS, Lilly, MSD, Novonordisk, Sanofi, Abbott
Loi du 4 mars 2002 (article L 4113-13 du code de	la santé publique) et décret du 28 mars 2007

Hyperglycémie fréquente à la phase aigue de l'AVC



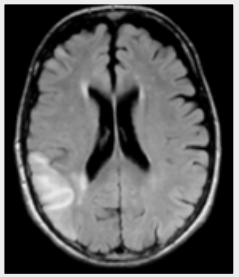


- Augmentation de la glycolyse aérobie
- Augmentation de la glycogénolyse
- Inhibition de la sécrétion insulinique

Herpich,Critical care 2020

Quels objectifs glycémiques à la phase aigue?

Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients With Acute Ischemic Stroke: The SHINE Randomized Clinical Trial[1]



Pronostic à 90 j post AVC entre les groupes intensif et standard

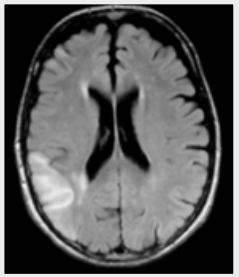
Glycémie >110 mg/dl à l'admission si diabète ou >150 mg/dl si non diabétique

Groupe intensif
Infusion insulinique 80-130 mg/dl
N=581

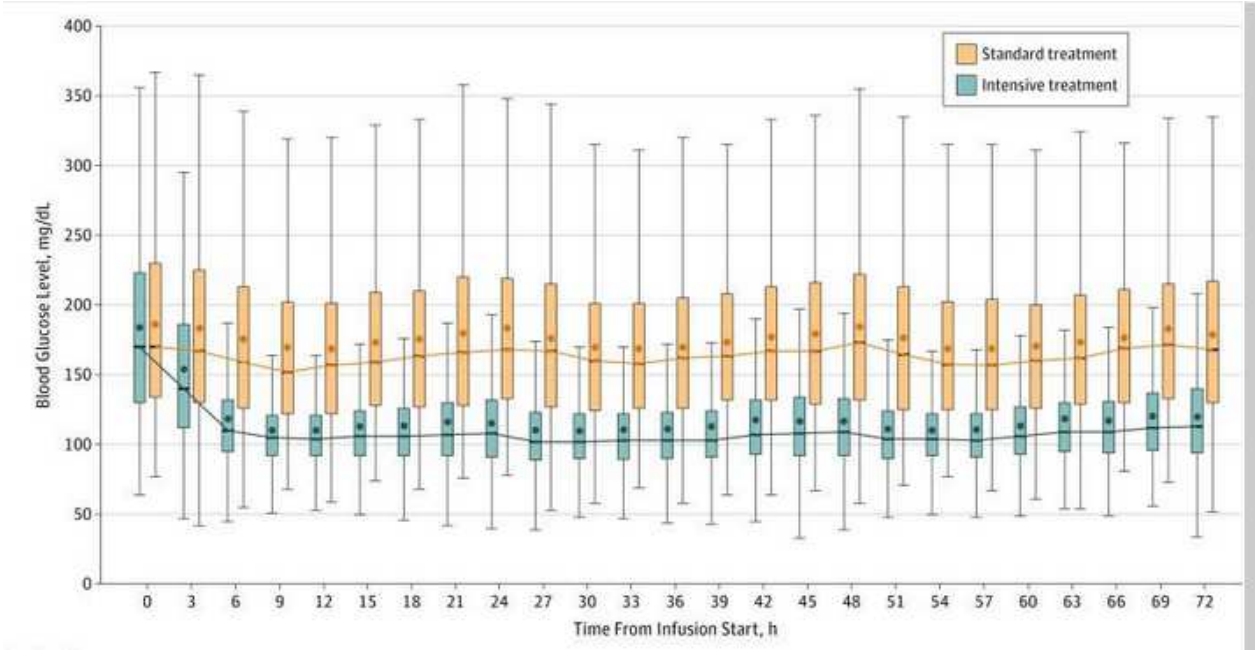
Groupe standard
Sliding scale 80-179 mg/dl
N=570

1. Johnston KC et al. JAMA. 2019;322:326-335.

Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients With Acute Ischemic Stroke: The SHINE Randomized Clinical Trial[1]



Niveau glycémique moyen sur les 3ers j

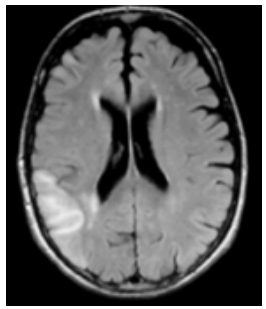


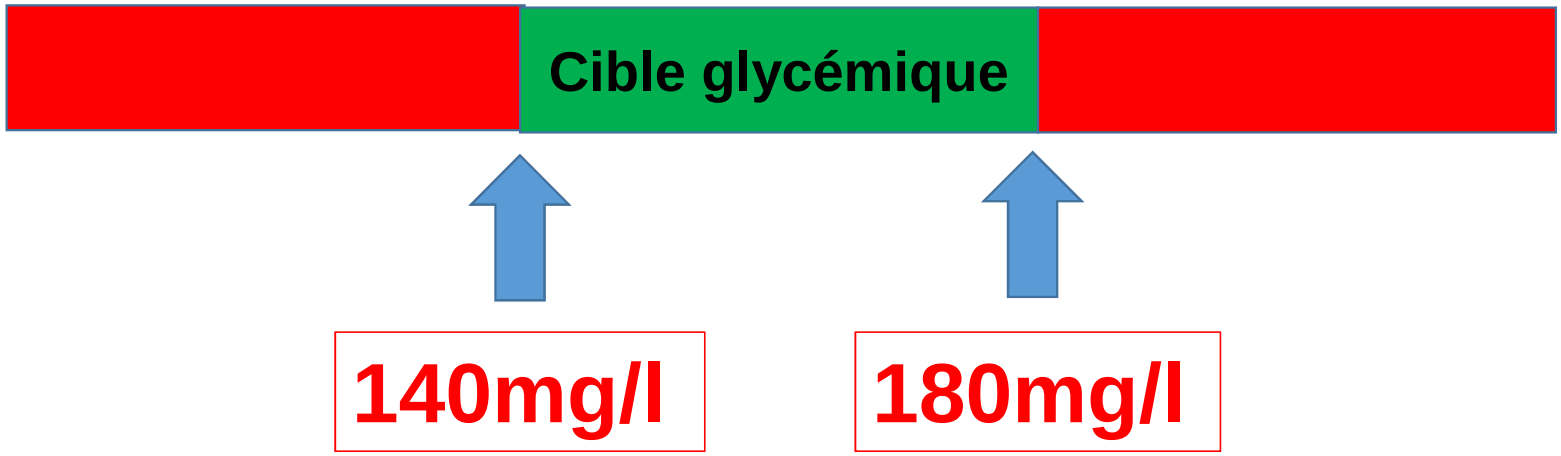
Résultats :

- aucune différence sur les échelles de pronostic (score de Rankin)
- **2,6%** hypo sévères dans le bras intensif versus **0** dans le bras standard

