Le bénéfice CV des nouveaux hypoglycémiants est-il la principale raison pour les initier ?

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Divulgations

Recherche subventionnée: Novartis, Boehringer-Ingelheim, Astra-Zeneca

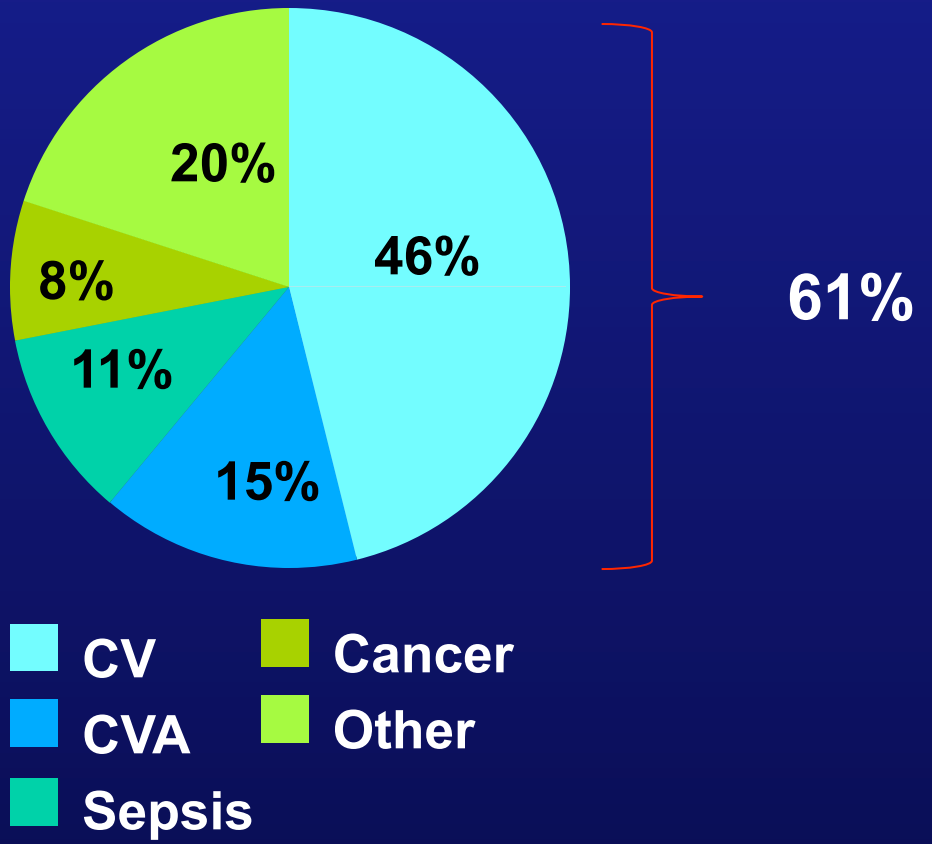
Conférences: Merck, Abbott, Servier, Tribute, Boehringer-Ingelheim, Sanofi, Janssen, Bayer, Pfizer, Valeant

Comité aviseur: Merck, Abbott, Amgen, Bayer, Takeda, Servier, Boehringer-Ingelheim, Jansen, Sanofi, Valeant

Objectifs

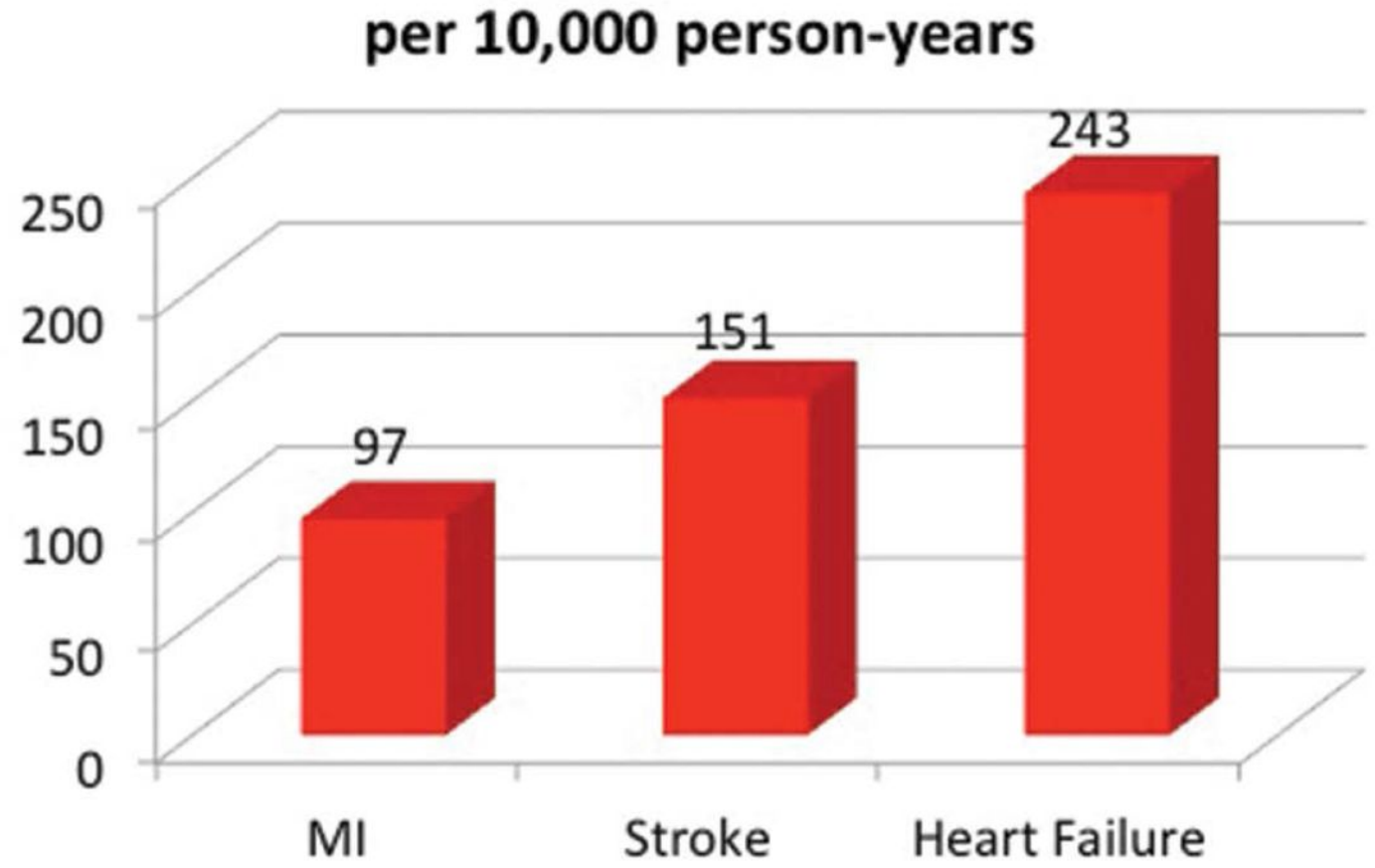
- Connaître les bénéfices des nouveaux hypoglycémiants dans la prévention secondaire des maladies cardiovasculaires.
- Décrire les effets des nouveaux hypoglycémiants sur les accidents vasculaires cérébraux.
- Discuter de l'innocuité des hypoglycémiants en insuffisance cardiaque.

Causes de décès en diabète



Hux JE, et al. Diabetes in Ontario, an ICES Practice Atlas 2003.

This figure illustrates the importance of heart failure consideration in primary endpoint trials with antihyperglycemic agents.



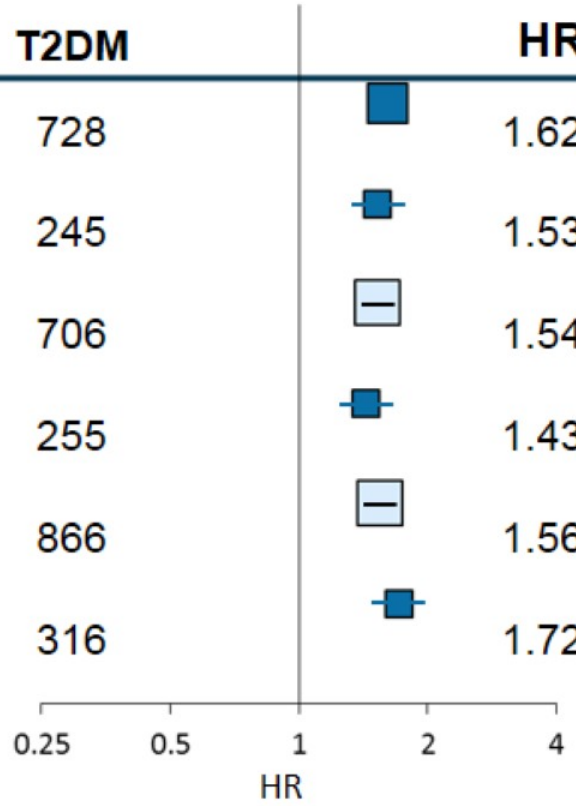
Vani P. Sanon et al. Clin Diabetes 2014;32:121-126

American Diabetes Association.

Association of T2DM With 6 Common CVDs/Events

Total cohort: n = 1,921,260
w/o T2DM: n = 1,887,062
w/ T2DM: n = 34,198

Initial Presentation of CVD	Number of Events: No Diabetes	Number of Events: T2DM	HR (95% CI)	*P* value
Stable angina	12,232	728	1.62 (1.49-1.77)	< .0001
UA	5286	245	1.53 (1.32-1.76)	< .0001
Nonfatal MI	15,191	706	1.54 (1.42-1.67)	< .0001
Unheralded coronary death	5101	255	1.43 (1.23-1.65)	< .0001
HF	13,072	866	1.56 (1.45-1.69)	< .0001
Ischemic stroke	5643	316	1.72 (1.52-1.95)	< .0001



Shah AD. *Lancet Diabetes Endocrinol.* 2015;3:105-113.

Événements macrovasculaires et maîtrise glycémique

	Études DCCT et EDIC (DCCT n = 1 441)[1] (EDIC n = 1 375)		Étude UKPDS[2] (n = 3 867)		Étude ADVANCE[3] (n = 11 140)		Étude VADT[4] (n = 1 791)		Étude ACCORD[5] (n = 10 251)	
	Étude initiale 6,5 ans	*Prolongation 17 ans*	*Étude initiale 10 ans*	*Prolongation 20 ans*	*Étude initiale 4,5 ans*	*Prolongation 10 ans*	*Étude initiale 5,6 ans*	*Prolongation 9,8 ans*	*Étude initiale 3,7 ans*	*Prolongation 8,8 ans*
Taux d'HbA_{1C} atteint (%)*	*7,2 vs 9,1*		7,0 *vs* 7,9		6,5 *vs* 7,3		6,9 *vs* 8,4		6,4 *vs* 7,5	
Infarctus du myocarde (RRI)			NS		NS				↓ 0,76	
Mortalité CV (RRI)			NS		NS		NS		↑ 1,35	
Toutes les complications macrovasculaires (RRI)	NS		NS		NS		NS		NS	

*Taux moyen d'HbA_{1C} atteint, traitement intensif *vs* traitement standard,
NS = non significatif; RRI = rapport des risques instantanés

1. DCCT Research Group. *N Engl J Med* 1993;329:977-86; DCCT/EDIC Study Research Group. *N Engl J Med* 2005;353:2643-53. 2. UKPDS Group. *Lancet* 1998;352:837–853; UKPDS Group. *Lancet* 1998;352:854-865; 3. ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–2572; ADVANCE-ON Collaborative Group. *N Engl J Med* 2014;371:1392-406; 4.Duckworth W, *et al. N Engl J Med* 2009;360:129–139; VADT Investigators. *N Engl J Med* 2015;372:2197-2206; 5.Ismail-Beigi F, *et al. Lancet* 2010; 376:419-30.; The ACCORD Study Group. *N Engl J Med* 2011;364:818-28.

