Interrelations des maladies métaboliques et de l'insuffisance cardiaque

Antoine Avignon

Nutrition – Diabète

CHU & Université de Montpellier

Conflits d’intérêts

- **Interventions**

Novo-Nordisk, MSD, Roche Diabète, Astra-Zeneca, Pfizer, Sanofi-Aventis, Servier, Lifescan, Bayer health Care, ASDIA, Axis Santé

- **Expertise scientifique**

Novo-Nordisk, Astra-Zeneca, Sanofi-Aventis, Lifescan

- **Hospitalité**

Novo-Nordisk, MSD, Roche-Diabète, Lilly, AMGEN, Astra-Zenzca, Pfizer, Sanofi-Aventis, Urgo, Servier, Lifescan, SOS Oxygène, Ypsomed, Medtronic, ASDIA

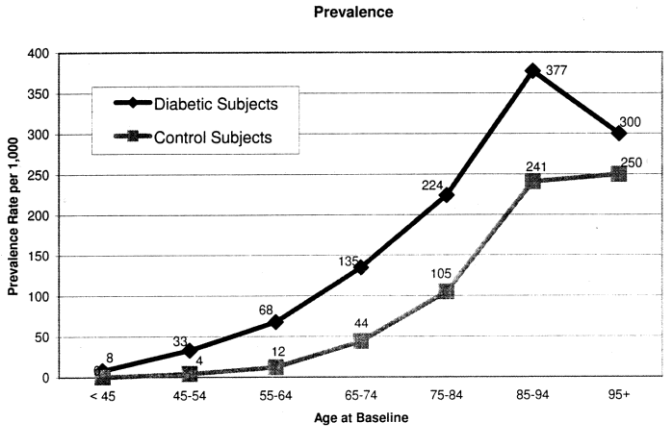
Données épidémiologiques

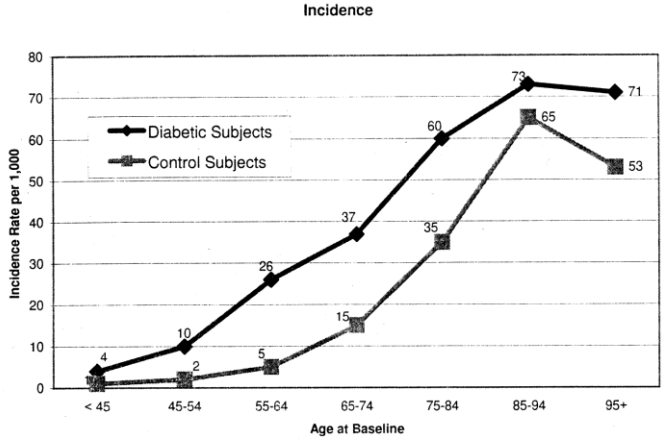
Prévalence IC et Diabète

Kaiser Permanente Northwest Division (Portland, Oregon)

11,8% vs 4,4%

DT2 vs non Diab



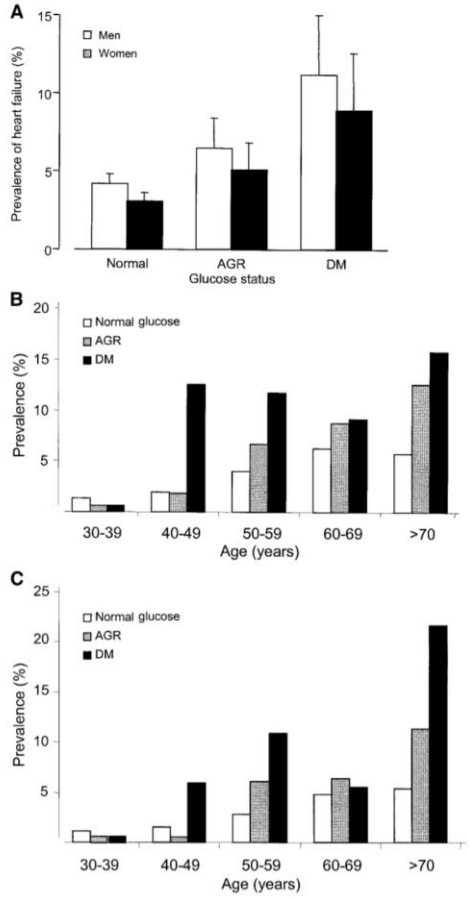


Diabetes Care. 2001;24(9):1614-1619

Reykjavik Study

11,8% vs 3,2%

DT2 vs non Diab



H

F

Diabetes Care 28:612–616, 2005

Etudes DT2 et IC

Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

European Journal of Heart Failure (2018) 20, 853–872

Table 1 Prevalence of heart failure in selected trials of type 2 antidiabetic drugs