1. Johnston KC et al. JAMA. 2019;322:326-335.

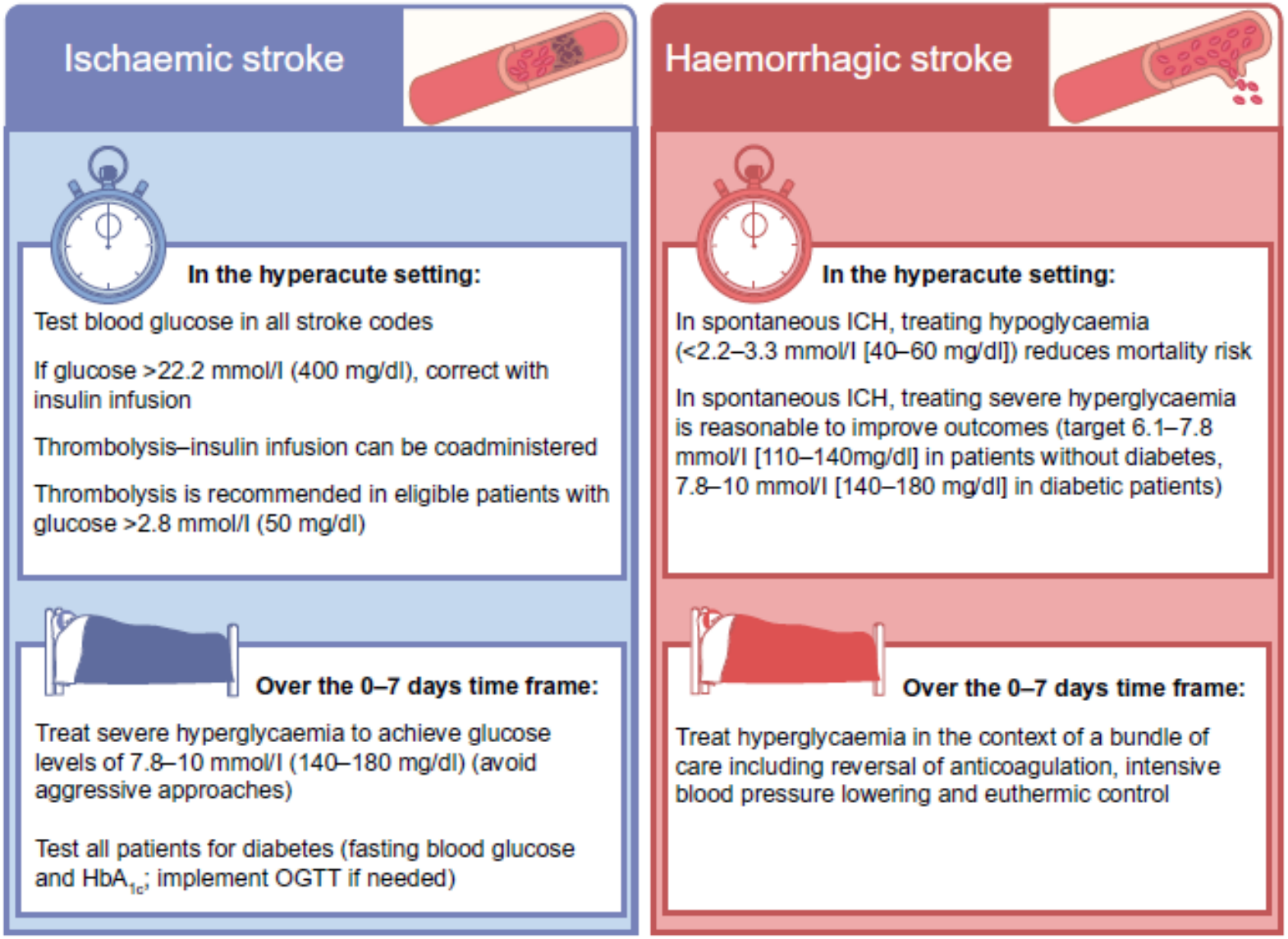
Objectifs glycémiques à la phase aigue





Sliding scale

Herpich,Critical care 2020

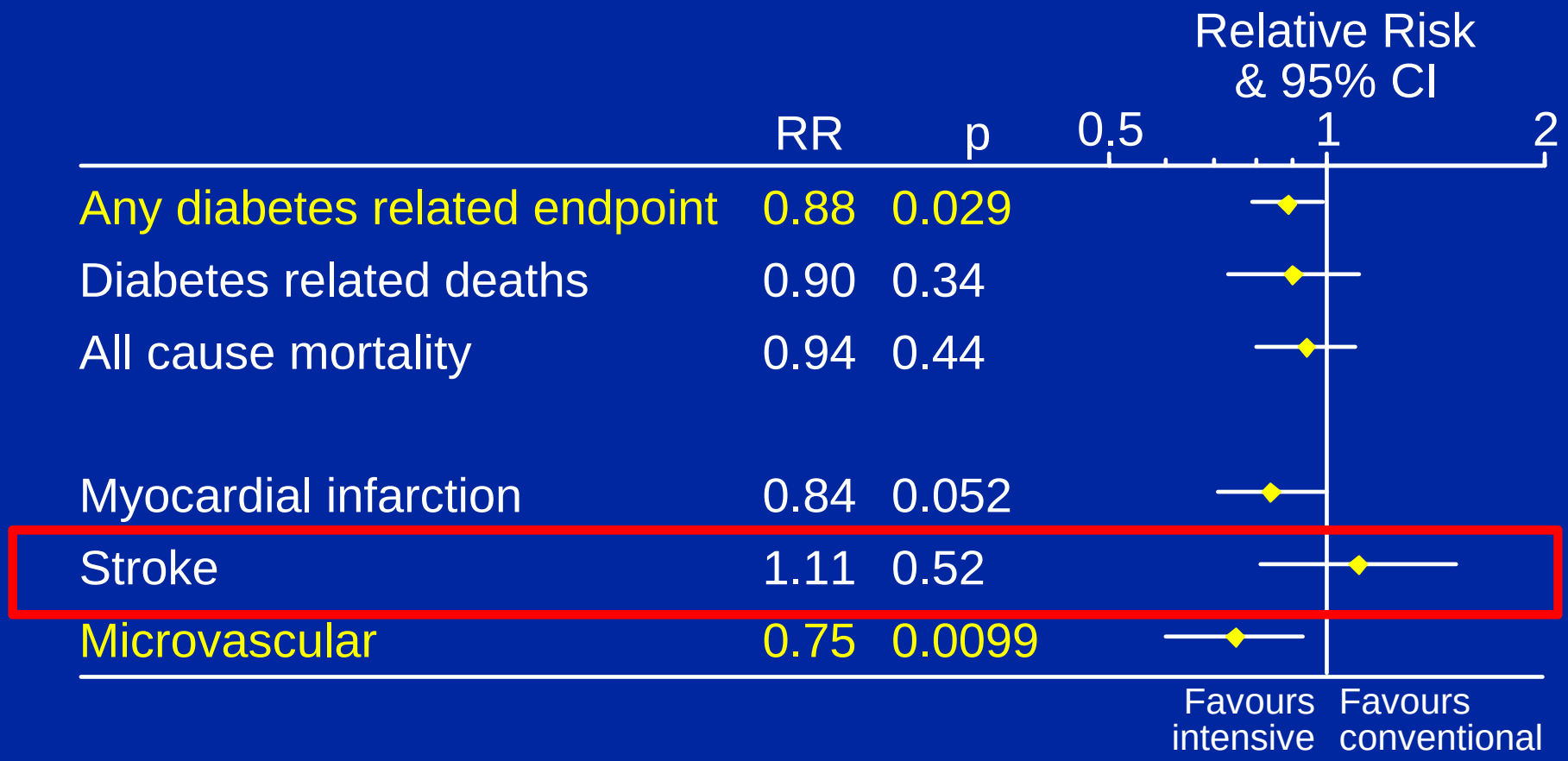


Simona Sacco1,Diabetologia (2024) 67:1192–1205

PREVENTION

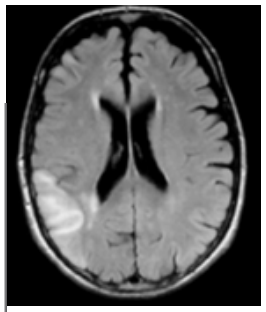
Rôle de l’hyperglycémie

Aggregate Clinical Endpoints



ukpds

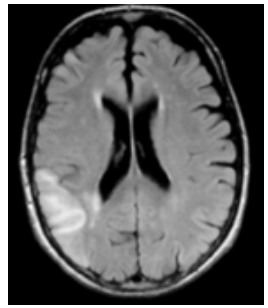
UKPDS post trial



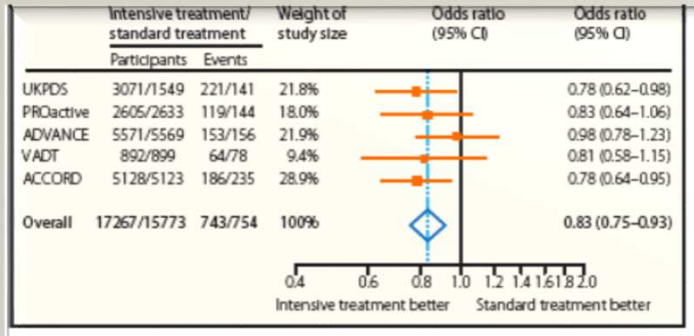
Aggregate Outcome	Patients with Clinical Outcome		Absolute Risk†		P Value‡	Risk Ratio for Intensive-Therapy Regimen (95% CI)
	Intensive Therapy	Conventional Therapy	Intensive Therapy	Conventional Therapy		
	no. of patients					
Sulfonyurea–insulin group	2729	1138				
Any diabetes-related end point	1571	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)

NEJM 2008

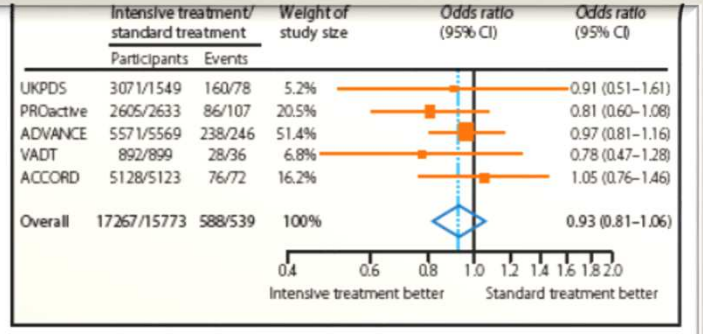
Méta analyse

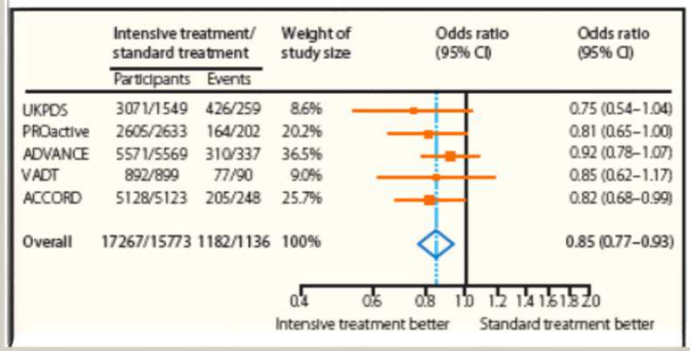


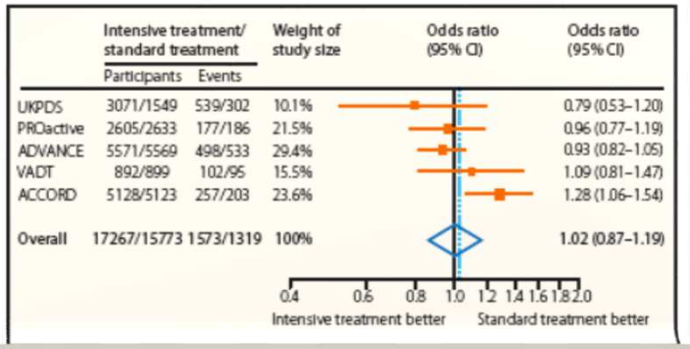
IDM Non Fatals



AVC





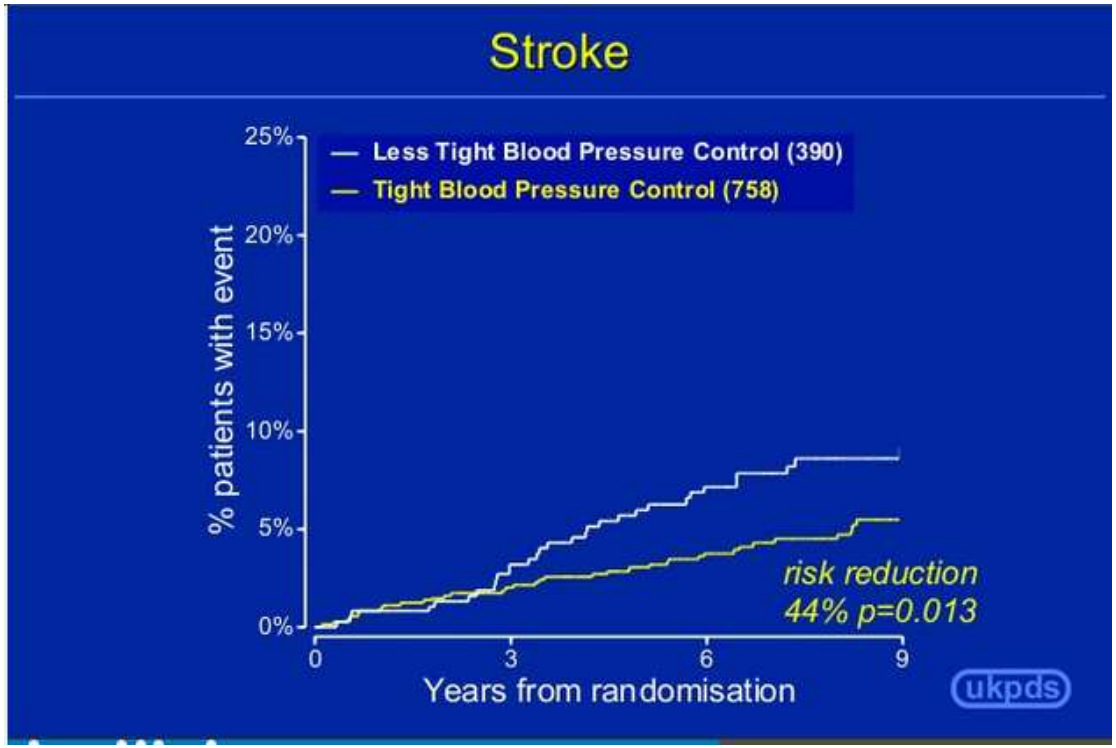


IDM+Mort cardiaque

Mortalité

Ray et al. Lancet 2009; 373: 1765 – 1772.

Pour comparaison , HTA



Primary & Secondary Outcomes

	Intensive Events (%/yr)	Standard Events (%/yr)	HR (95% CI)	P
Primary	208 (1.87)	237 (2.09)	0.89 (0.73-1.07)	0.20
Total Mortality	150 (1.28)	144 (1.19)	1.07 (0.85-1.35)	0.55
Cardiovascular Deaths	60 (0.52)	58 (0.49)	1.06 (0.74-1.52)	0.74
Nonfatal MI	126 (1.13)	146 (1.28)	0.87 (0.68-1.10)	0.25
Nonfatal Stroke	34 (0.30)	55 (0.47)	0.63 (0.41-0.97)	0.03
Total Stroke	36 (0.32)	62 (0.53)	0.59 (0.39-0.89)	0.01

Also examined Fatal/Nonfatal HF (HR=0.94, p=0.67), a composite of fatal coronary events, nonfatal MI and unstable angina (HR=0.94, p=0.50) and a composite of the primary outcome, revascularization and unstable angina (HR=0.95, p=0.40)

ACCORD

144/82 mmHg versus 154/87 mmHg

133 mmHg versus 119 mmHg

UKPDS,BMJ, 1998
ACCORD Study, NEJM 2010

PREVENTION

Prise en charge multifactorielle

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Naveed Sattar, M.D., Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Björn Zethelius, M.D., Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.

Rawshani, NEJM, Aout 2018

The NEW ENGLAND JOURNAL of MEDICINE

Étude de cohorte sur un registre suèdois

Suivi de la mortalité en fonction du contrôle des FDR

271 174 DT2

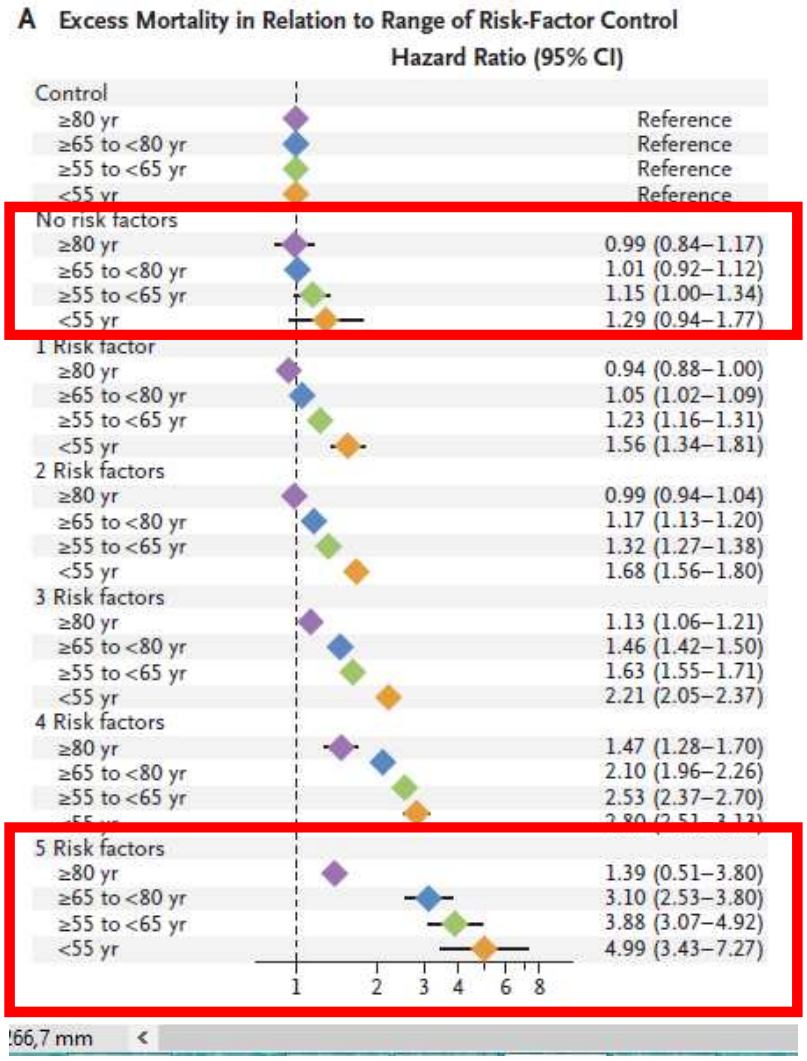
1,355,870 contrôles

5,7 années

	HbA1c	Tabac	albU	HTA	LDL
seuil	7%	Oui ou non	Micro ou macro	>140/80mm	>2.5mmol 97 mg/dl