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Taux d'HbA_{1C} atteint (%)*	*7,2 vs 9,1*		7,0 *vs* 7,9		6,5 *vs* 7,3		6,9 *vs* 8,4		6,4 *vs* 7,5	
Infarctus du myocarde (RRI)			NS	↓ 0,85	NS	NS			↓ 0,76	NS
Mortalité CV (RRI)			NS	↓ 0,87 (mortalité totale)	NS	NS	NS	NS	↑ 1,35	↑ 1,20
Toutes les complications macrovasculaires (RRI)	NS	↓ 0,43	NS		NS	NS	NS	↓ 0,83	NS	NS

*Taux moyen d'HbA_{1C} atteint, traitement intensif *vs* traitement standard
NS = non significatif, RRI = rapport des risques instantanés

1. DCCT Research Group. *N Engl J Med* 1993;329:977-86; DCCT/EDIC Study Research Group. *N Engl J Med* 2005;353:2643-53. 2. UKPDS Group. *Lancet* 1998;352:837–853; UKPDS Group. *Lancet* 1998;352:854-865; 3. ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–2572; ADVANCE-ON Collaborative Group. *N Engl J Med* 2014;371:1392-406; 4.Duckworth W, *et al. N Engl J Med* 2009;360:129–139; VADT Investigators. *N Engl J Med* 2015;372:2197-2206; 5. Ismail-Beigi F, *et al. Lancet* 2010; 376:419-30.; The ACCORD Study Group. *N Engl J Med* 2011;364:818-28.

Résumé des paramètres d'évaluation primaires
Risque relatif d'événements CV *vs* un placebo

Études distinctes, ne sont pas des comparaisons directes.

		Médicament à l'étude n/N (%)	Placebo n/N (%)	Rapport des risques instantanés	IC à 95 %	Valeur *p*
Inhibiteurs de la DPP-4	EXAMINE (alogliptine *vs* placebo)	305/2701 (11,3 %)	316/2679 (11,8 %)	0,96	NA*, 1,16	0,315 †
	SAVOR-TIMI 53 (saxagliptine *vs* placebo)	613/8280 (7,4 %)	609/8212 (7,4 %)	1,00	0,89, 1,12	0,99 †
	TECOS (sitagliptine *vs* placebo)	839/7332 (11,4 %)	851/7339 (11,6 %)	0,98	0,89, 1,08	0,65 †
Agonistes des récepteurs du GLP-1	ELIXA (lixisénatide *vs* placebo)	406/3034 (13,4 %)	399/3034 (13,2 %)	1,02	0,89, 1,17	< 0,001 (pour la non infériorité)
	LEADER (liraglutide *vs* placebo	608/4668 (13%)	694/4672 (14,9%)	0,87	0,78, 0,97	0,01†

Peterson ED. Results from the Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS). American Diabetes Association, 75e séance scientifique, du 5 au 9 juin 2015, Boston, MA; SAVOR-TIMI 53 : Scirica BM, *et al. N Engl J Med*. 2013;369:1317-26; EXAMINE : White WB, *et al. N Engl J Med*. 2013;369:1327-35; TECOS : Green JB *et al. N Engl J Med*. 2015. doi: 10.1056/NEJMoa1501352; Marso S, *et al*. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. Juin 2016 doi: 10.1056/NEJMoa1603827.

Quel est l'impact des nouveaux antihyperglycémiants sur la prévention des évènements cérébrovasculaires ?

TECOS
Major Secondary Endpoints

	Placebo (N=7266)	Sitagliptin (N=7250)	Hazard Ratio (95% CI)	P Value
	n (%)			
Secondary end point				
CV death	366 (5.0)	380 (5.2)	1.03 (0.89–1.19)	0.71
Hospitalization for unstable angina	129 (1.8)	116 (1.6)	0.90 (0.70-1.16)	0.42
Fatal or non-fatal MI	316 (4.3)	300 (4.1)	0.95 (0.81-1.11)	0.49
Fatal or non-fatal stroke	183 (2.5)	178 (2.4)	0.97 (0.79-1.19)	0.76
Death from any cause	537 (7.3)	547 (7.5)	1.01 (0.90-1.14)	0.88
Hospitalization for heart failure	229 (3.1)	228 (3.1)	1.00 (0.83-1.20)	0.98

CV = cardiovascular; MI = myocardial infarction; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Green JB et al. *N Engl J Med.* 2015 doi: 10.1056/NEJMoa1501352.

SAVOR-TIMI 53
Major Secondary Endpoints

Cardiovascular Endpoints	Placebo (N=8212)	Saxagliptin (N=8280)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Death from cardiovascular causes	260 (2.9)	269 (3.2)	1.03 (0.87–1.22)	0.72
Myocardial infarction	278 (3.4)	265 (3.2)	0.95 (0.80–1.12)	0.52
Ischemic stroke	141 (1.7)	157 (1.9)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	81 (1.0)	97 (1.2)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	228 (2.8)	289 (3.5)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	459 (5.6)	423 (5.2)	0.91 (0.80–1.04)	0.18

CI = confidence interval; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53 .

Scirica BM *et al. N Engl J Med*. 2013;369:1317-26.

EXAMINE
Major Safety Endpoints

	Placebo (N=2679)	Alogliptin (N=2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value*
	no. (%)			
Components of primary endpoint				
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)	0.10
Non-fatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)	0.47
Non-fatal stroke	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)	0.71
Principal secondary end-point§	359 (13.4)	344 (12.7)	0.95 (≤1.14)‡	0.26
Other end-points				
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)	0.23
Death from cardiovascular causes¶	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)	0.21
Hospital admission for heart failure	89 (3.3)	106 (3.9)	1.19 (0.90–1.58)	0.22

*P values for testing the superiority of alogliptin to placebo were calculated with the use of a Cox regression analysis.
‡ The parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01.
§ The secondary endpoint was a composite of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or urgent revascularization due to unstable angina within 24 hours after hospital admission.
¶ Included are deaths that occurred as primary end-point events and deaths that occurred after a non-fatal primary end-point event.
CI = confidence interval
White WB *et al. N Engl J Med.* 2013;369:1327-35.; Zannad F et al. *Lancet.* 2015;385:2067-76.

ELIXA

Table 2. Incidence Rates and Hazard Ratios, with Adjustment for Geographic Region, for the Primary Composite End Point, Its Components, and Other Efficacy Outcomes.

End Point	Placebo (N=3034)		Lixisenatide (N=3034)		Adjusted Hazard Ratio (95% CI)	P Value
	Patients with Event	No. of Events/ 100 Patient-Yr	Patients with Event	No. of Events/ 100 Patient-Yr		
Primary end point: death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, or unstable angina — no. (%)	399 (13.2)	6.3	406 (13.4)	6.4	1.02 (0.89–1.17)	0.81
Components of primary end point — no./total no. (%)						
Death from cardiovascular causes	93/399 (23.3)	—	88/406 (21.7)	—	—	—
Nonfatal myocardial infarction	247/399 (61.9)	—	255/406 (62.8)	—	—	—
Nonfatal stroke	49/399 (12.3)	—	54/406 (13.3)	—	—	—
Unstable angina	10/399 (2.5)	—	9/406 (2.2)	—	—	—
Patients with each primary end-point event — no. (%)*						
Death from cardiovascular causes	158 (5.2)	2.4	156 (5.1)	2.3	0.98 (0.78–1.22)	0.85
Myocardial infarction	261 (8.6)	4.1	270 (8.9)	4.2	1.03 (0.87–1.22)	0.71
Stroke	60 (2.0)	0.9	67 (2.2)	1.0	1.12 (0.79–1.58)	0.54
Unstable angina	10 (0.3)	0.1	11 (0.4)	0.2	1.11 (0.47–2.62)	0.81
Secondary end points — no. (%)						
Primary end-point event or hospitalization for heart failure	469 (15.5)	7.6	456 (15.0)	7.3	0.97 (0.85–1.10)	0.63
Primary end-point event, hospitalization for heart failure, or revascularization	659 (21.7)	11.2	661 (21.8)	11.1	1.00 (0.90–1.11)	0.96
Additional end points — no. (%)						
Hospitalization for heart failure	127 (4.2)	1.9	122 (4.0)	1.8	0.96 (0.75–1.23)	0.75
Death from any cause	223 (7.4)	3.3	211 (7.0)	3.1	0.94 (0.78–1.13)	0.50

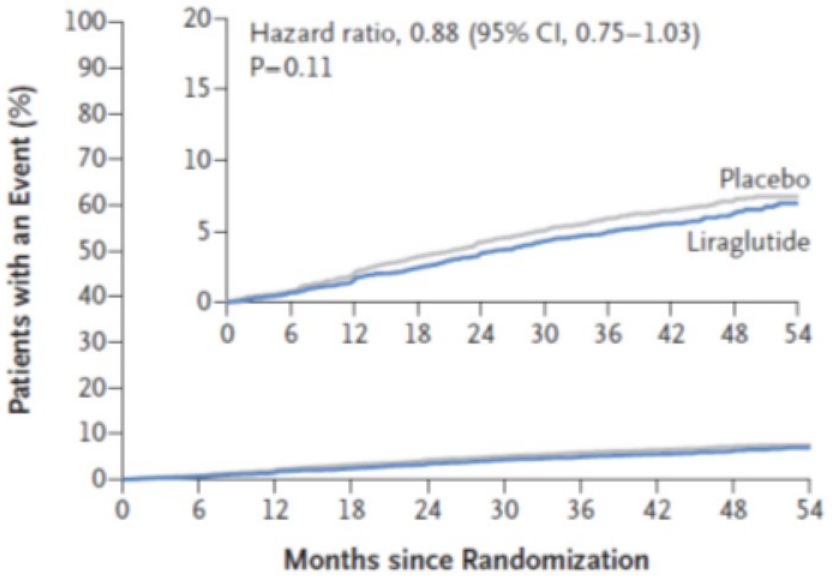
* Some patients had more than one component of the primary end point. In the analyses for the separate components, they were included once for each end point they had, regardless of whether it was their first event.