Trial	Prevalence of HF at baseline
Glucose-lowering trials	
UKPDS 33[11]	NR (severe concurrent illness excluded)
ADVANCE[12,13]	NR
ACCORD[14]	4.3%
VADT[15]	NR
DPP4 inhibitor trials	
SAVOR-TIMI 53[16,17]	13%
TECOS[18]	18%
EXAMINE[19]	28%
SGLT2 inhibitor trials	
EMPA-REG OUTCOME[20]	10%
CANVAS[21]	14–15%
GLP-1 receptor agonist trials	
LEADER[22]	14%
ELIXA[23]	22%
EXSCEL[24]	16%

Table 3 Prevalence of type 2 diabetes mellitus in selected trials of heart failure

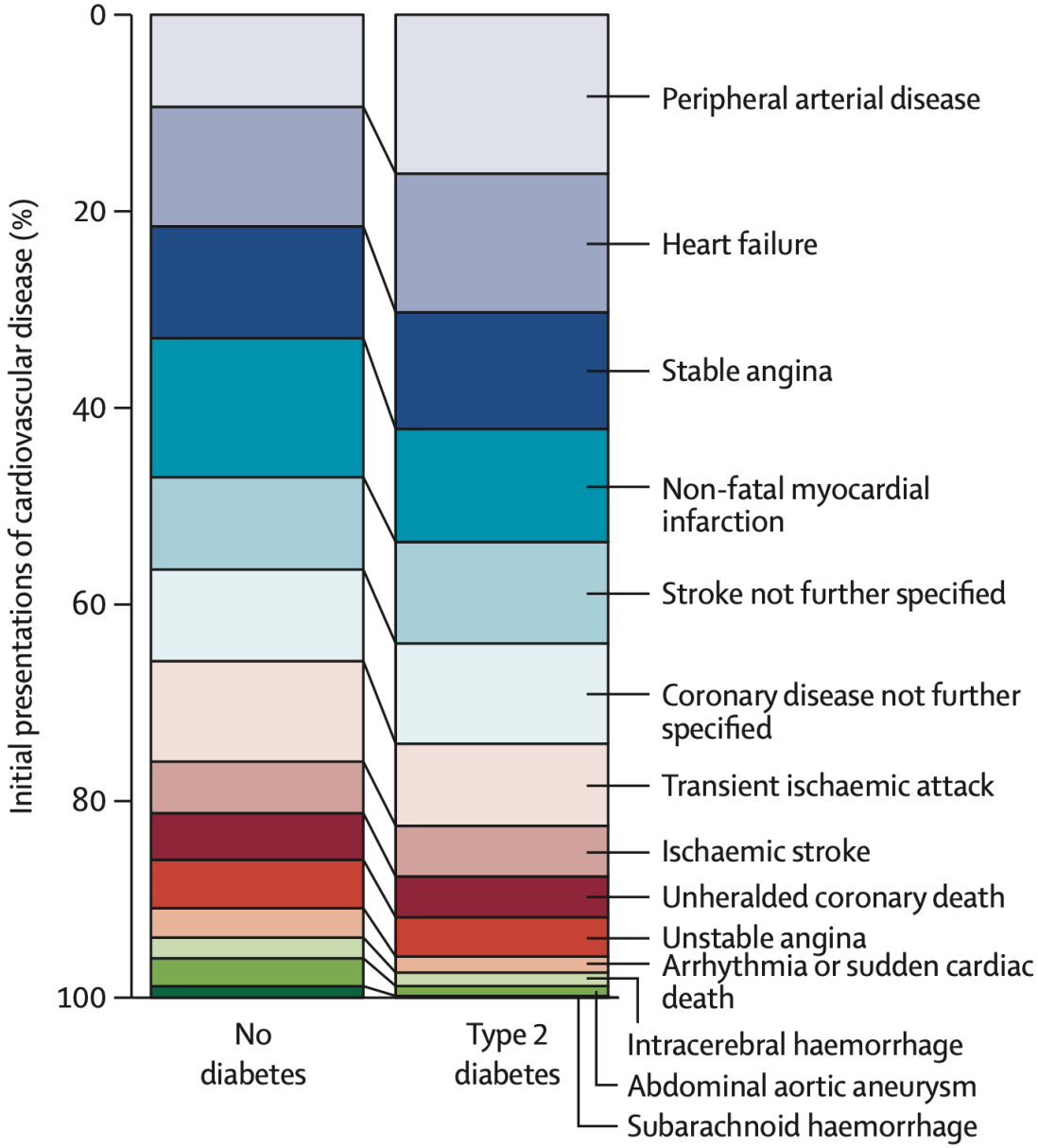
Trial	Prevalence of T2DM
Trials of HFrEF	
PARADIGM-HF[31]	35%
SHIFT[32]	30%
EchoCRT[33]	41%
HF-ACTION[34]	32%
SENIORS[35]	26%
SOLVD[36]	15%
MERIT-HF[37]	25%
CHARM-Added[38]	29%
DIG-REF[39]	28%
Trials of HFpEF	
I-Preserve[40]	27%
PEP-CHF[41]	21%
DIG-PEF[42]	29%
CHARM-Preserved[43]	28%
TOPCAT[44]	33%
Trials of acute HF	
EVEREST[45]	39%
TRUE-AHF[46]	39%
ASCEND-HF[47]	42.6%
RELAX-AHF-2[48]	47%