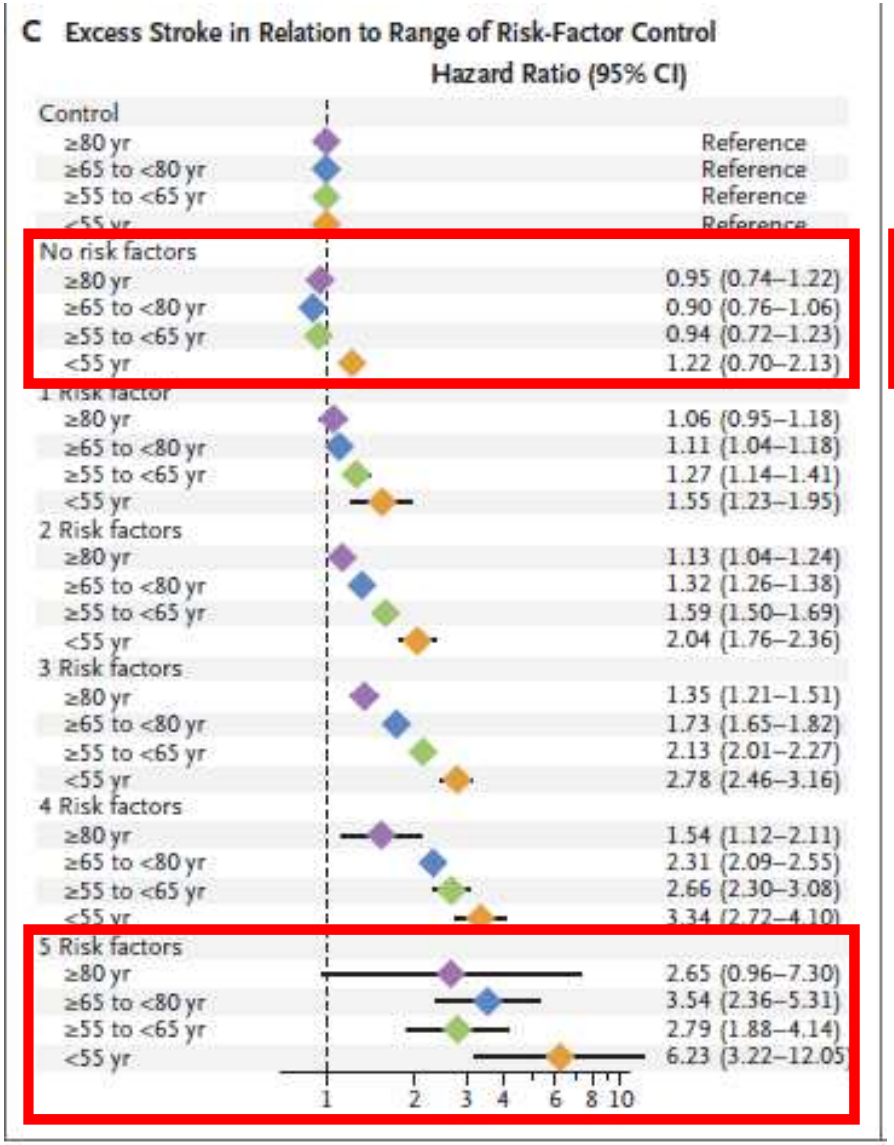
Rawshani, NEJM, Aout 2018

Mortalité toutes causes

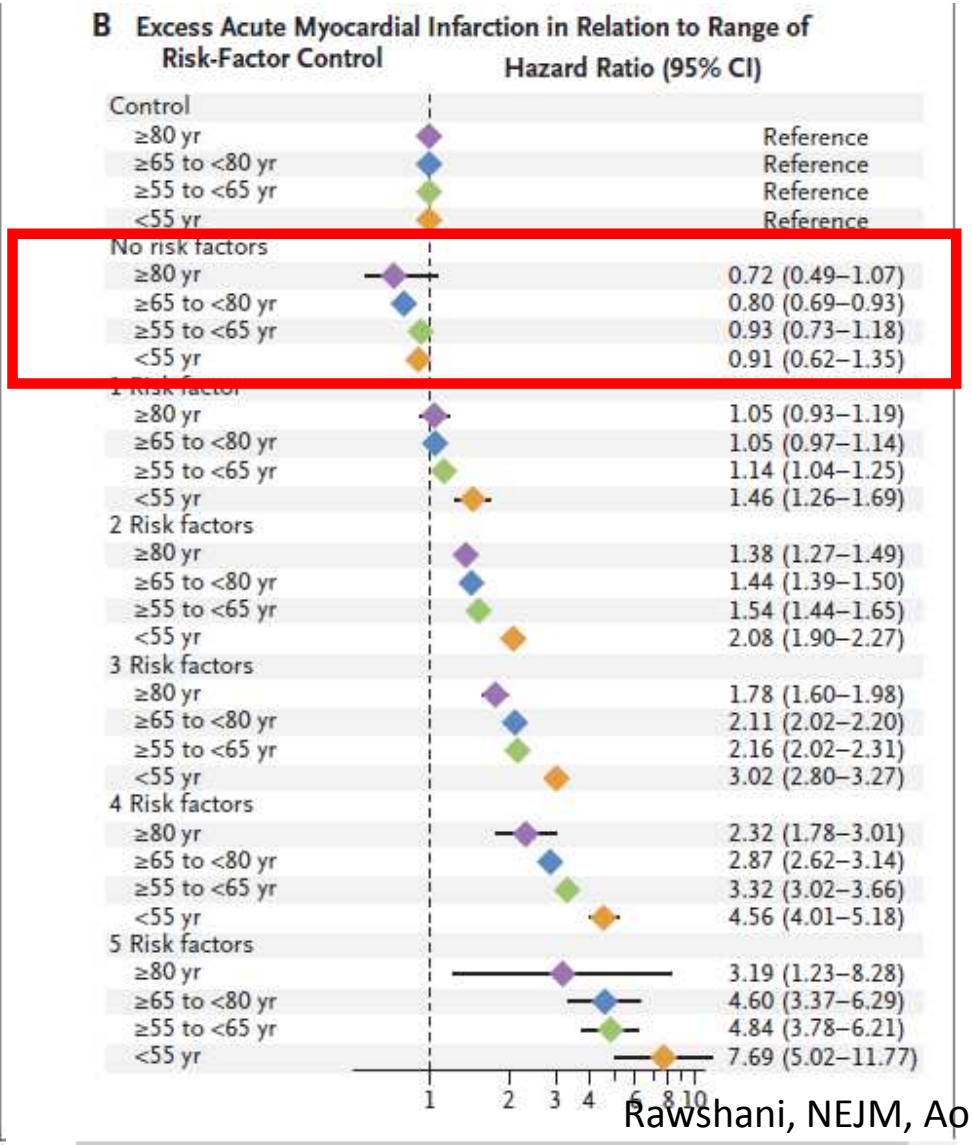


Rawshani, NEJM, Aout 2018

AVC



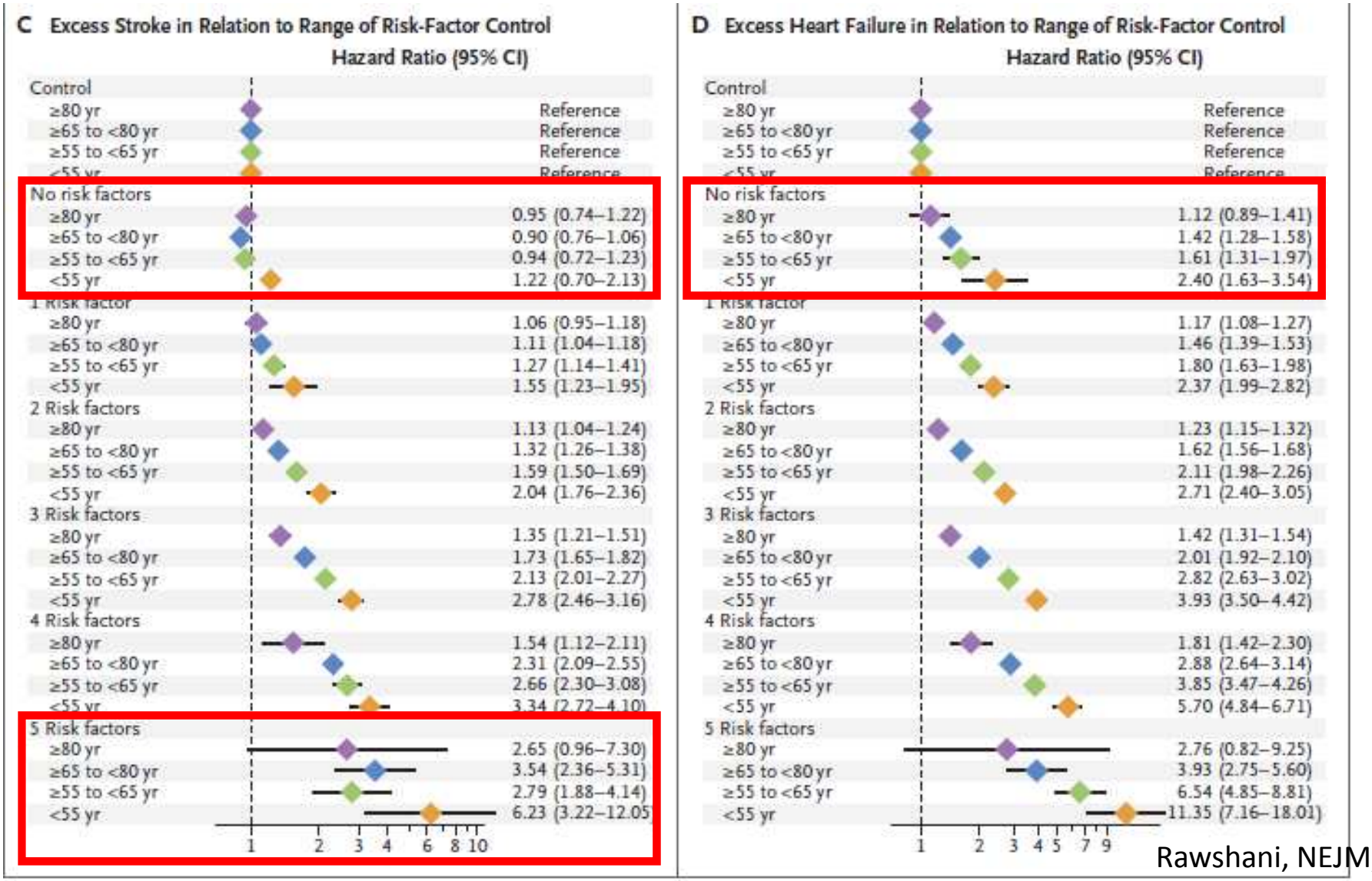
IDM



Rawshani, NEJM, Aout 2018

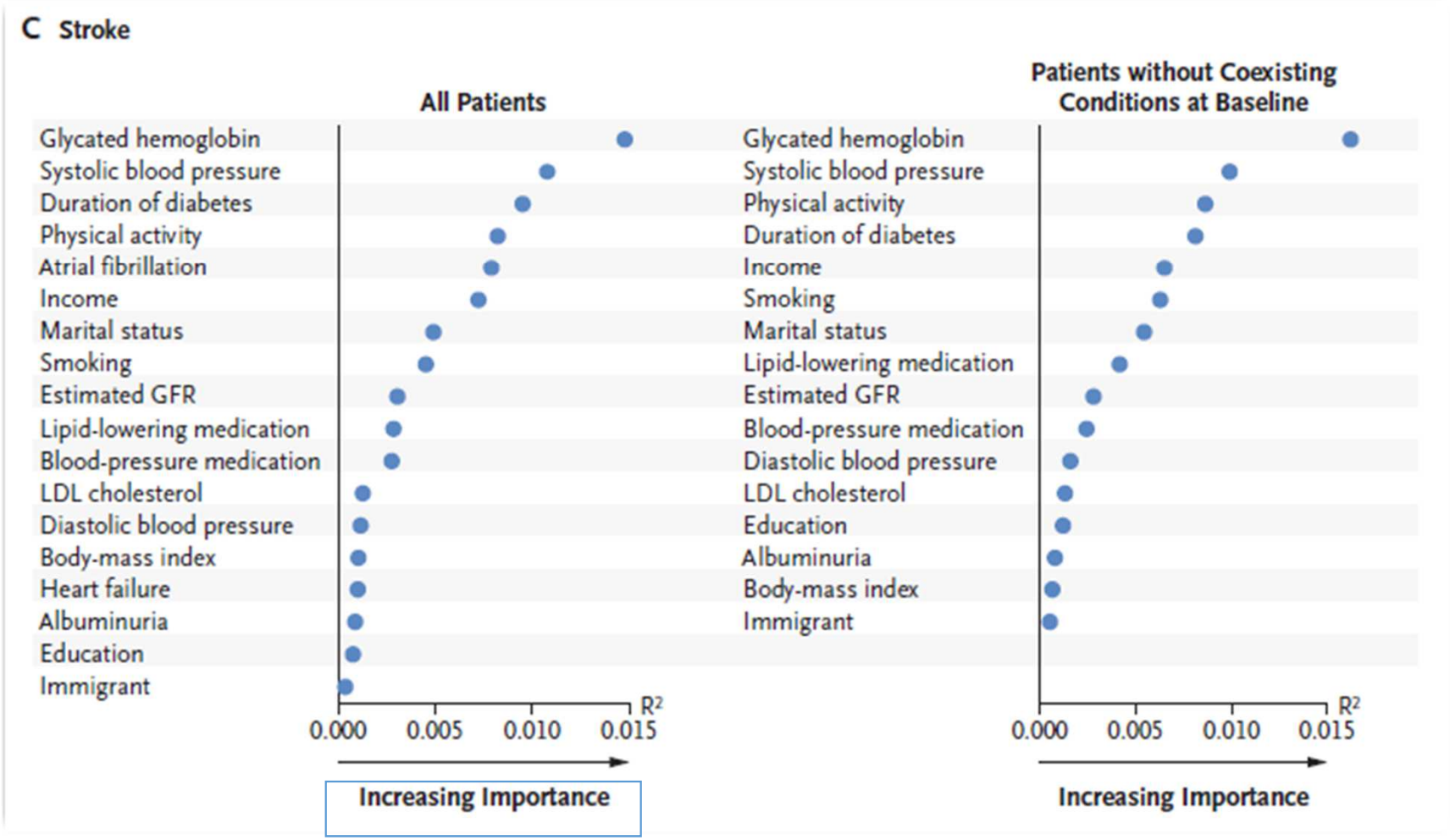
AVC

HF



Rawshani, NEJM, Aout 2018

HbA1c: prédicteur le plus significatif



Rawshani, NEJM, Aout 2018

PREVENTION

Rôle des molécules anti-hyperglycémiantes

Metformine

Reference	Trial name/type	Duration (years)	Oral antidiabetic drug	Active drug [*n*/*N* (%)]	Placebo or comparator [*n*/*N* (%)]	Hazard ratio (95% CI)	*P*
Metformin							
Interventional studies (RCTs)							
UKPDS Group 1998 [10]	UKPDS 34	6.6	Metformin	3.3/1000 patient-years 12/342 (3.51)	6.2/1000 patient-years 60/961 (6.24)	NA	0.03
Cryer et al., 2005 [11]	COSMIC	1	Metformin	29/7227 (0.40)	10/1505 (0.66)	0.60 (0.29–1.24)	NS
Meta-analysis							
Boussageon et al., 2012 [7]	Four trials (n = 10,412)		Metformin	57/8033 (0.71)	47/2379 (1.98)	0.76 (0.51–1.14)	0.18
Observational studies							
Fung et al., 2015 [13]		5-year follow-up	Metformin monotherapy cohort study	5.4/1000 patient-years	6.9/1000 patient-years	Full cohort (n = 11,293) 0.75 (0.57–0.98) Propensity score-matched cohort (n = 6800) 0.70 (0.51–0.95)	0.036 0.024
Floyd et al., 2016 [15]	Case control		Insulin-treated + metformin *vs.* no metformin	NA	NA	0.54 (0.31–0.95)	< 0.05