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

The NEW ENGLAND JOURNAL of MEDICINE

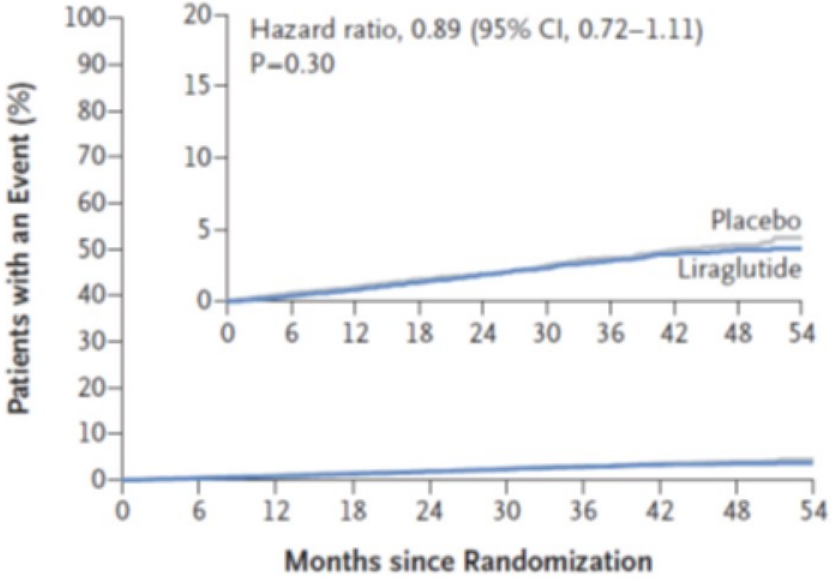
LEADER: Time to Nonfatal MI and Nonfatal Stroke

Nonfatal MI



No. at Risk										
Liraglutide	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Placebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

Nonfatal Stroke



No. at Risk										
Liraglutide	4668	4624	4564	4504	4426	4351	4269	4194	1662	465
Placebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	445

Marso SP, et al. LEADER Trial Investigators. *N Engl J Med.* 2016 Jun 13. [Epub ahead of print]

SUSTAIN-6

Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

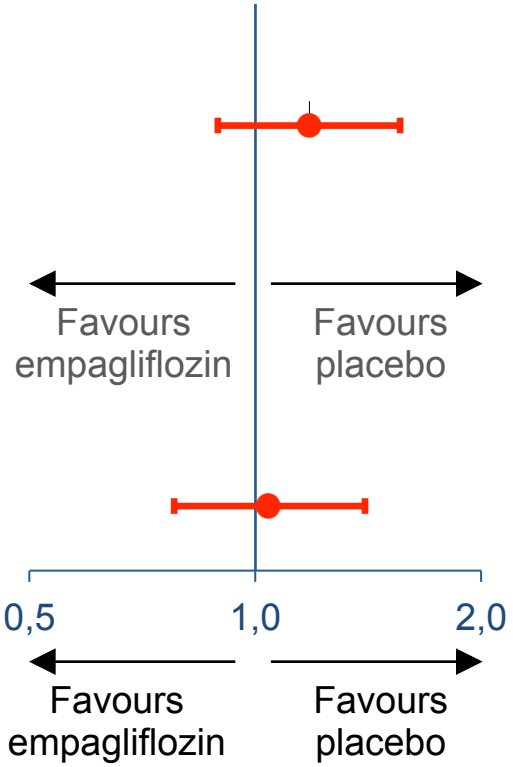
Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

N Engl J Med 2016; 375:1834-1844

Fatal and non-fatal stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
Intent-to-treat population					
	164/4687	69/2333	1.18	(0.89, 1.56)	0.2567
On-treatment analysis*					
	141/4607	66/2308	1.04	(0.78, 1.40)	0.7849

Numerical difference largely driven by events occurring >30 days after treatment stop



Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio;
*Excluding events >30 days after last intake of study drug and patients who received study drug for <30 days (cumulative)

Zinman B *et al*. *N Engl J Med* 2015;373:2117;

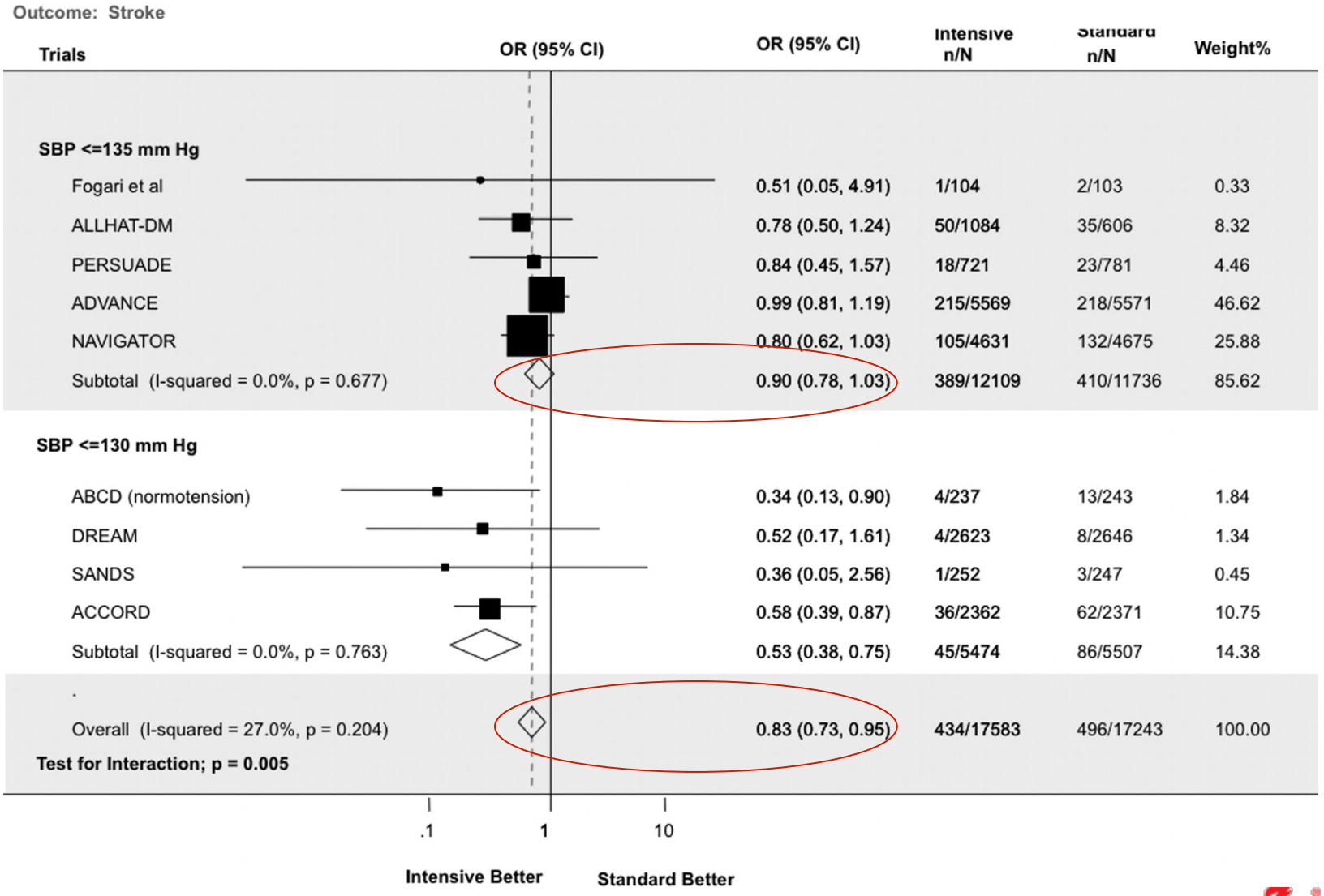
The majority of events that contributed to the overall numerical differences in stroke rates between empagliflozin and placebo occurred more than 3 months after patients had stopped taking study medication

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
30–60 days after last intake of trial medication	0	1 (on day 42)	1 (on day 39)
60–90 days after last intake of trial medication	0	0	1 (on day 69)
>90 days after last intake of trial medication	3	11	7

- No plausible association of empagliflozin and stroke >90 days after last intake of drug
- On-treatment analysis supports the conclusion that the numerical difference in the intention-to-treat analysis is not related to empagliflozin

Data are n (%) in the treated set
Data on File. CONFIDENTIAL

Intensive versus standard blood pressure control and stroke.



Bangalore S et al. Circulation 2011;123:2799-2810

Quel est l'impact des nouveaux antihyperglycémiants sur la prévention de l'insuffisance cardiaque ?

Diabète et insuffisance cardiaque

§ Les personnes atteintes de diabète ont un risque de 2 à 5 fois plus ? d'insuffisance cardiaque.
- Coronaropathie concomitante
- Cardiomyopathie diabétique / ischémique
- Hypertension
- Expansion du volume du liquide extracellulaire
- Néphropathie concomitante

§ Facteurs de risque d'hospitalisation en raison d'une insuffisance cardiaque :
- Antécédents d'insuffisance cardiaque
- Dysfonction rénale (DFGe ≤ 60 mL/min) ou
- Élévation du taux de NT-proBNP au départ

⇒ Chaque 1% ↑ du A1C engendre une ↑ 8% de l'insuffisance cardiaque

NP, peptide natriurétique

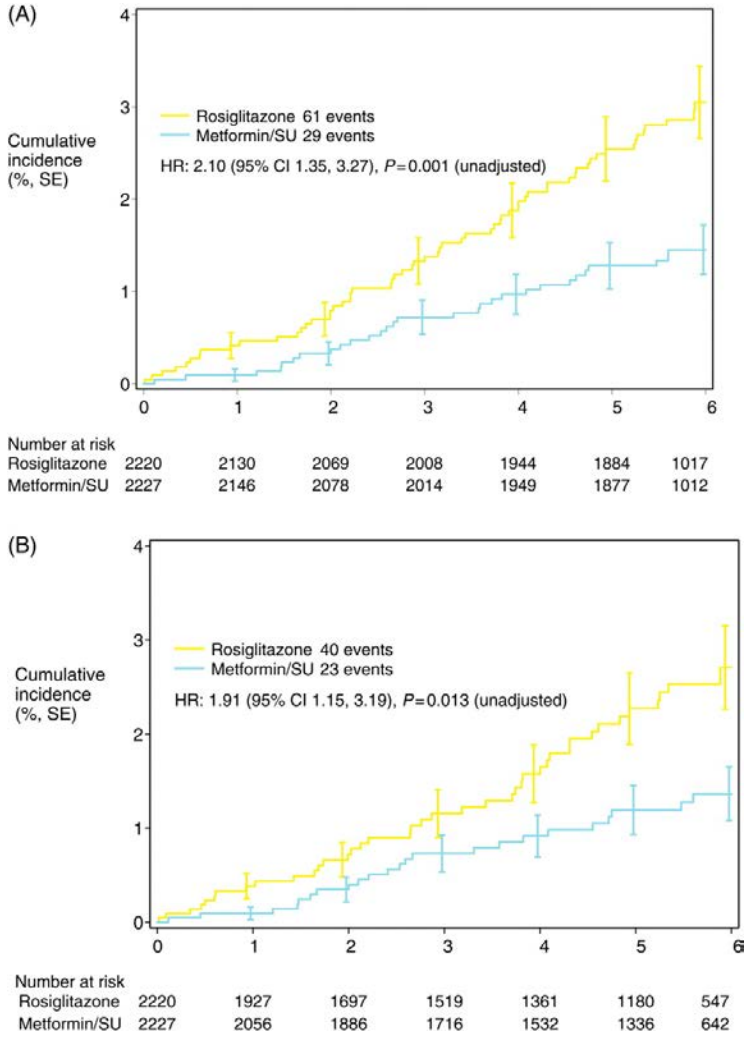
Gilbert RE, Krum H. *Lancet* 2015;385:2107-17; Bhatt DL, Cavender MA. JACC: *Heart Fail* 2014;2:583-5 ; Kannel WB, *et al*. *Am J Cardiol* 1974;34:29.

Les raisons possibles susceptibles d'expliquer les différences de résultats sur l'insuffisance cardiaque entre les études EXAMINE, SAVOR-TIMI 53 et TECOS peuvent inclure :

- Les différences entre les patients admis aux études
- Les différences entre les soins de base fournis
- Les variations dans la définition et la consignation des événements liés à l'insuffisance cardiaque entre les études
- Les différences pharmacologiques intrinsèques entre les inhibiteurs de la DPP-4
- L'effet du hasard

Peterson ED. Results from the Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS). American Diabetes Association, 75e séance scientifique,
du 5 au 9 juin 2015, Boston, MA;
Krum H, *et al. European J Heart Fail* 2014;16:603-607

Kaplan–Meier plots of time to heart failure (fatal or non-fatal) in the RECORD study (yellow, rosiglitazone group, blue, active control group).