Présentation initiale des M. CV et DT2

DT2 associé à :

- *PAD (HR 2.98 [95% CI 2.76–3.22]),*
- *AVC ischémiques (1.72 [1.52–1.95]),*
- *Angor stable (1.62 [1.49–1.77])*
- *IC (1.56 [1.45–1.69]),*
- *IDM non létal (1.54 [1.42–1.67]),*

Cohorte anglaise 1 921 260 individus, 1887062 (98·2%) non diab, 34198 (1·8%) DT2



Lancet Diabetes Endocrinol 2015; 3: 105–13

DT2 et IC : surmortalité

Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

European Journal of Heart Failure (2018) 20, 853–872

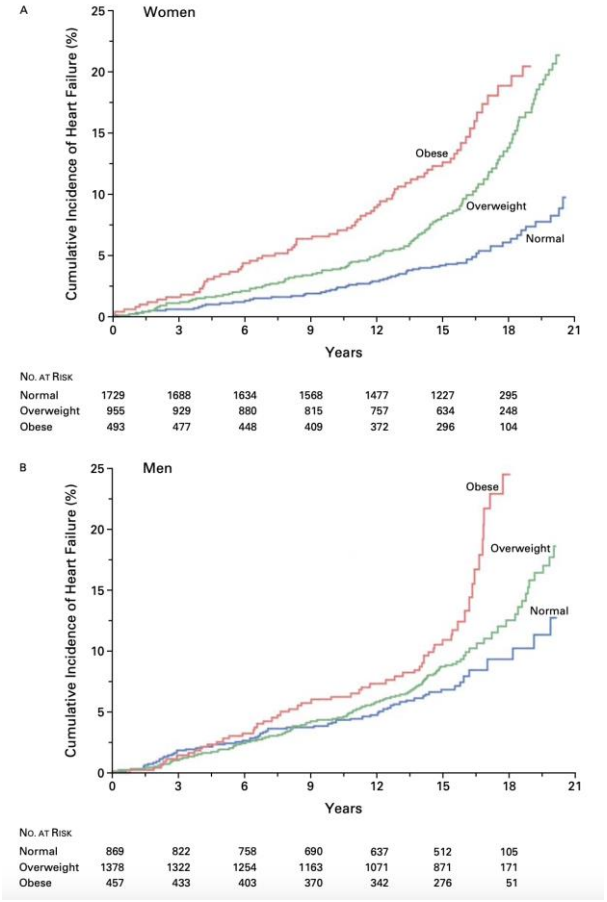
Table 4 Type 2 diabetes mellitus and mortality in heart failure in population studies, outpatient clinics and hospitalized patients