Plutôt favorable sur l'incidence voire pronostic neurologique
MAIS niveau de preuve FAIBLE

Scheen , Diabetes&Metabolism, 2017

Sulfamides

SUs							
Interventional studies (RCTs)							
UKPDS Group 1998 [20]	UKPDS Intensive	11.1	Chlorpropamide	33/619 (5.33)	47/896 (5.25)	1.01 (0.65–1.58)	0.96
			Glibenclamide	45/615 (7.32)	47/896 (5.25)	1.38 (0.52–2.08)	0.12
Meta-analyses							
Phung et al., 2013 [21]	All (13 studies)		All SUs	NA	NA	1.09 (0.90–1.32)	NS
	Nine RCTs		All SUs	NA	NA	1.14 (0.86–1.51)	NS
	Four observational studies		All SUs	NA	NA	1.05 (0.81–1.36)	NS
Liu et al., 2016 [22]	17 RCTs (n = 27,505)		All SUs: monotherapy + combination	243/11,441 (2.12)	292/16,327 (1.79)	1.39 (1.16–1.65)	0.659
			Monotherapy only	203/8822 (2.30)	265/13,682 (1.94)	1.37 (1.14–1.66)	0.307
Bain et al., 2016 [23]	82 RCTs (n = 35,624)		SU *vs.* metformin	NA	NA	1.40 (0.92–2.22)	NA
			SU *vs.* DPP-4i			9.40 (3.27–41.9)	
			SU *vs.* GLP-1RA			45.4 (1.99–362.7)	
			SU *vs.* glitazones			1.75 (1.20–2.69)	
			SU *vs.* insulin			1.46 (1.01–2.14)	
Observational studies							
Roumie et al., 2012 [24]	Retrospective cohort		SU *vs.* metformin	NA	NA	1.11 (1.10–1.12)	
Floyd et al., 2016 [15]	Case control		Insulin-treated + SU *vs.* no SU	NA	NA	1.22 (0.74–2.00)	NS
Glinides							
Interventional studies (RCTs)							
Holman et al., 2010 [33]	NAVIGATOR[a]	6.5	Nateglinide	111/4645 (2.4)	126/4661 (2.7)	0.89 (0.69–1.15)	0.36

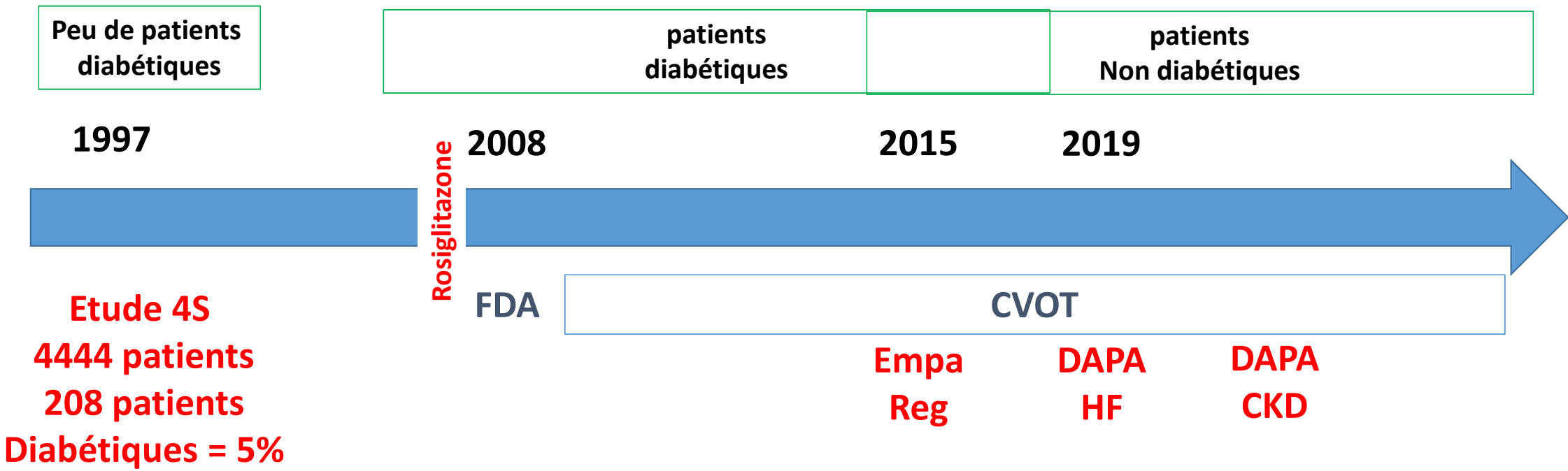
Taking all these data together, including numerous uncertainties, the cardiovascular safety of SUs remains controversial, and their use in patients at risk of cardiovascular disease (CVD), including stroke, is probably not to be recommended [29].

Scheen , Diabetes&Metabolism, 2017

Nouvelles classes thérapeutiques

Prévention cardiovasculaire et diabète

UN NOUVEAU PARADIGME



Recommandations de la FDA (2008) pour l'industrie

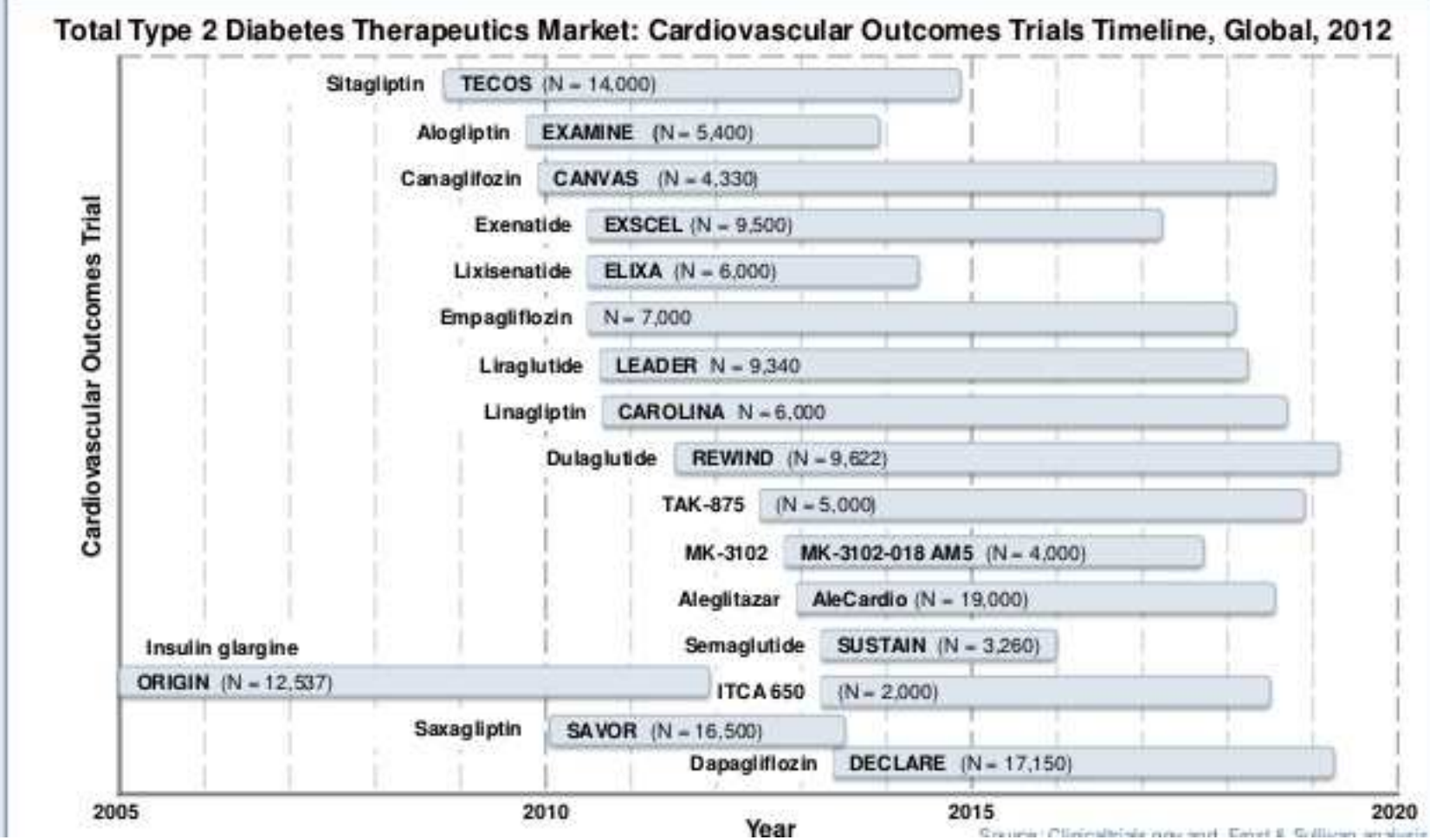
objectifs

Etablir la sécurité des nouvelles médications
Montrer que l'antidiabetique n'augmente pas le risque CV de façon inacceptable

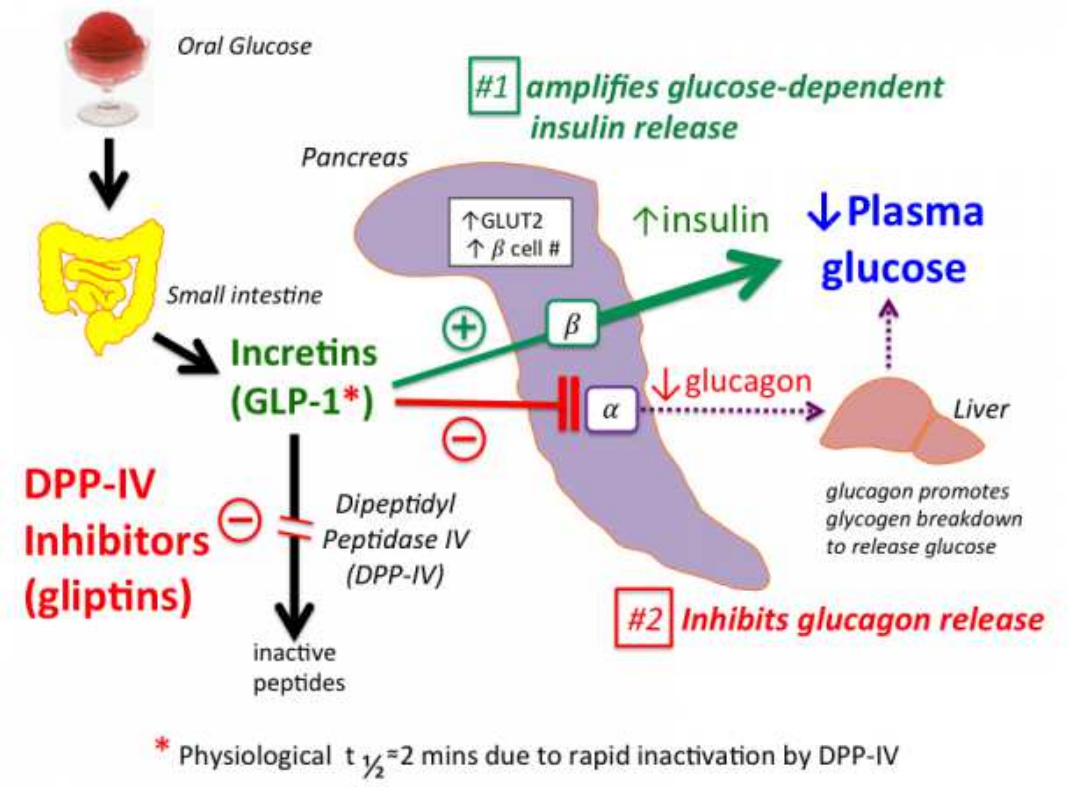
Méthodologie

Analyser les evts CV importants
Population à haut risque cV
Durée d'étude 2-3 ans
Adjudication des evts par un comité indépendant

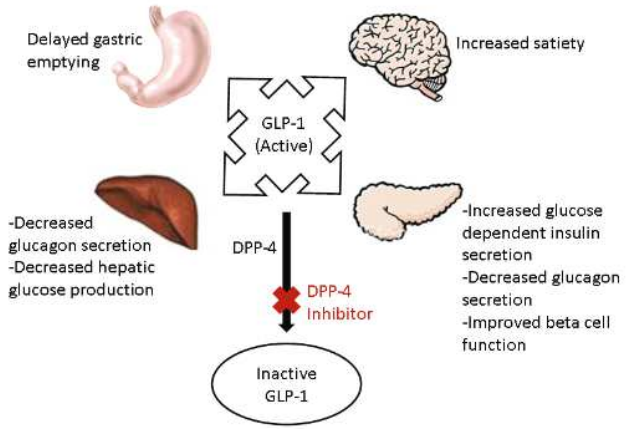
Cardiovascular Outcomes Trials Timeline



Les incrétines



1/ DPP-4 inhibitors



Class and Drug	Decrease in Glycated Hemoglobin Level	Mechanism	Selected Adverse Effects	Benefits and Considerations
DPP-4 inhibitors Sitagliptin Saxagliptin Linagliptin Alogliptin	Up to 1.0%	Inhibit the enzyme that breaks down incretins, leading to increase in glucose-dependent pancreatic insulin release, decrease in glucagon release	Nausea, diarrhea Upper respiratory symptoms Possible pancreatitis† Rare severe joint pains Warning regarding heart failure (saxagliptin, alogliptin)	Weight neutral Low risk of hypoglycemia High cost

Neumiller, Pharmacotherapy,2010

Kalyani, NEJM, 2021

1/ DPP-4 inhibitors

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with DPP4i				
Cardiovascular mortality Follow-up duration: range 1.0 to 3.0 years	42 per 1,000	42 per 1,000 (38 to 45)	OR 1.00 (0.91 to 1.09)	47968 (6 RCTs)	⊕⊕⊕⊕ HIGH	
Myocardial infarction (fatal or non-fatal) Follow-up duration: range 1.7 to 3.0 years	38 per 1,000	37 per 1,000 (33 to 41)	OR 0.97 (0.88 to 1.08)	42334 (4 RCTs)	⊕⊕⊕⊕ HIGH	
Stroke (fatal or non-fatal) Follow-up duration: range 1.0 to 3.0 years	21 per 1,000	21 per 1,000 (18 to 24)	OR 1.00 (0.87 to 1.14)	42588 (5 RCTs)	⊕⊕⊕⊕ HIGH	The VIVID trial (McMurray 2018) only showed wide range of 95% CI with small sample size (total 254 participants).
All-cause mortality Follow-up duration: range 1.0 to 3.0 years	63 per 1,000	65 per 1,000 (61 to 70)	OR 1.03 (0.96 to 1.11)	47968 (6 RCTs)	⊕⊕⊕⊕ HIGH	
Hospitalisation for HF Follow-up duration: range 1.7 to 3.0 years	34 per 1,000	34 per 1,000 (27 to 41)	OR 0.99 (0.80 to 1.23)	42334 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1]	The results between them showed significant heterogeneity (I^2 = 71%, P = 0.02)