Michel Komajda et al. Eur Heart J 2010;31:824-831

European Heart Journal

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

	Pioglitazone (n=2605)		Placebo (n=2633)		p
	Number of events	Number of patients	Number of events	Number of patients	
Any report of heart failure*	417	281 (11%)	302	198 (8%)	<0·0001
Heart failure not needing hospital admission*	160	132 (5%)	117	90 (3%)	0·003
Heart failure needing hospital admission*	209	149 (6%)	153	108 (4%)	0·007
Fatal heart failure†	25	25 (1%)	22	22 (1%)	0·634

*Not adjudicated. †Adjudicated cause of death.

Table 9: **Reports of heart failure**

The Lancet,2005, 366.9493

Hospitalisation pour insuffisance cardiaque Études EXAMINE, SAVOR-TIMI 53, TECOS, ELIXA, LEADER et SUSTAIN-6

Études distinctes, ne sont pas des comparaisons directes.

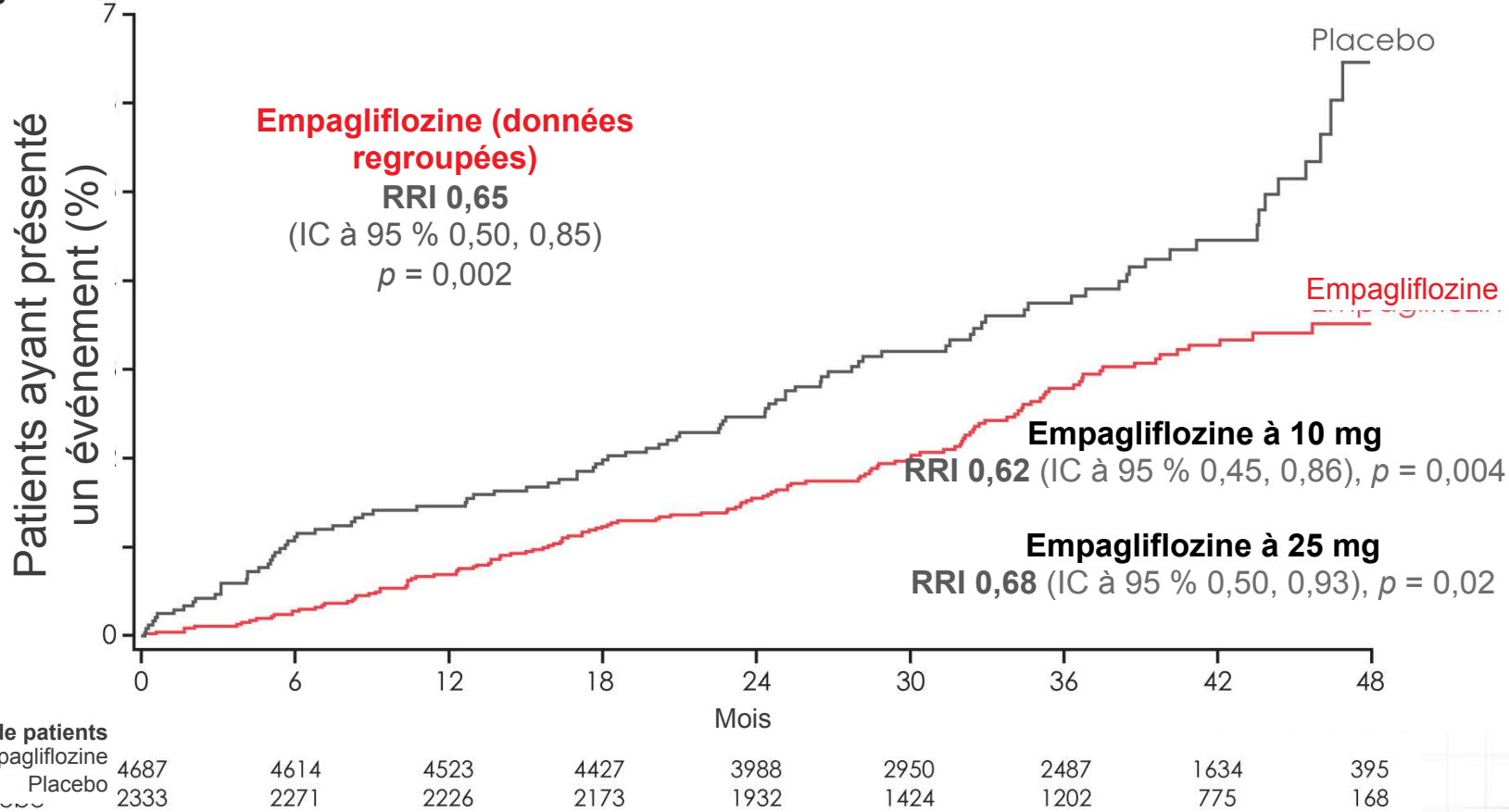
		Médicament à l'étude n/N (%)	Placebo n/N (%)	Rapport des risques instantanés	IC à 95 %	Valeur *p*
Inhibiteurs de la DPP-4	**EXAMINE** (alogliptine *vs* placebo)	106/2701 (3,9 %)	89/2679 (3,3 %)	1,19	0,90, 1,58	0,220
	SAVOR-TIMI 53 (saxagliptine *vs* placebo)	289/8280 (3,5 %)	228/8212 (2,8 %)	1,27	1,07, 1,51	0,007
	TECOS (sitagliptine *vs* placebo)	228/7332 (3,1 %)	229/7339 (3,1 %)	1,00	0,83, 1,20	0,983
Agonistes des récepteurs du GLP-1	**ELIXA** (lixisénatide *vs* placebo)	122/3034 (4,0 %)	127/3034 (4,2 %)	0,96	0,75, 1,23	NS
	LEADER (liraglutide *vs* plabebo)	218/4668 (4,7%)	248/4672 (5,3%)	0,87	0,73, 1,05	0,14
	SUSTAIN-6 (semaglutide vs placebo)	59/1648 (3,6%)	54/1649 (3,3%)	1,11	0,77, 1,61	0,57

IC = intervalle de confiance

Peterson ED. Results from the Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS). American Diabetes Association, 75e séance scientifique, du 5 au 9 juin 2015, Boston, MA; SAVOR-TIMI 53 : Scirica BM, *et al. N Engl J Med*. 2013;369:1317-26; EXAMINE : Zannad F *et al. Lancet*. 2015;385:2067-76; TECOS: Green JB *et al. N Engl J Med*. 2015;373:232-42; Marso S, *et al*. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. Juin 2016 doi: 10.1056/NEJMoa1603827; Marso S et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes *N Engl J Med* septembre 2016 doi: 10.1056/NEJMoa1607141.

EMPA-REG OUTCOME
Hospitalisation en raison d'une insuffisance cardiaque

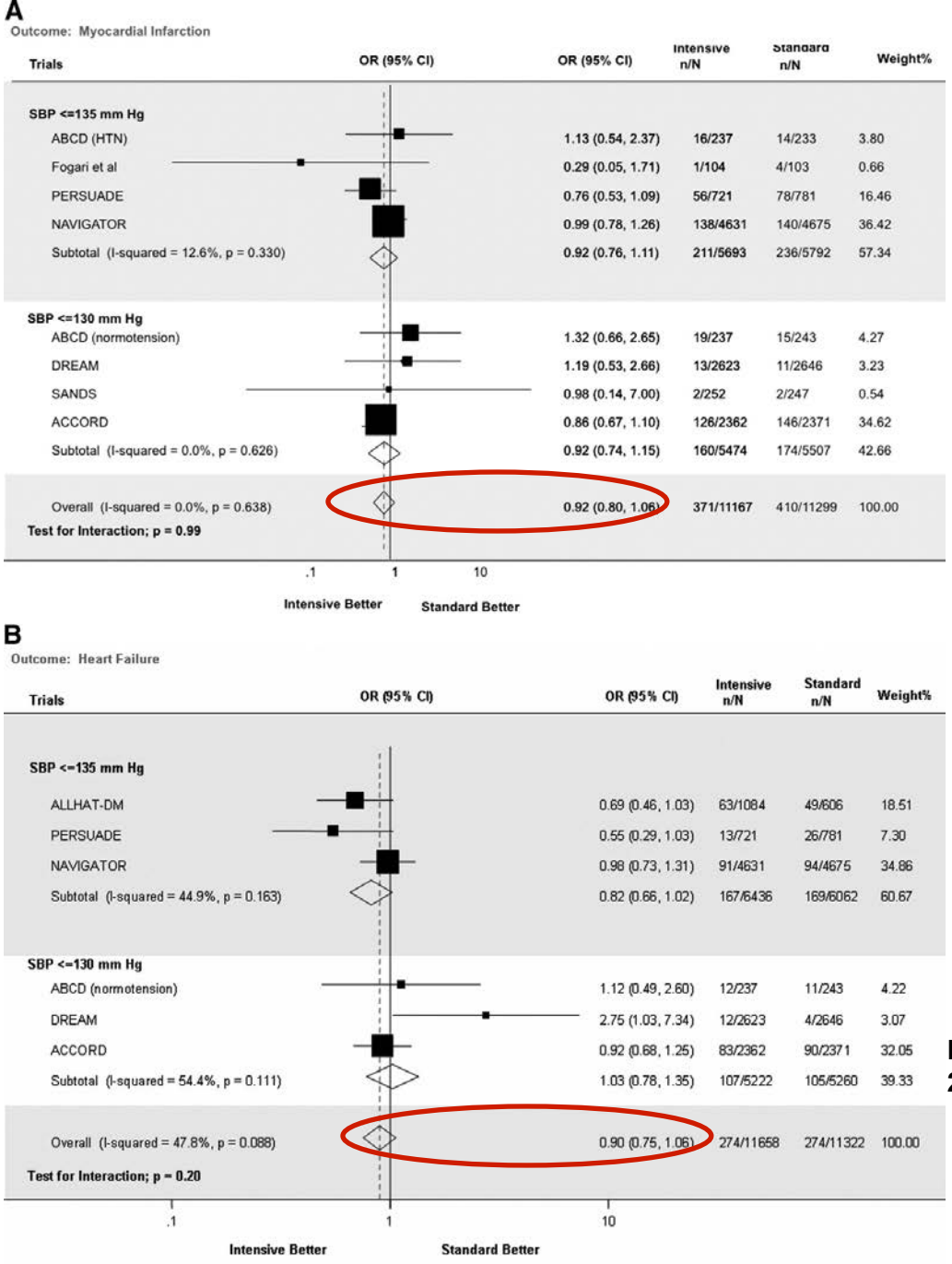
Les investigateurs ont été encouragés à traiter les facteurs de risque CV pour atteindre les meilleures normes de soins conformément aux lignes directrices régionales.



Fonction d'incidence cumulée. RRI, rapport des risques instantanés

Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. Le 17 septembre, 2015. 10.1056/NEJMoa1504720

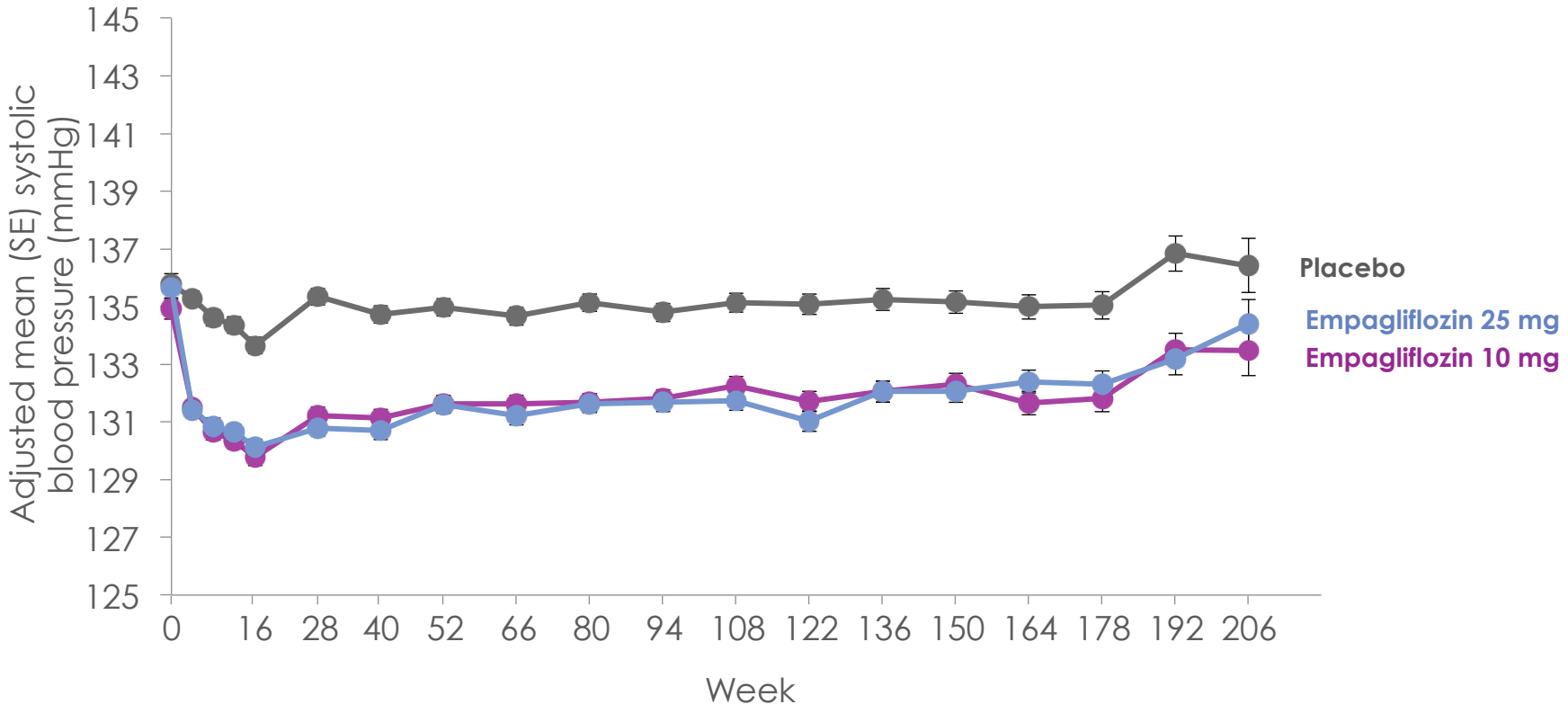
Intensive versus standard blood pressure control and (A) myocardial infarction and (B) heart failure



Bangalore S et al. Circulation 2011;123:2799-2810

American Heart Association
Learn and Live

Systolic blood pressure



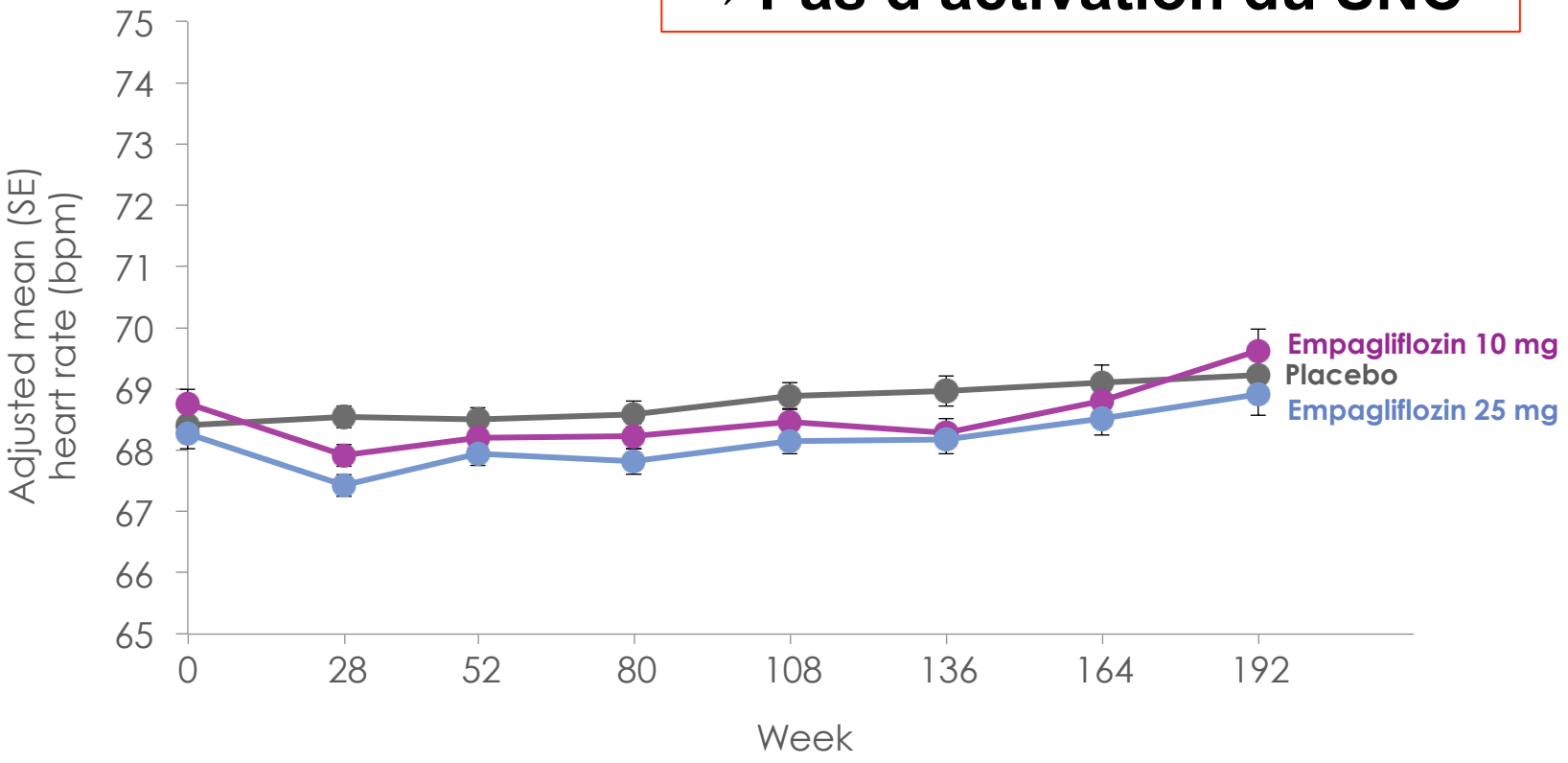
Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)
X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

EMPA-REG OUTCOME®

Heart rate (ECG)

→ Pas d'activation du SNC



Placebo	2174	2127	2032	1928	1796	1300	1002	552
Empagliflozin 10 mg	2205	2137	2064	2006	1877	1366	1045	597
Empagliflozin 25 mg	2192	2127	2066	2006	1907	1383	1086	633

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)
X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

EMPA-REG OUTCOME®

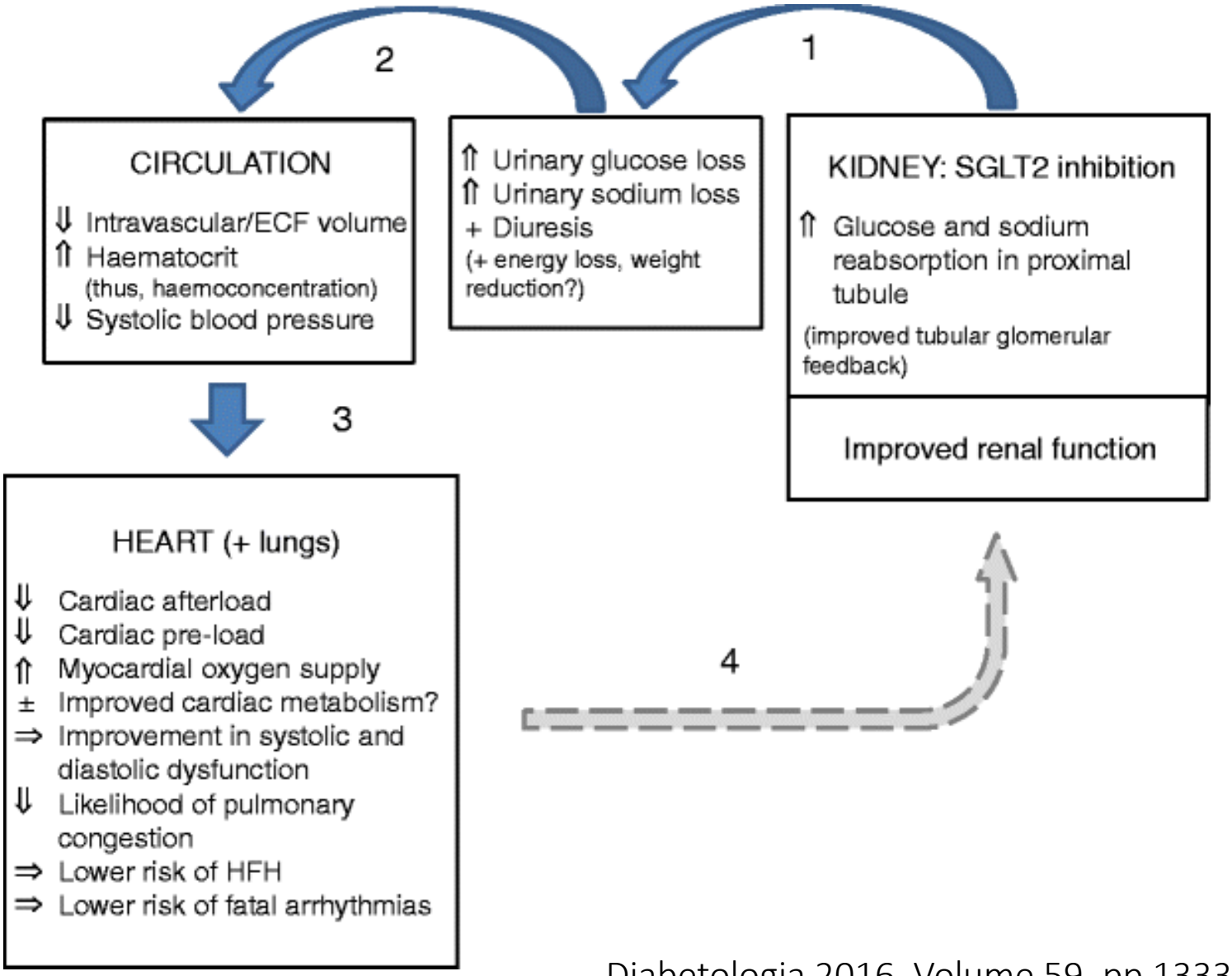
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Table S5. Categories of cardiovascular death.