Kani , Cochrane Database of Systematic Reviews 2021

iDPP4:**sitagliptine, vildagliptine, saxagliptine**

Reference	Trial name/type	Duration (years)	Oral antidiabetic drug	Active drug [*n*/*N* (%)]	Placebo or comparator [*n*/*N* (%)]	Hazard ratio (95% CI)	*P*
DPP-4is							
Interventional studies (RCTs)							
Scirica et al., 2013 [86]	SAVOR-TIMI 53	2.1	Saxagliptin	157/8280 (1.9)	141/8212 (1.7)	1.11 (0.88–1.39)	0.38
White et al., 2013 [85]	EXAMINE	1.5	Alogliptin	29/2701 (1.1)	32/2679 (1.2)	0.91 (0.55–1.50)	0.71
			Non-fatal stroke				
Greene et al., 2015 [87]	TECOS	3.0	Sitagliptin	178/7257 (2.4)	183/7266 (2.5)	0.97 (0.79–1.19)	0.76
Meta-analyses							
Monami et al., 2013 [88]	29 trials with events (*n* = 22,452)		All DPP-4i	41/12,812 (0.32)	33/9640 (0.34)	0.77 (0.48–1.24)	0.290
Barkas et al., 2016 [89]	19 small RCTs (*n* = 9278)		All DPP-4i	23/6088 (0.38)	17/3190 (0.53)	0.639 (0.336–1.212)	0.170
	Three big RCTs (*n* = 36,395)		All three DPP-4i	315/18,238 (1.7)	315/18,157 (1.7)	0.996 (0.850–1.166)	0.958
Observational studies							
Seong et al., 2015 [90]	Cohort		DPP-4i *vs.* SU	259/55,756 patient-years (4.65/1000 patient-years)	1178/142,940 patient-years (8.24/1000 patient-years)	0.66 (0.56–0.78)	NA
			DPP-4i *vs.* pioglitazone	259/55,756 patient-years (4.65 1000 patient-years)	50/12,903 patient-years (3.88/1000 patient-years)	1.23 (1.01–1.49)	NA

Données expérimentales plutôt positives , indépendantes du GLP1-R

Données cliniques : pas de résultats significatifs

Scheen , Diabetes&Metabolism, 2017

Les agonistes des R-GLP1 « disponibles »

AstraZeneca

NovoNordisk

Molécule	Nom	T 1/2	Administration
Exénatide	Byetta®	3 heures	2x/jour
Liraglutide	Victoza®	12-15 heures	1x/jour
Exénatide hebdomadaire	Bydureon®	-	1x/semaine
Dulaglutide	Trulicity®	5 jours	1x/semaine
Sémaglutide	Ozempic®	7 jours	1X/semaine

AstraZeneca

Lilly

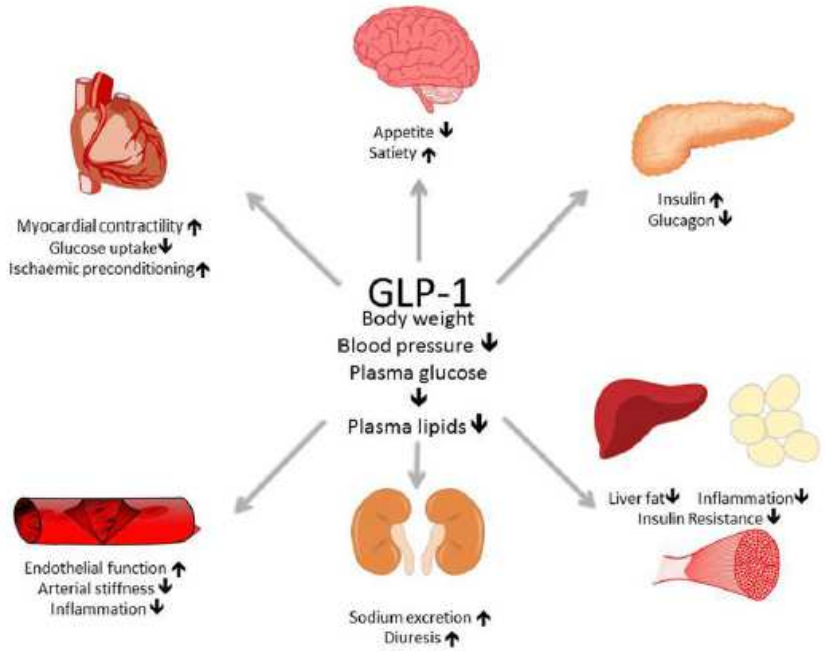
NovoNordisk

2/ GLP-1 Receptor Agonists

Medications	Decrease in Glycated Hemoglobin Level†	Mechanism	Selected Adverse Effects	Benefits and Considerations
GLP-1 receptor agonists Shorter acting: exenatide, lixisenatide Longer acting: exenatide extended release, liraglutide, dulaglutide, semaglutide (subcutaneous), semaglutide (oral)‡	Up to 1.5%	Are also known as incretin mimetics; mimic action of GLP-1 hormone, which increases glucose-dependent pancreatic insulin release, suppresses glucagon secretion, slows gastric emptying, and suppresses appetite	Nausea, vomiting, abdominal pain, diarrhea Possible pancreatitis§ Acute gallbladder disease (liraglutide, exenatide extended release) Not usually recommended in patients with severe gastroparesis Diabetic retinopathy complications (semaglutide, dulaglutide) Long-acting GLP-1 receptor	Weight loss¶ Low risk of hypoglycemia High cost Both injectable and oral formulations (semaglutide) **Indications in patients with established CVD or heart failure or with multiple risk factors for CVD, according to FDA:** Decrease in MACE in type 2 diabetes and established CVD (liraglutide, semaglutide) and in type 2 diabetes and established CVD or multiple risk factors for CVD (dulaglutide)

Kalyani, NEJM, 2021

2/ GLP-1 Receptor Agonists



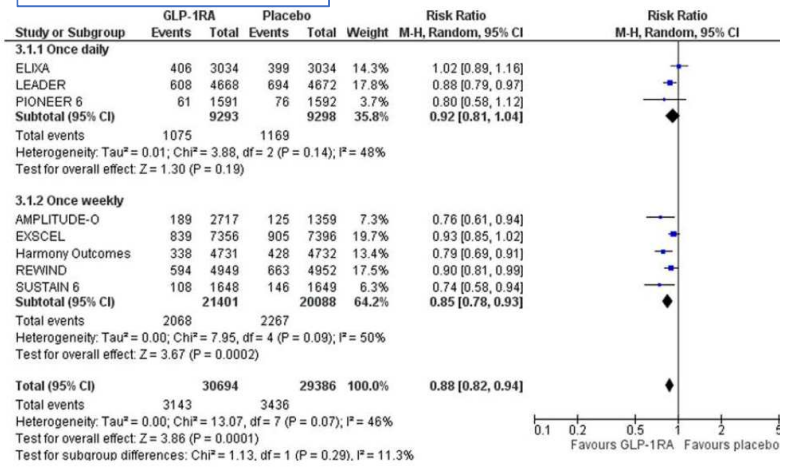
Boyle, Clinical Science,2018

Neumiller, Pharmacotherapy,2010

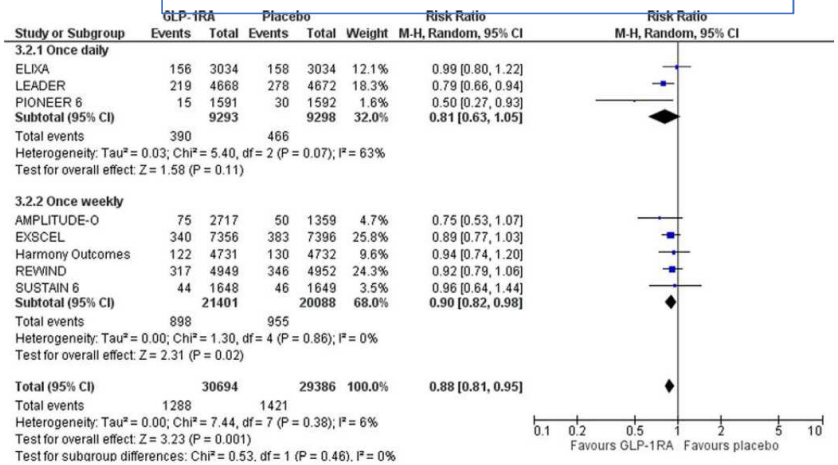
Kalyani, NEJM, 2021

2/ GLP-1 Receptor Agonists

MACE – 12%



Cardiovascular death – 12%



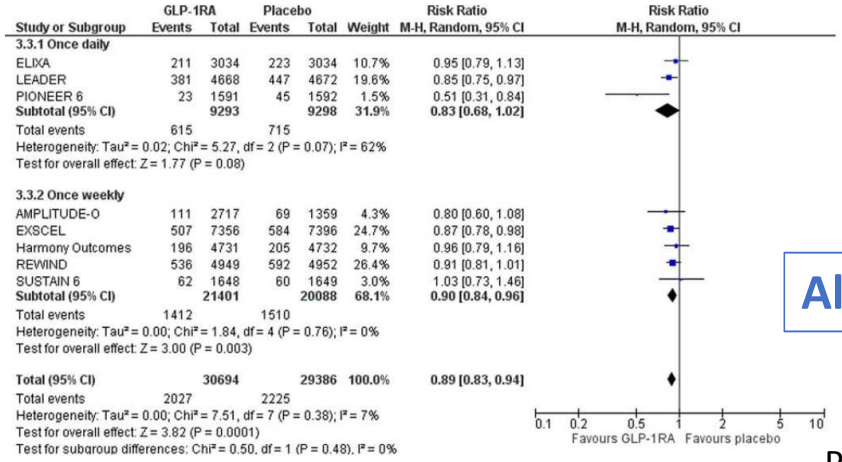
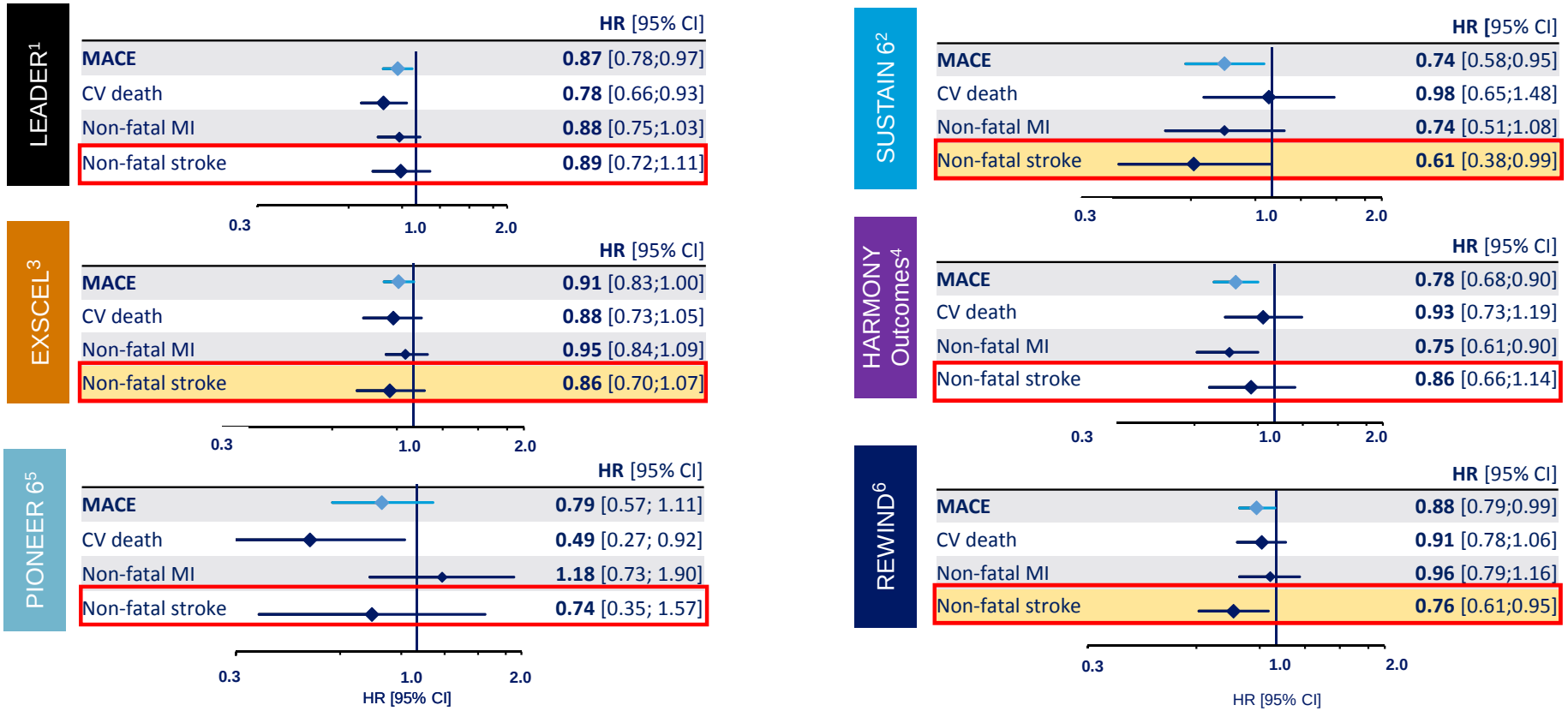


Figure 3. Effect of GLP-1RAs compared with placebo on the risk for all-cause death.