	Placebo (N = 2333)	Empagliflozin 10 mg (N = 2345)	Empagliflozin 25 mg (N = 2342)	Pooled empagliflozin (N = 4687)
	no. (%)			
Patients with cardiovascular death	137 (5.9)	90 (3.8)	82 (3.5)	172 (3.7)
Sudden death	38 (1.6)	30 (1.3)	23 (1.0)	53 (1.1)
Worsening of heart failure	19 (0.8)	7 (0.3)	4 (0.2)	11 (0.2)
Acute myocardial infarction	11 (0.5)	6 (0.3)	9 (0.4)	15 (0.3)
Stroke	11 (0.5)	9 (0.4)	7 (0.3)	16 (0.3)
Cardiogenic shock	3 (0.1)	1 (<0.1)	2 (0.1)	3 (0.1)
Other cardiovascular death*	55 (2.4)	37 (1.6)	37 (1.6)	74 (1.6)

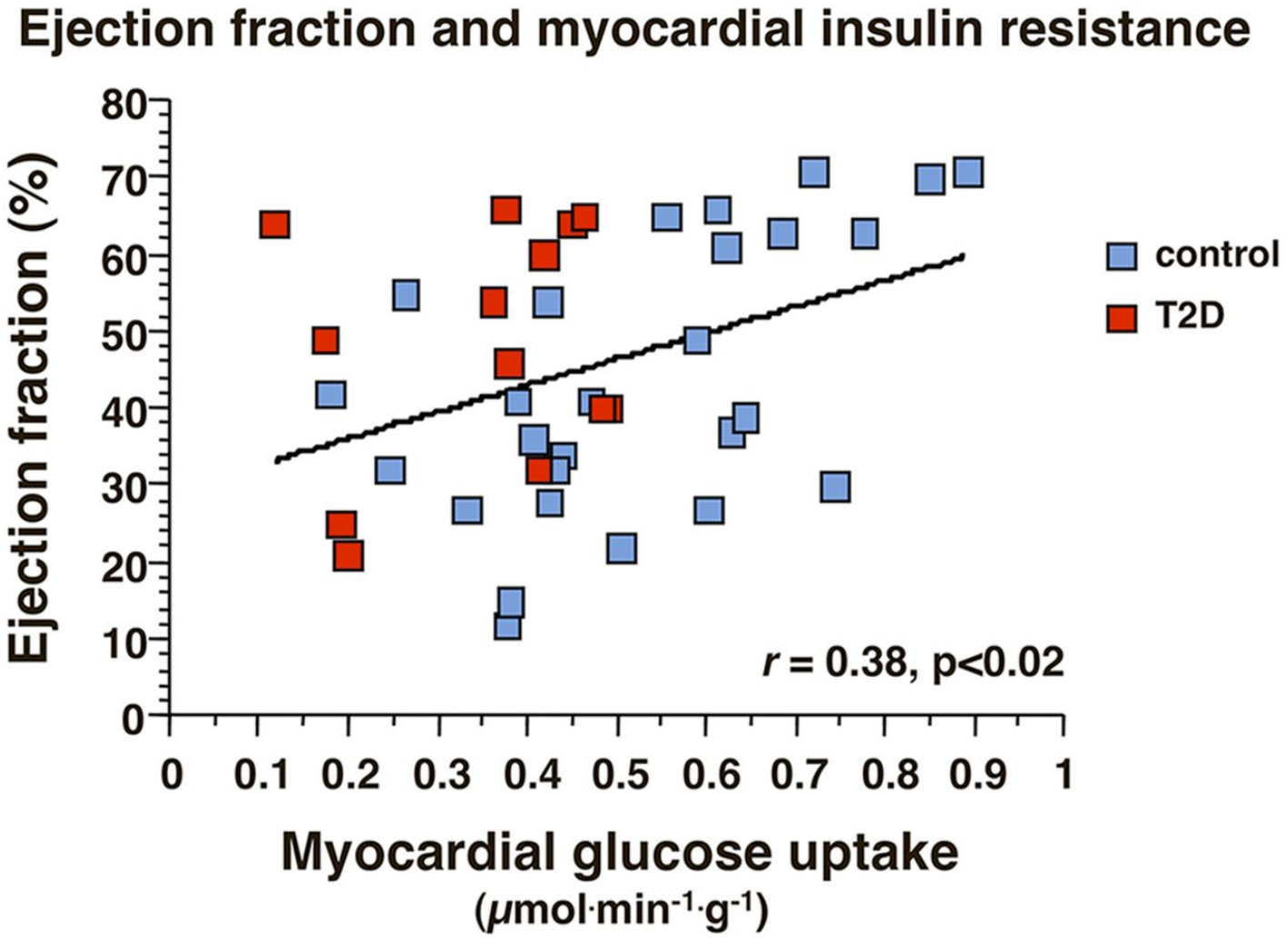
N Engl J Med 2015; 373:2117-2128

Potential pathway linking empagliflozin (and possibly other SGLT2 inhibitors) with lower risks for HFH (and, linked to this, death due to cardiovascular disease)



Diabetologia 2016, Volume 59, pp 1333–1339

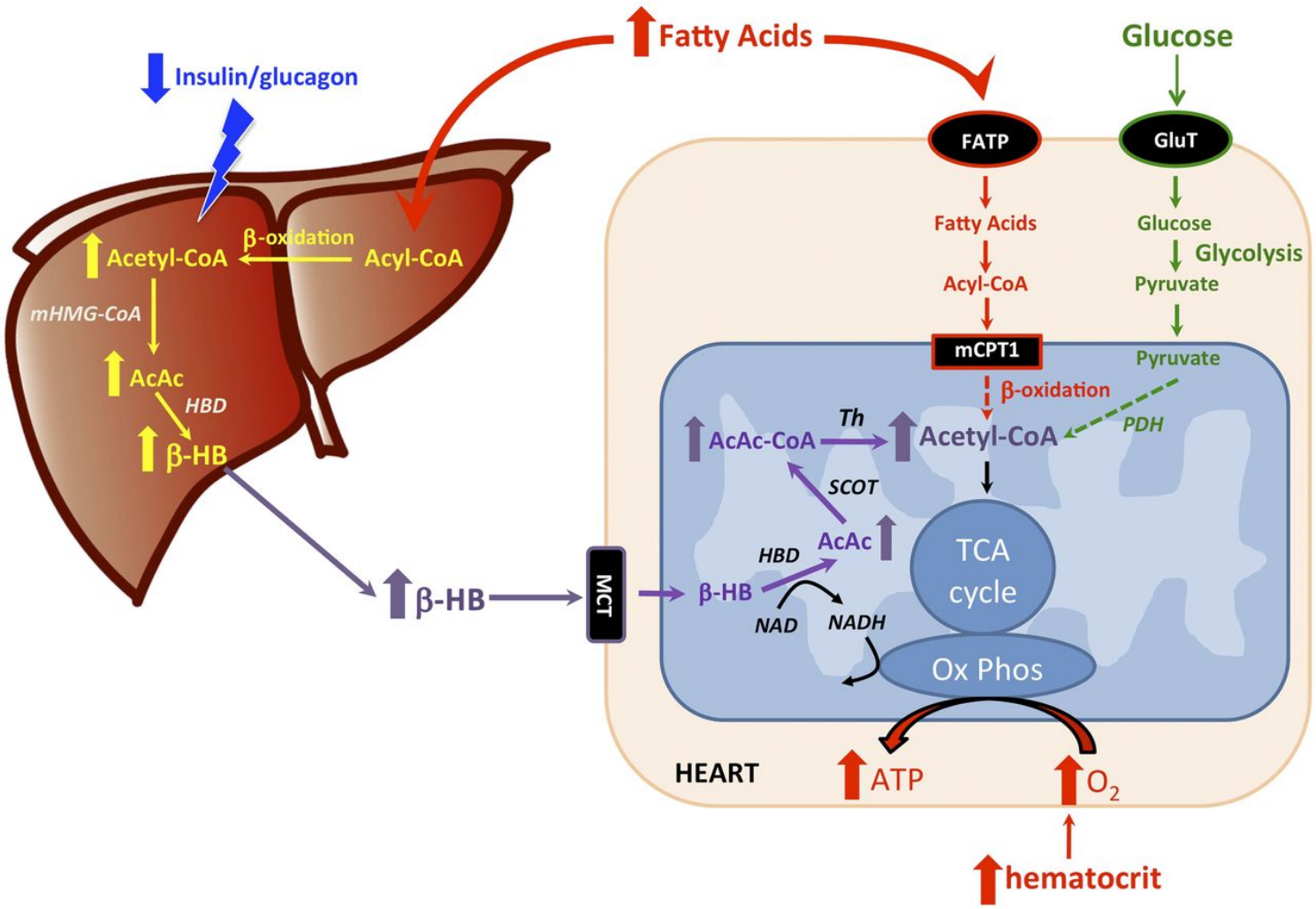
Direct association between insulin-induced myocardial glucose uptake and ejection fraction in control subjects and T2D patients.



Ele Ferrannini et al. Dia Care 2016;39:1108-1114

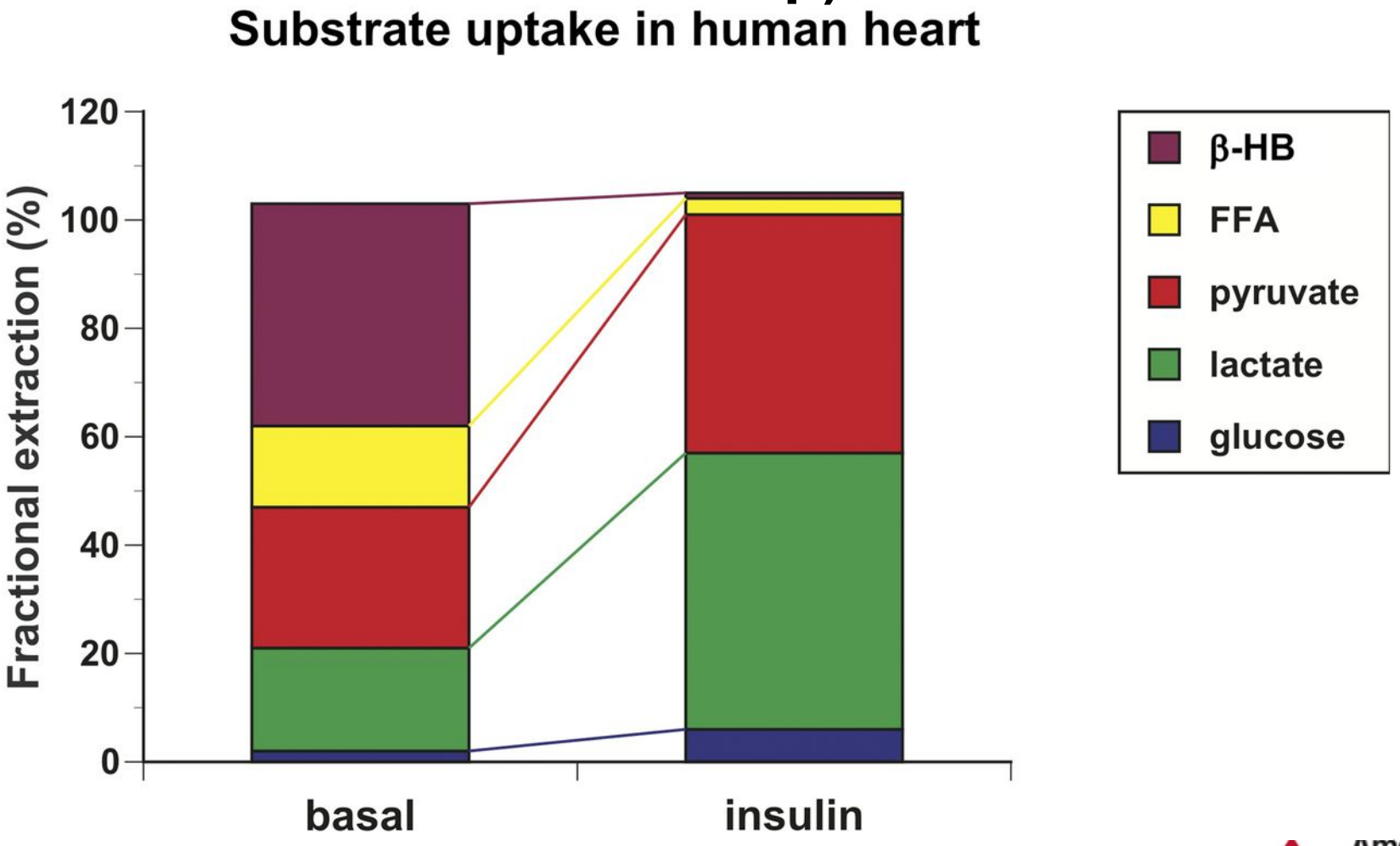
American Diabetes Association

Raised circulating FFAs are taken up by the liver and metabolized via β-oxidation.



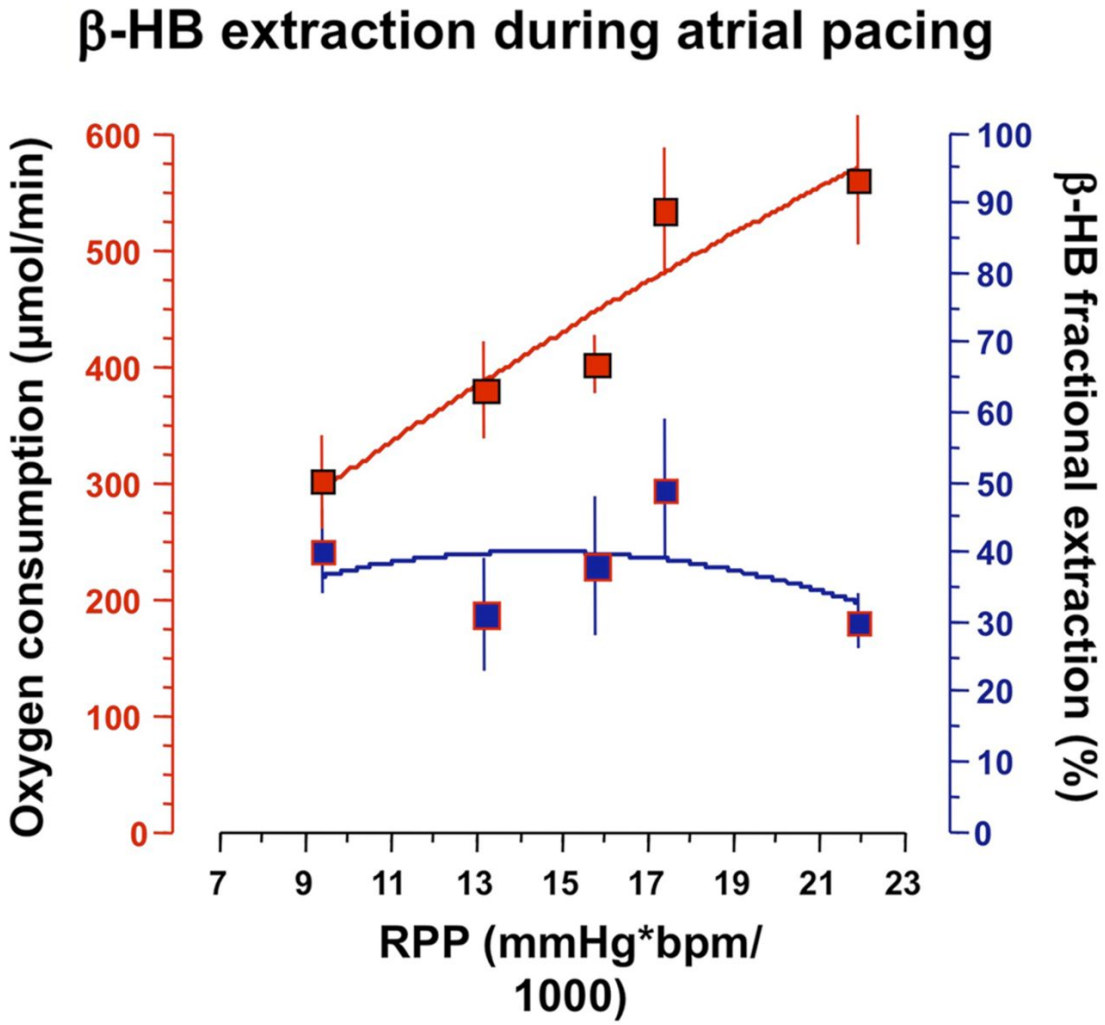
Ele Ferrannini et al. Dia Care 2016;39:1108-1114

Fractional extraction of substrates by the human heart under basal (overnight fast) and systemic hyperinsulinemia (euglycemic-hyperinsulinemic clamp).



Ele Ferrannini et al. Dia Care 2016;39:1108-1114

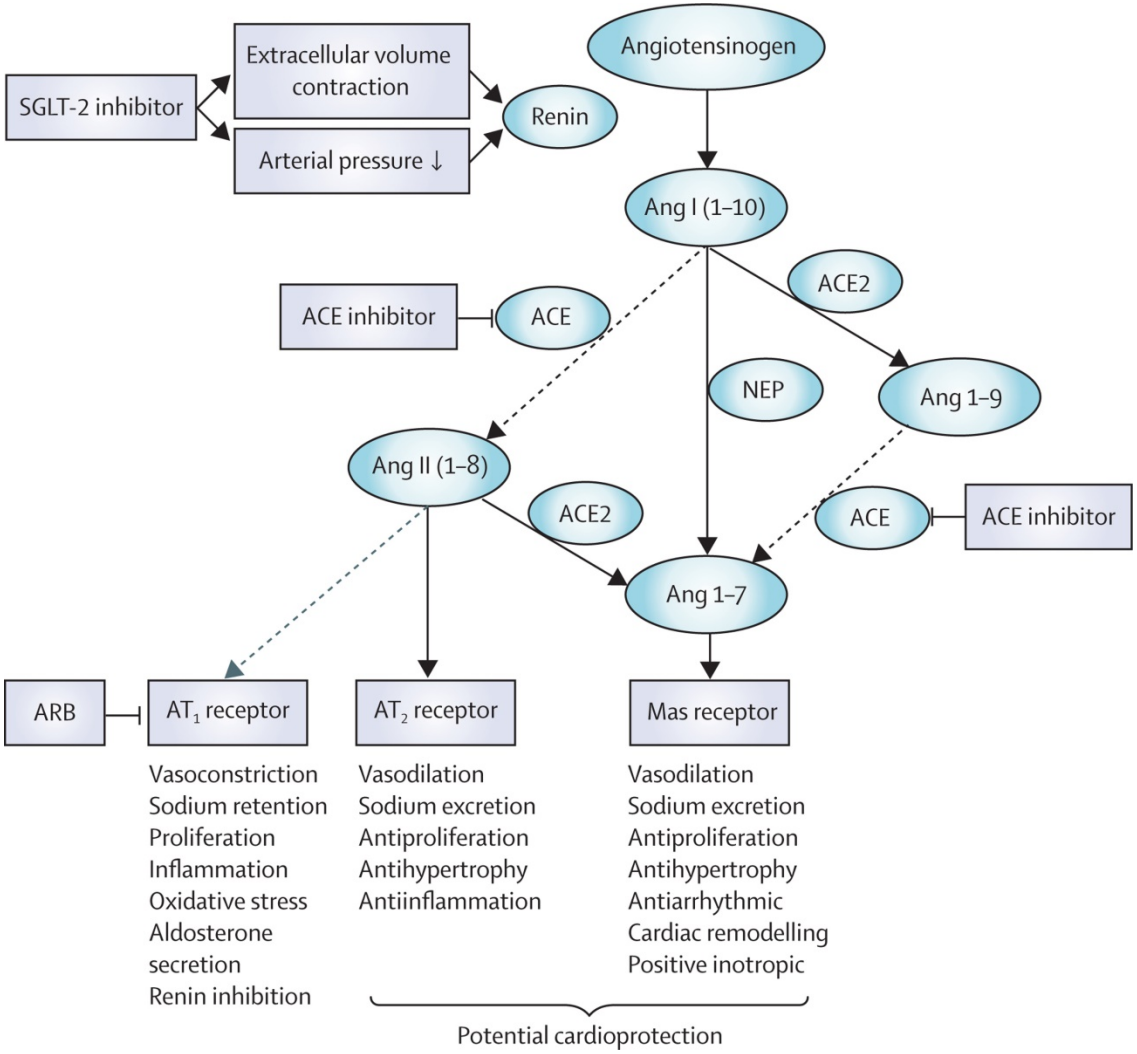
β-hydroxybutyrate (β-HB) extraction by the normal human heart during graded atrial pacing.



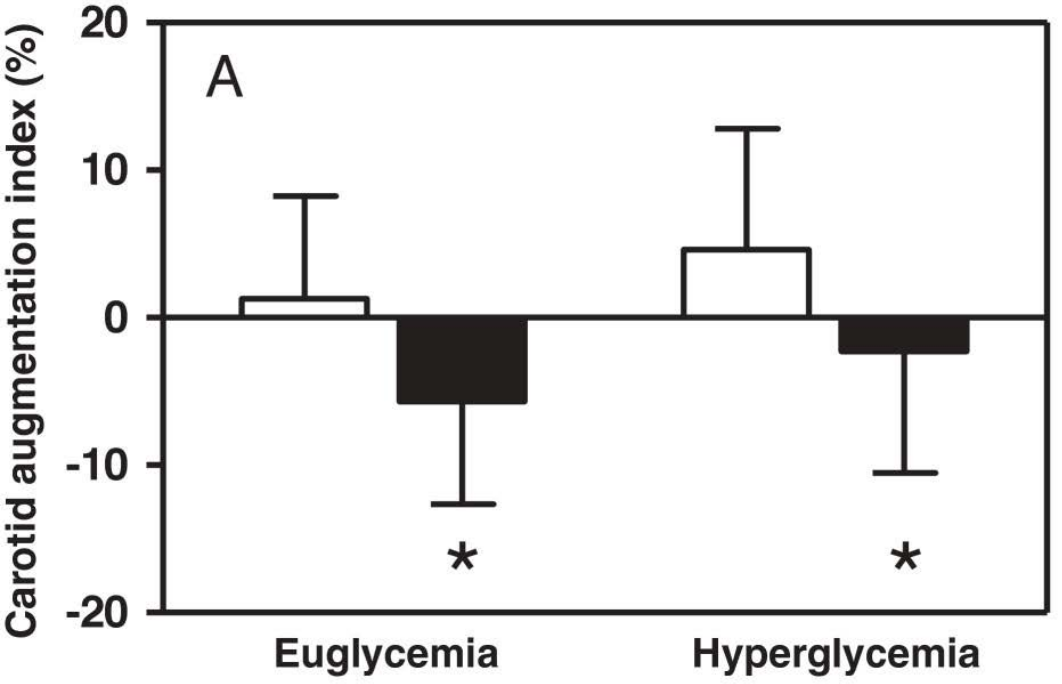
Ele Ferrannini et al. Dia Care 2016;39:1108-1114

American Diabetes Association.