All cause death -11%

Patoulias, Am J Cardiol. 2021

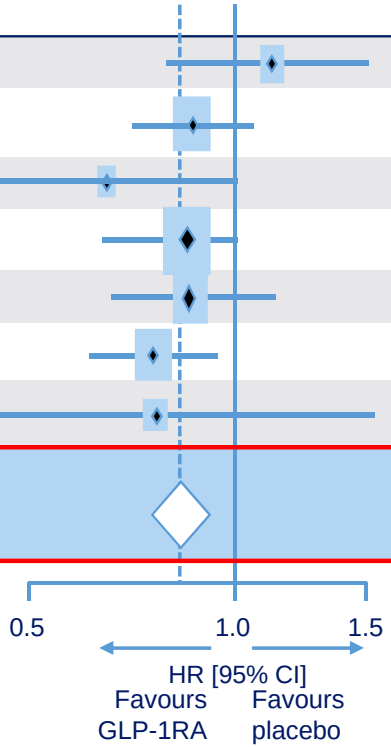
HRs for the non-fatal stroke component of MACE were <1 in all GLP-1RA CVOTs



SK V1 janvier 2021- données AVC

A meta-analysis of GLP-1RA CVOTs showed a significant 16% risk reduction for stroke*

	GLP-1RA, n/N (%)	Placebo, n/N (%)	Hazard ratio [95% CI]	NNT [95% CI]	p-value
ELIXA	67/3,034 (2%)	60/3,034 (3%)	**1.12** [0.79;1.58]		**0.54**
LEADER	173/4,668 (4%)	199/4,672 (4%)	**0.86** [0.71;1.06]		**0.16**
SUSTAIN 6	30/1,648 (2%)	46/1,649 (3%)	**0.65** [0.41;1.03]		**0.066**
EXSCEL	187/7,356 (3%)	218/7,396 (3%)	**0.85** [0.70;1.03]		**0.095**
Harmony Outcomes	94/4,731 (2%)	108/4,732 (2%)	**0.86** [0.66;1.14]		**0.30**
REWIND	158/4,949 (3%)	205/4,952 (4%)	**0.76** [0.62;0.94]		**0.01**
PIONEER 6	13/1,591 (1%)	17/1,592 (1%)	**0.76** [0.37;1.56]		**0.43**
Overall (I^2=0.0%, p=0.557)	722/27,977 (3%)	853/28,027 (3%)	**0.84** [0.76;0.93]	**209** [139;477]	**<0.001**



*Fatal or non-fatal stroke.
CI, confidence interval; CVOT, cardiovascular outcome trial; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio: NNT, number needed to treat.
Kristensen SL et al. Lancet Diabetes Endocrinol 2019;7:776–85.

SK V1 janvier 2021- données AVC

Effect of GLP-1 analogues on stroke and stroke subtypes

TIME-TO-FIRST EVENT ANALYSIS: LEADER + SUSTAIN 6 + PIONEER 6 POOLED ANALYSIS

	n (%)		HR [95% CI]	p-value
	GLP-1 analogues‡ (N=7,907)	Placebo (N=7,913)		
All strokes	216 (2.7)	262 (3.3)	0.82 [0.68;0.98]	0.030
Ischaemic stroke*	186 (2.4)	220 (2.8)	0.84 [0.69;1.02]	0.08
Large artery atherosclerosis	53 (0.7)	56 (0.7)	0.94 [0.65;1.37]	0.75
Cardioembolism	21 (0.3)	23 (0.3)	0.91 [0.50;1.64]	0.75
Small vessel occlusion	93 (1.2)	119 (1.5)	0.78 [0.59;1.02]	0.07
Other determined cause	5 (0.1)	4 (0.1)	1.25 [0.34;4.65]	0.74
Undetermined cause†	17 (0.2)	21 (0.3)	0.81 [0.43;1.53]	0.51
Haemorrhagic stroke	23 (0.3)	32 (0.4)	0.72 [0.42;1.22]	0.22
Undetermined stroke	10 (0.1)	14 (0.2)	0.71 [0.32;1.60]	0.41

*Ischaemic strokes were subcategorised according to TOAST criteria by an external, blinded reviewer. †Included patients with ≥2 causes of stroke, undetermined cause despite extensive evaluation and cause of stroke not known due to incomplete evaluation.
‡Included liraglutide, and QW s.c. and OD oral semaglutide.
CI, confidence interval; GLP-1, glucagon-like peptide-1; HR, hazard ratio; OD, once daily; QW, once weekly; s.c., subcutaneous; TOAST, Trial of Org10172 in Acute Stroke Treatment.
Strain WD et al. Presented at the 56th Annual Meeting of the European Association for the Study of Diabetes (EASD), 21–25 September 2020. Oral Presentation 258.

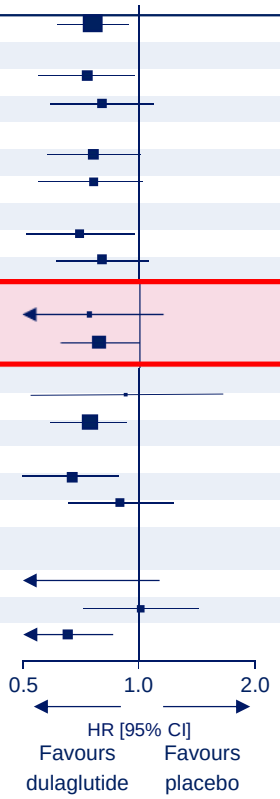
SK V1 janvier 2021- données AVC

SK V1 janvier 2021- données AVC

Subgroup analysis for stroke according to baseline characteristics

REWIND TRIAL

	Dulaglutide		Placebo			
	Events/patients	Events per 100 person-years	Events/patients	Events per 100 person-years	HR [95% CI]	$p_{interaction}$
Randomly assigned	158/4,949 (3.2%)	0.61	205/4,952 (4.1%)	0.81	0.76 [0.62;0.94]	
Age (years)						
≥66	81/2,314 (3.5%)	0.69	111/2,350 (4.7%)	0.94	0.73 [0.55;0.97]	
<66	77/2,635 (2.9%)	0.55	94/2,602 (3.6%)	0.69	0.80 [0.59;1.08]	0.66
Sex						
Male	88/2,643 (3.3%)	0.65	115/2,669 (4.3%)	0.85	0.76 [0.58;1.01]	
Female	70/2,306 (3.0%)	0.58	90/2,283 (3.9%)	0.76	0.76 [0.55;1.03]	0.97
CV disease						
Previous CV disease	63/1,560 (4.0%)	0.80	88/1,554 (5.7%)	1.14	0.70 [0.51;0.97]	
No previous CV disease	91/3,093 (2.9%)	0.56	113/3,128 (3.6%)	0.69	0.80 [0.61;1.06]	0.54
Stroke or TIA						
Previous stroke or TIA	35/445 (7.9%)	1.62	48/454 (11.0%)	2.18	**0.74 [0.48;1.15]**	
No previous stroke or TIA	123/4,485 (2.7%)	0.52	155/4,470 (3.5%)	0.67	**0.78 [0.62;0.99]**	0.83
Atrial fibrillation						
Yes	23/328 (7.0%)	1.42	23/308 (7.5%)	1.54	0.93 [0.52;1.65]	
No	135/4,586 (2.9%)	0.56	182/4,613 (3.9%)	0.77	0.74 [0.59;0.92]	0.48
HbA_{1c} (%)						
≥7.2	82/2,610 (3.1%)	0.61	121/2,603 (4.6%)	0.91	0.67 [0.50;0.88]	
<7.2	76/2,329 (3.3%)	0.62	84/2,334 (3.6%)	0.70	0.89 [0.66;1.22]	0.17
Systolic blood pressure (mmHg)						
<120	11/680 (1.6%)	0.31	21/712 (2.9%)	0.56	0.54 [0.26;1.13]	
120–140	69/2,273 (3.0%)	0.58	67/2,244 (3.0%)	0.57	1.01 [0.73;1.42]	
>140	78/1,996 (3.9%)	0.76	117/1,996 (5.9%)	1.17	0.65 [0.49;0.86]	0.089



CI, confidence interval; CV, cardiovascular; HR, hazard ratio. TIA, transient ischaemic attack.
Cukierman-Yaffe T et al. Lancet Neurol 2020;19:582–90.

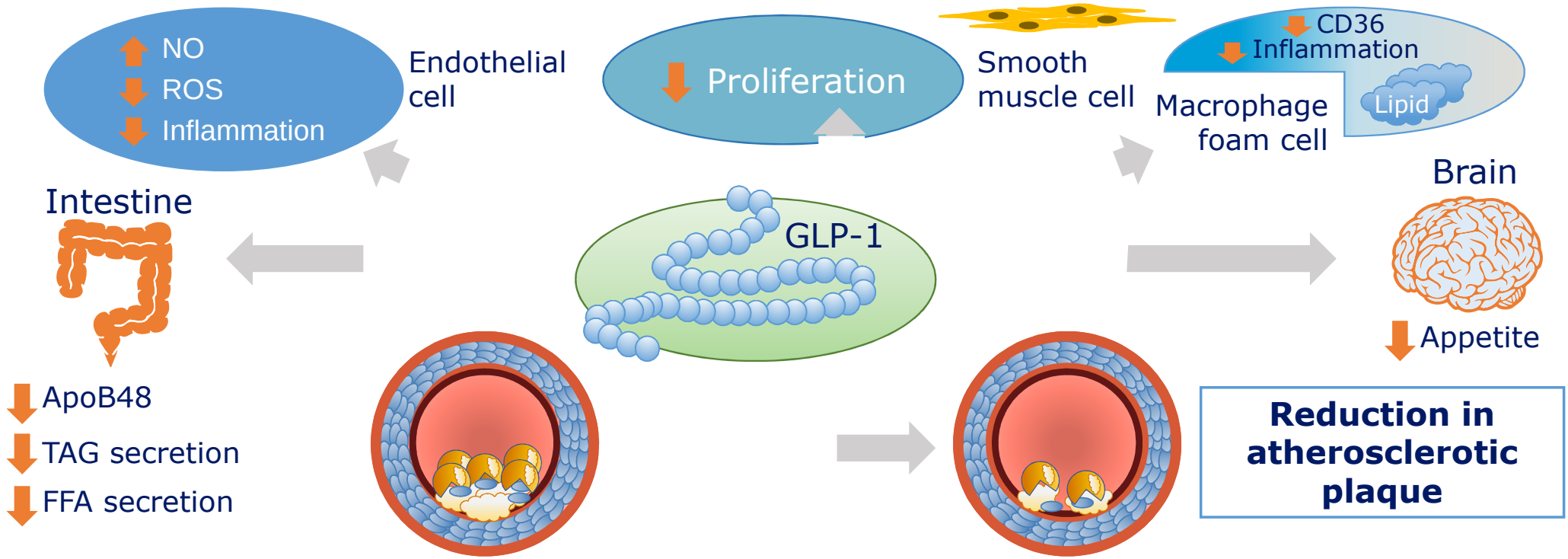
Effect of treatment allocation on stroke outcomes

REWIND TRIAL

	Dulaglutide (n=4,949)	Placebo (n=4,952)	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. *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.*
CI, confidence interval; HR, hazard ratio.
Cukierman-Yaffe T et al. Lancet Neurol 2020;19:582–90.

Anti-atherosclerotic potential of GLP-1



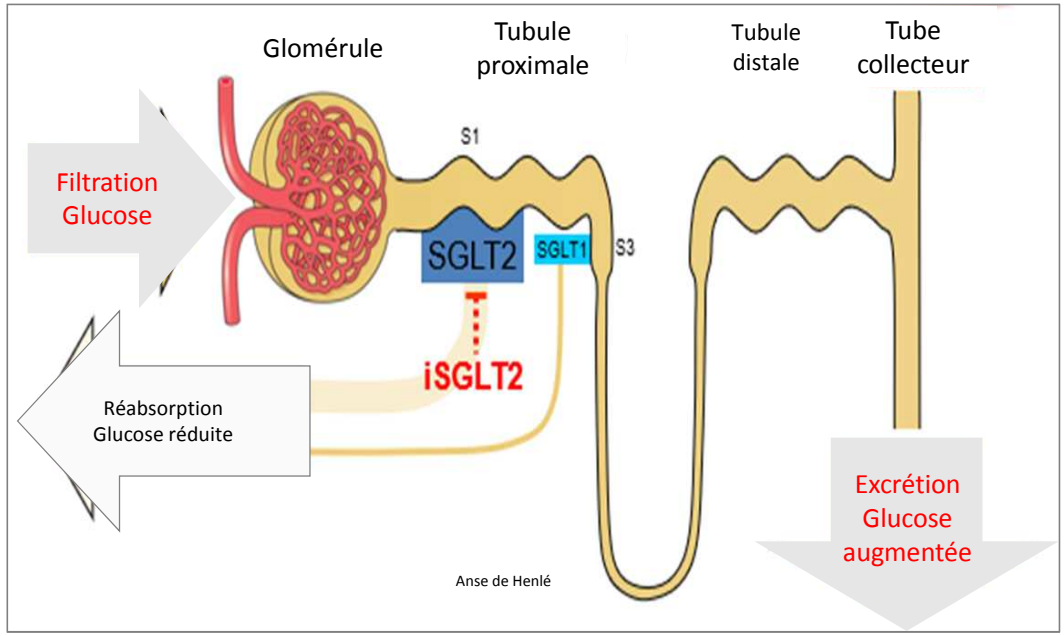
ApoB48, apolipoprotein B-48; FFA, free fatty acid; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; NO, nitric oxide; ROS, reactive oxygen species; TAG, triacylglycerol.
Ussher JR, Drucker DJ. Endocr Rev 2012;33:187–21.