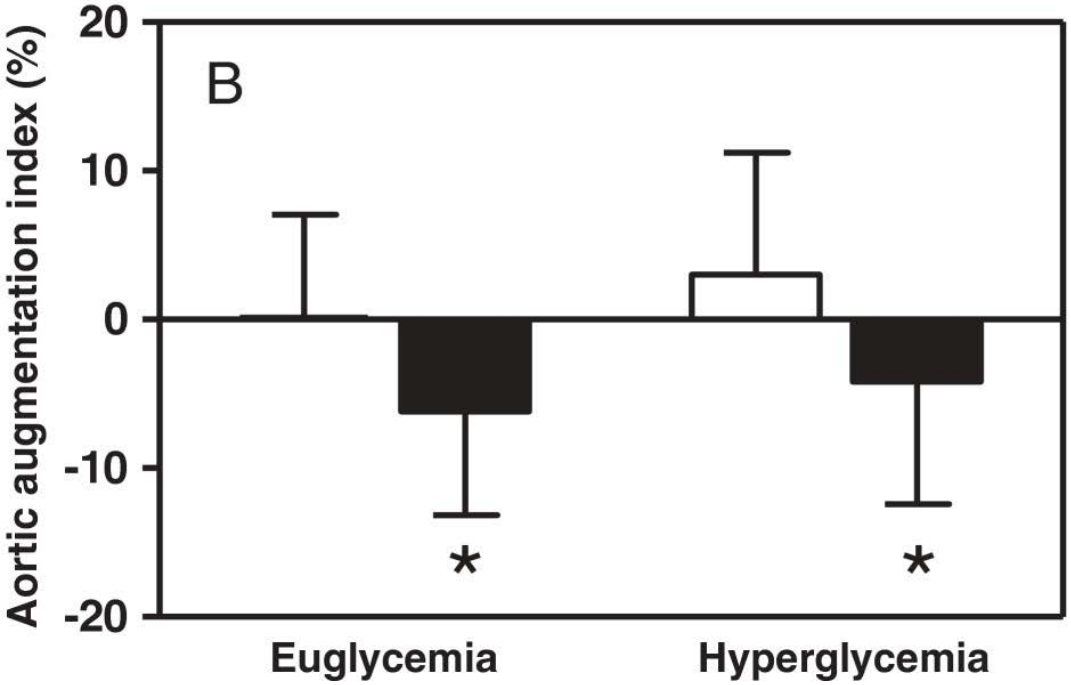
Rationale for potential benefit of combined SGLT2 and RAAS-inhibition in type 2 diabetes



The Lancet Diabetes & Endocrinology 2015, 3; No. 12, p928–929

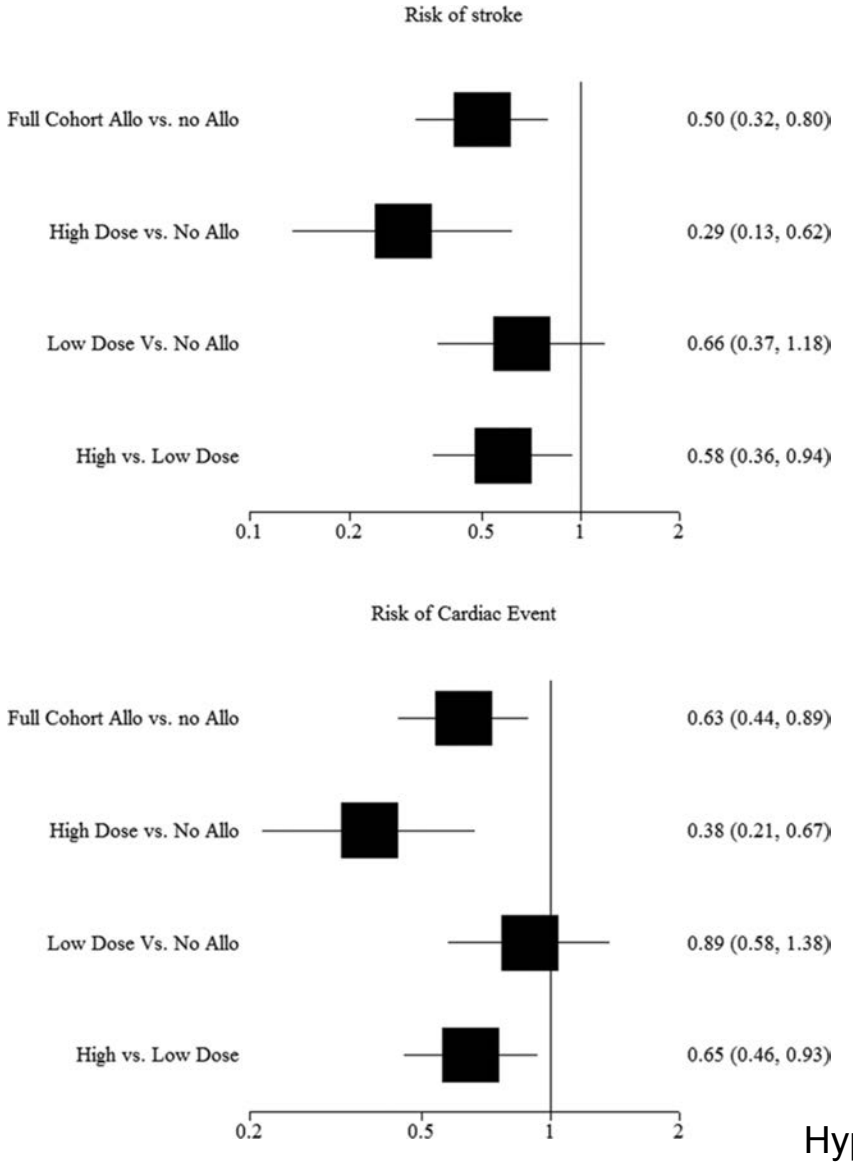


The effect of empagliflozin on carotid (A) and aortic (B) augmentation indices during clamped euglycaemia and hyperglycaemia in patients with type 1 diabetes. *p < 0.0001



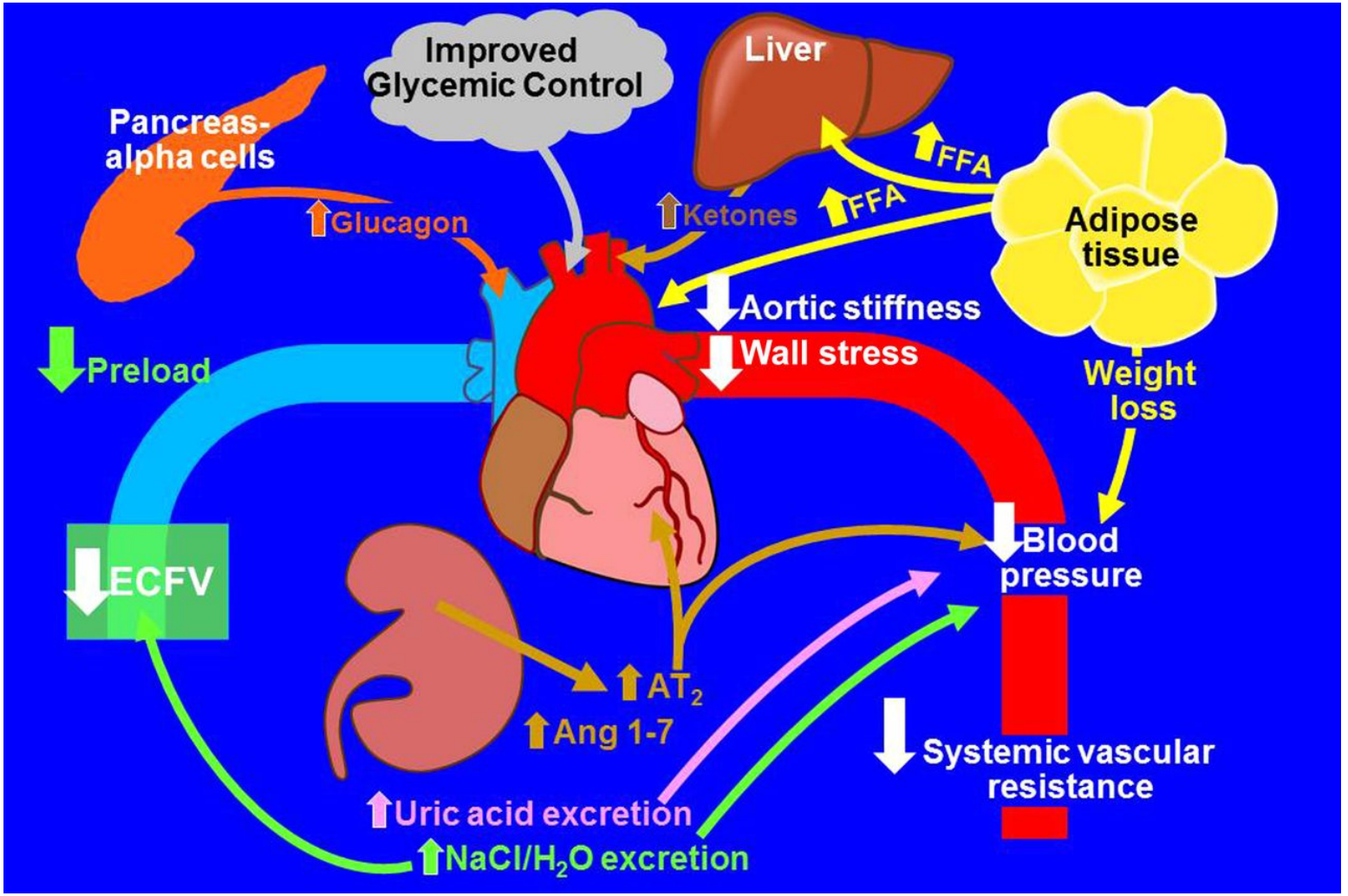
Cardiovascular Diabetology201413:28

Effet uricosurique des iSGLT2



Hypertension. 2016;67:535-540

Schematic representation of the possible metabolic and hemodynamic mechanisms via which empagliflozin reduced mortality and hospitalization for heart failure in the EMPA-REG OUTCOME study.



Muhammad Abdul-Ghani et al. Dia Care 2016;39:717-725

American Diabetes Association

Résumé

- Les nouveaux antihyperglycémiants sont sécures, car ne causent pas d'évènements CV, d'hypoglycémie ou de gain de poids (sauf les TZD's)
- Plus spécifiquement, certains agonistes de la GLP (liraglutide, semaglutide) peuvent davantage prévenir des évènements CV
- L'empagliflozine dans l'étude EMPA-REG est le seul iSGLT2 qui allie perte de poids, ↓ de la TA et prévention secondaire des évènements CV.
- Les mécanismes protecteurs en émergence des iSGLT2 au niveau cardiaque, vasculaire et rénal sont uniques et vont au-delà du simple contrôle glycémique

⇒ Le choix d'un antihyperglycémiant se tourne maintenant vers sa capacité à mieux prévenir les évènements CV

Merci !