Inhibiteurs des SGLT2

1/ diminution de l'hyperglycémie

Dapagliflozine / Empagliflozine / Canagliflozine/ Ertugliflozine

Inhibition du SGLT2 : Améliore la glycémie en réduisant la réabsorption rénale du glucose de 30 à 50 %



Élimination
80 à 100 g de GlC/j
soit 300 à 400 Kcal

HbA1c:
-0.6 à -0.8%

SGLT2 *vs* SGLT1	Empa	Ertu	Cana	Dapa
	5000[2]	2000[4]	160[3]	**1400[1,3]**

1.Résumé des Caractéristiques du Produit Forxiga®. Disponible sur : http://www.ema.europa.eu (30/07/18). **2.** Résumé des Caractéristiques du Produit Jardiance®. Disponible sur : http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Risk-management-plan_summary/human/002677/WC500163291.pdf (14/08/18). **3.** Sha S, et al. Diabetes, Obesity and Metabolism 2015; 17: 188–97. **4**. ertugliflozin selectivity reported in dose ranging study Diabetes, Obesity and Metabolism 17: 591–598, 2015 **5**, S.Halimi. MmM- Mars 2019-Vol 13-Supplement 1.

3/ SGLT2 inhibitors

Medications	Decrease in Glycated Hemoglobin Level†	Mechanism	Selected Adverse Effects	Benefits and Considerations
SGLT2 inhibitors Canagliflozin Empagliflozin Dapagliflozin Ertugliflozin	Up to 1.0%	Block reabsorption of glucose from urine by inhibiting SGLT2 in proximal tubules of kidney, resulting in glucosuria	Increased urination Volume depletion Acute kidney injury Genital mycotic and urinary tract infections Euglycemic diabetic ketoacidosis Increased LDL cholesterol level (empagliflozin, ertugliflozin) Fracture (canagliflozin) Warning regarding leg amputation (canagliflozin, ertugliflozin) Rare Fournier's gangrene	Weight loss, reduced blood pressure Should be discontinued before major surgery due to risk of diabetic ketoacidosis Low risk of hypoglycemia Additional benefits in chronic kidney disease‡ High cost **Indications in patients with established CVD or heart failure or with multiple risk factors for CVD, according to FDA:** Decrease in MACE (canagliflozin) or CVD death (empagliflozin) in type 2 diabetes and established CVD Decrease in hospitalization for heart failure in type 2 diabetes and established CVD or multiple CVD risk factors (dapagliflozin) Decrease in hospitalization for heart failure and CVD-related death in heart failure and reduced ejection fraction, with or without diabetes (dapagliflozin)§

Kalyani, NEJM, 2021

3/ SGLT2 inhibitors

Effects on the 3 components of the MACE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with SGLT2i				
Cardiovascular mortality Follow-up duration: range 0.8 to 3.5 years	86 per 1,000	72 per 1,000 (62 to 82)	OR 0.82 (0.70 to 0.95)	24962 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Although the I^2 statistic was 67%, SGLT2i reduced cardiovascular mortality. The heterogeneity might be derived from the differences in odds ratios (estimates).
Myocardial infarction (fatal or non-fatal) Follow-up duration: range 3.1 to 3.5 years	56 per 1,000	54 per 1,000 (47 to 62)	OR 0.97 (0.84 to 1.12)	15266 (2 RCTs)	⊕⊕⊕⊕ HIGH	
Stroke (fatal or non-fatal) Follow-up duration: range 3.1 to 3.5 years	31 per 1,000	34 per 1,000 (28 to 41)	OR 1.12 (0.92 to 1.36)	15266 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	
All-cause mortality Follow-up duration: range 0.8 to 3.5 years	113 per 1,000	96 per 1,000 (86 to 109)	OR 0.84 (0.74 to 0.96)	24962 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Despite heterogeneity of I^2 = 56%, the results seemed to be consistent.
Hospitalisation for HF	116 per 1,000	78 per 1,000 (72 to 85)	OR 0.65 (0.59 to 0.71)	24962 (5 RCTs)	⊕⊕⊕⊕ HIGH	Because the estimate of these 5 trials were quite similar, heterogeneity was low: I^2 = 33%.

Kani , Cochrane Database of Systematic Reviews 2021

iSGLT2: dapagliflozine, empagliflozine, canagliflozine

SGLT2 inhibitors							
Interventional studies (RCTs)							
Zinman et al., 2015 [97]	EMPA-REG OUTCOME	3.1	Empagliflozin Fatal+non-fatal stroke	164/4687 (3.5)	69/2333 (3.0)	1.18 (0.89–1.56)	0.26
Zinman et al., 2017 [100]			Empagliflozin Non-fatal stroke	150/4687 (3.2)	60/2333 (2.6)	1.24 (0.92–1.67)	0.16
			Empagliflozin TIAs	39/4687 (0.8)	23/2333 (1.0)	0.85 (0.51–1.42)	0.54
Meta-analyses							
Wu et al., 2016 [105]	(n=16,743)		Canagliflozin+empagliflozin Non-fatal stroke	NA	NA	1.30 (1.00–1.68)	0.049
Saad et al., 2017 [107]	(n=37,195)		All SGLT2i Stroke/TIAs	NA	NA	1.09 (0.87–1.37)	0.47
Monami et al., 2017 [108]	(n=47,287)		All SGLT2i Stroke	NA	NA	1.09 (0.86–1.38)	0.50
Wu et al., 2016 [105]	(n=9723)		Canagliflozin Non-fatal stroke	47/6396 (0.73)	16/3327 (0.48)	1.53 (0.87–2.69)	NS
Wu et al., 2016 [105]	(n=7020)		Empagliflozin Non-fatal stroke	150/4687 (3.20)	60/2333 (2.57)	1.24 (0.93–1.67)	NS
Sonesson et al., 2016 [106]	(n=6639)		Dapagliflozin Stroke	25/4227 (0.59)	18/2412 (0.75)	0.999 (0.536–1.864)	NS

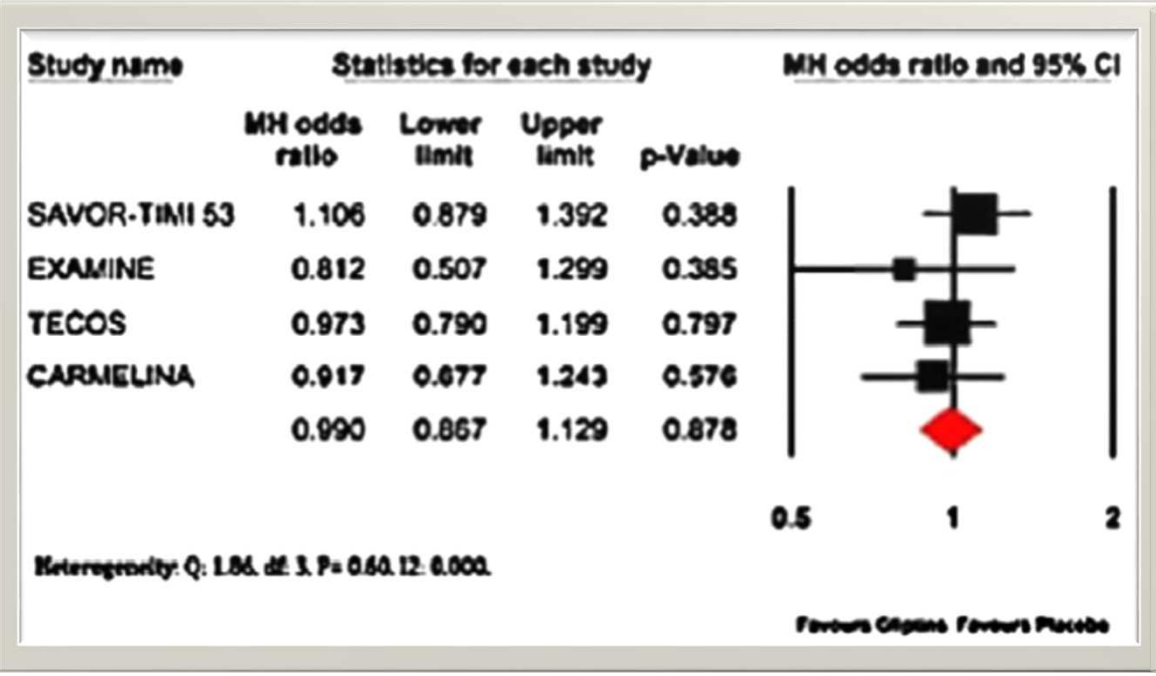
Données expérimentales plutôt positives , ROS, AGE, inflammation

Données cliniques : peu de résultats significatifs , plutôt à la hausse ou neutre

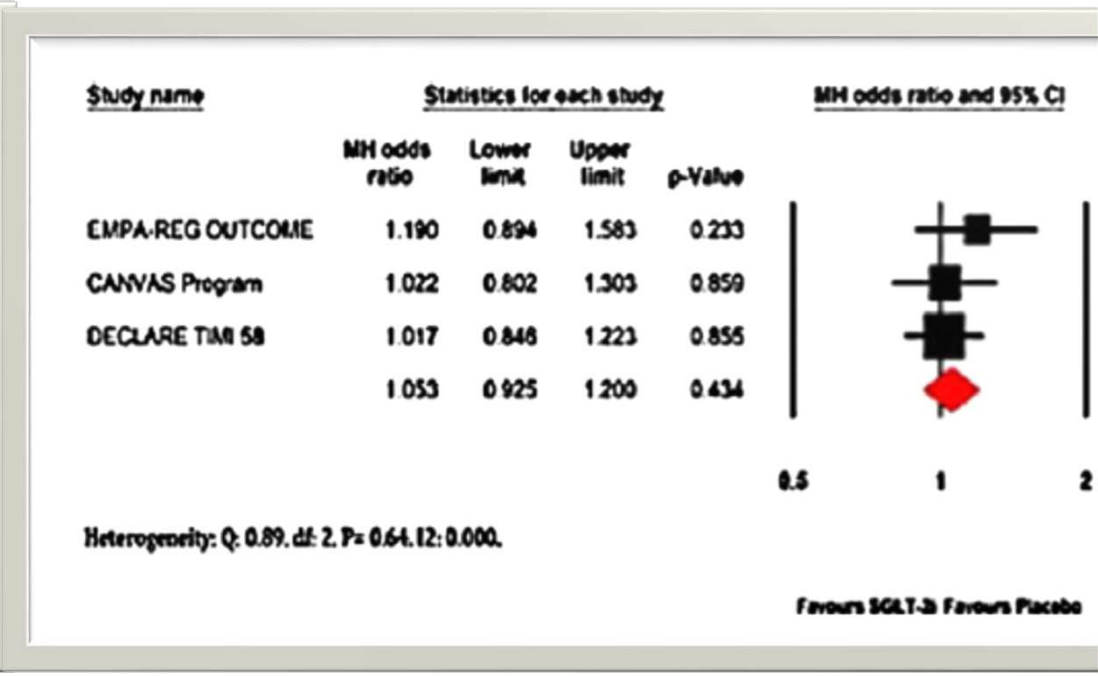
Scheen , Diabetes&Metabolism, 2017

META-ANALYSES

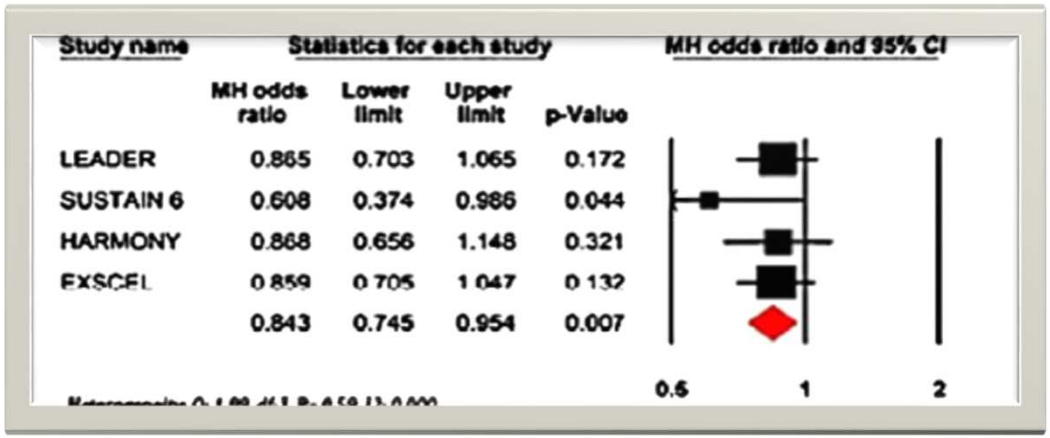
iDPP4



iSGLT2

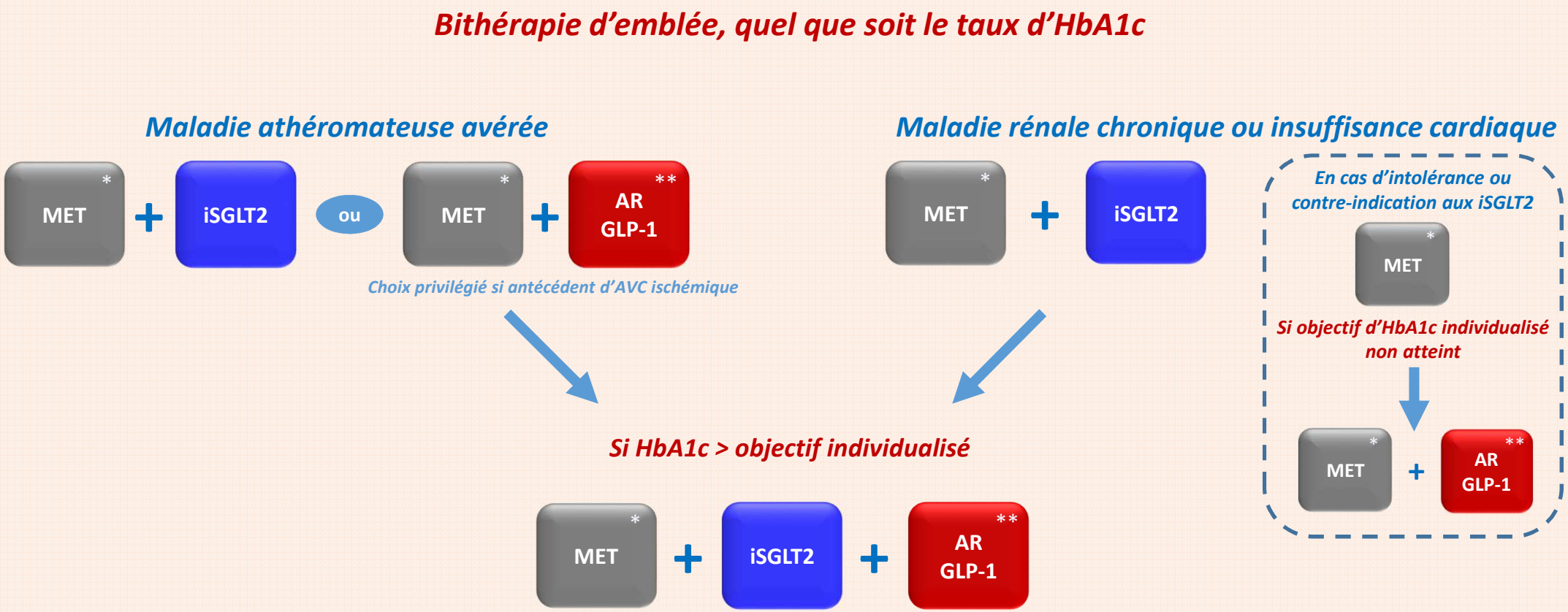


GLP1RA



Sina , Diab res Clin P,2019

Fig 7. Maladie athéromateuse avérée, maladie rénale chronique ou insuffisance cardiaque



** Ne pas utiliser la metformine en cas : d'insuffisance cardiaque décompensée (Stade IV NYHA), d'insuffisance rénale sévère (DFG < 30 ml/min/1.73 m²) et en phase aiguë d'IDM ou d'AVC*

*** Dans l'attente de nouvelles données, les AR GLP-1 devront être utilisés avec précaution en cas d'insuffisance cardiaque à fraction d'éjection diminuée (FEVG < 40%)*

Société francophone du diabète

COMMENTS AND OPINIONS

Benefits of GLP-1 (Glucagon-Like Peptide 1) Receptor Agonists for Stroke Reduction in Type 2 Diabetes: A Call to Action for Neurologists

Ronald M. Goldenberg, MD; Alice Y.Y. Cheng, MD; Tess Fitzpatrick, MD; Jeremy D. Gilbert, MD; Subodh Verma, MD, PhD; Julia J. Hopyan, MD

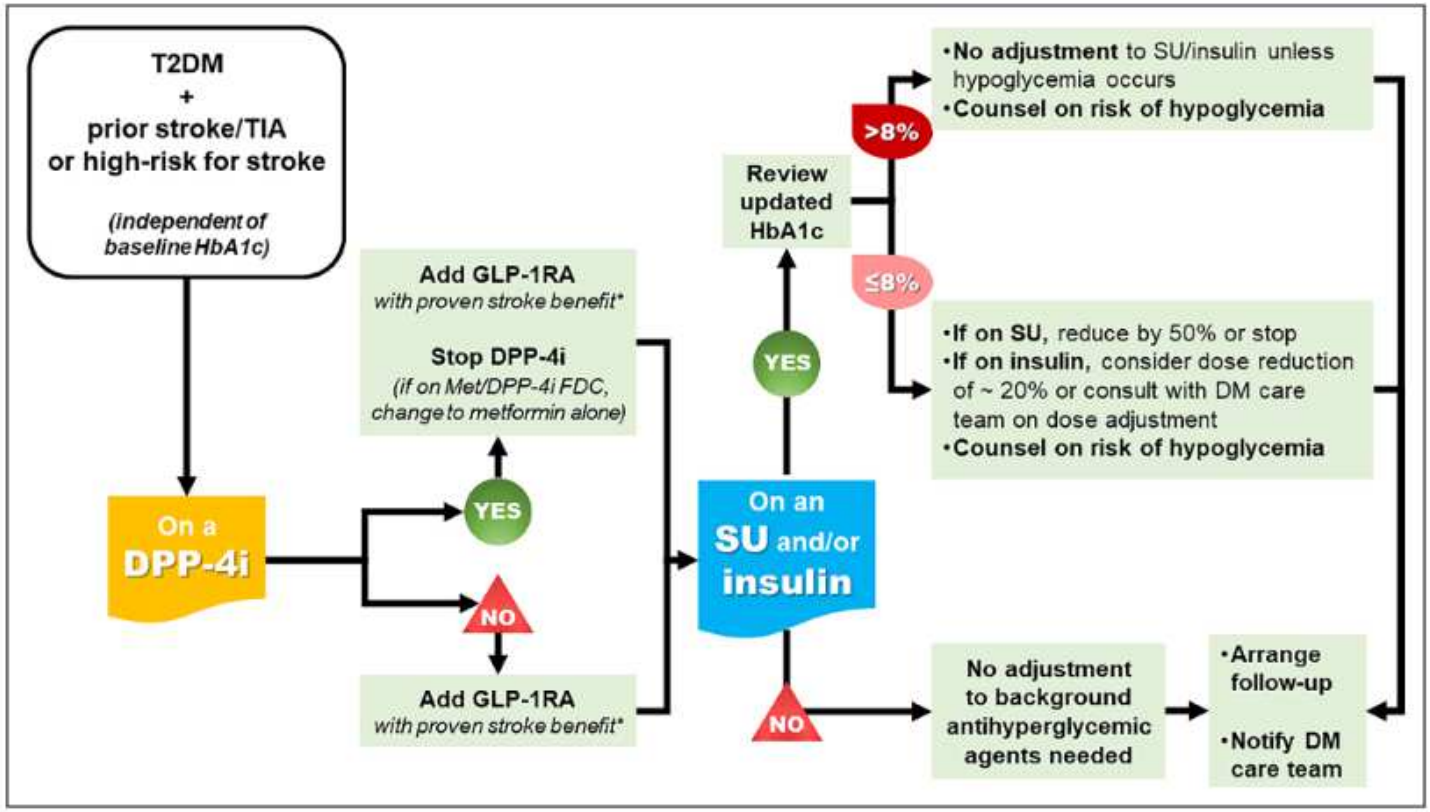
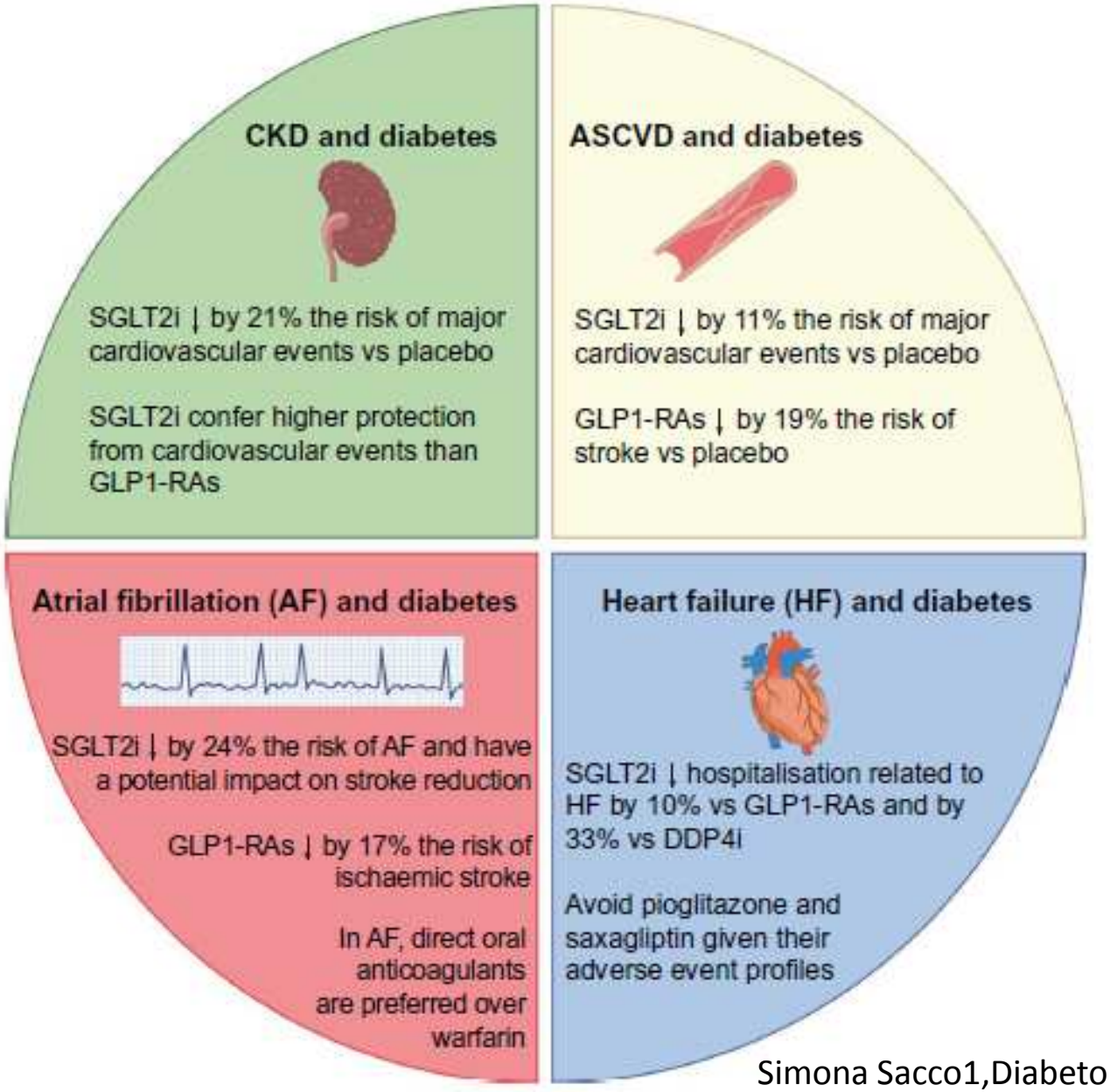


Figure 4. Proposed algorithm for prescribing GLP-1RAs (glucagon-like peptide 1 receptor agonists) for stroke prevention in type 2 diabetes.

Stroke 2022



Simona Sacco1,Diabetologia (2024) 67:1192–1205

Étude observationnelle française des patients DT2 avec AVC 2012-2018

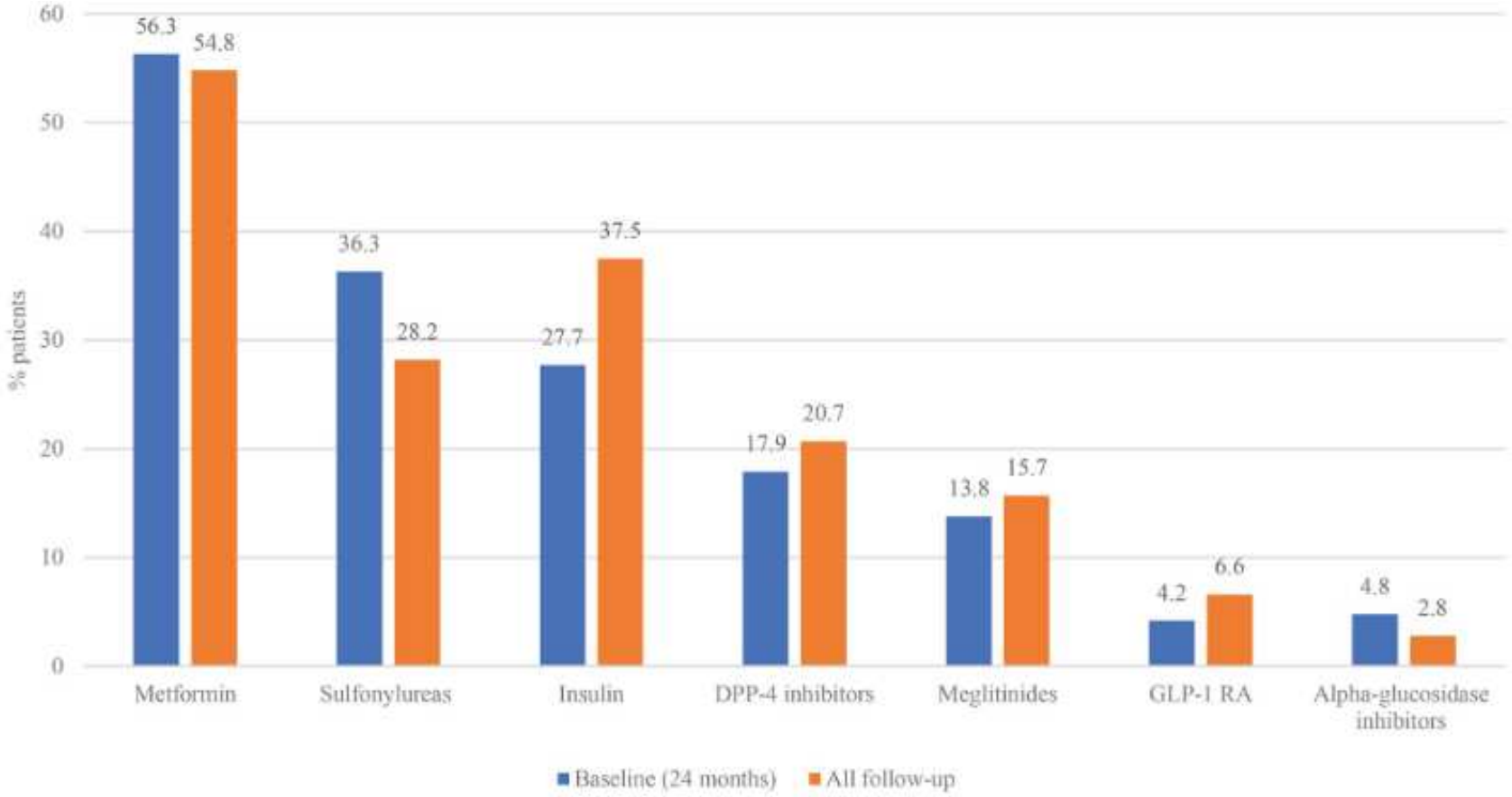


FIg. 3 Use of diabetes treatment before and after index stroke hospitalization. *DPP-4* dipeptidyl peptidase, *4 GLP-1* Glucagon-like peptide-1, *PAD* peripheral arterial disease, *RA* receptor agonist

Mohammedi et al. Cardiovascular Diabetology (2024) 23:183

Conclusions

- Prise en charge de l’ AVC chez le patient diabétique
  - Prise en charge globale multifactorielle
- Choix des molécules anti hyperglycémiants :
  - Elément à prendre en considération en fonction du risque CV