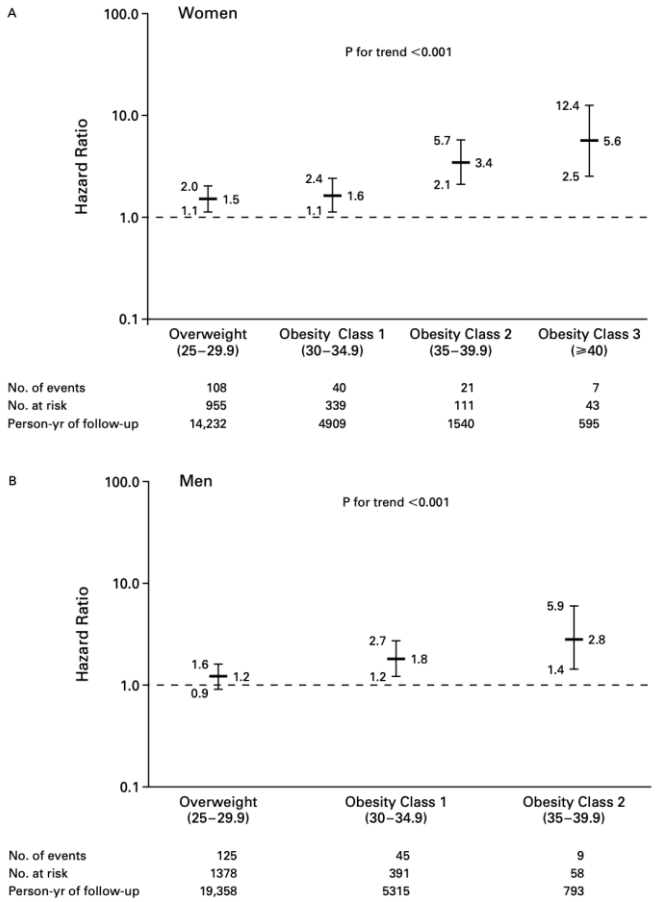
Country	Year of publication	Type of study	Total patients, *n*	Patients with T2DM, *n*	Adjusted all-cause mortality risk of T2DM*	Adjusted CV mortality risk of T2DM*
Population-based studies						
ESC-HFA HF Long-Term Registry[51]	2017	Population-based	9428	3440	1.28 (1.07–1.54)	1.28 (0.99–1.66)
ESC-HFA HF Long-Term Registry[73]	2017	Population-based	6926	3422	1.77 (1.28–2.45)	NA
Swedish HF Registry[74]	2014	Population and specialist outpatient-based	36 454	8809	1.60 (1.50-1.71)	NA
USA (Olmsted County)[29]	2006	Population-based	665	128	1.48 (1.20-1.82)	NA
Netherlands (Rotterdam)[26]	2001	Population-based	5540	557	3.19 (1.80–5.65)	3.25 (1.53–6.93) SCD: 3.65 (1.28–10.4)
Outpatient clinics						
UK[75]	2013	Cardiology clinics	1091	280	2.08 (1.61–2.69)	NA
USA[76,77]	2006	HF clinic	495	293	1.71 (1.16–2.51)	NA
Italy (BRING-UP Registry)[78]	2003	Outpatient-based	2843	621	1.44 (1.16–1.78)	NA
Hospitalized patients						
Spain (RICA Registry)[79]	2014	Hospitalization-based, multicentre	1082	490	1.54 (1.20–1.97)	NA
Spain (INCAex)[80]	2013	Hospitalization-based, single-centre	1659	NR	1.35 (1.11–1.66)	NA
USA (Medicare)[81]	1999	Hospitalization-based	170 239	NA	Black: 1.11 (1.06–1.16) White: 1.22 (1.24–1.25)	NA

Prévalence IC et obésité

Framingham Heart Study

5881 participants (âge moyen, 55 ans ; 54 % de femmes)





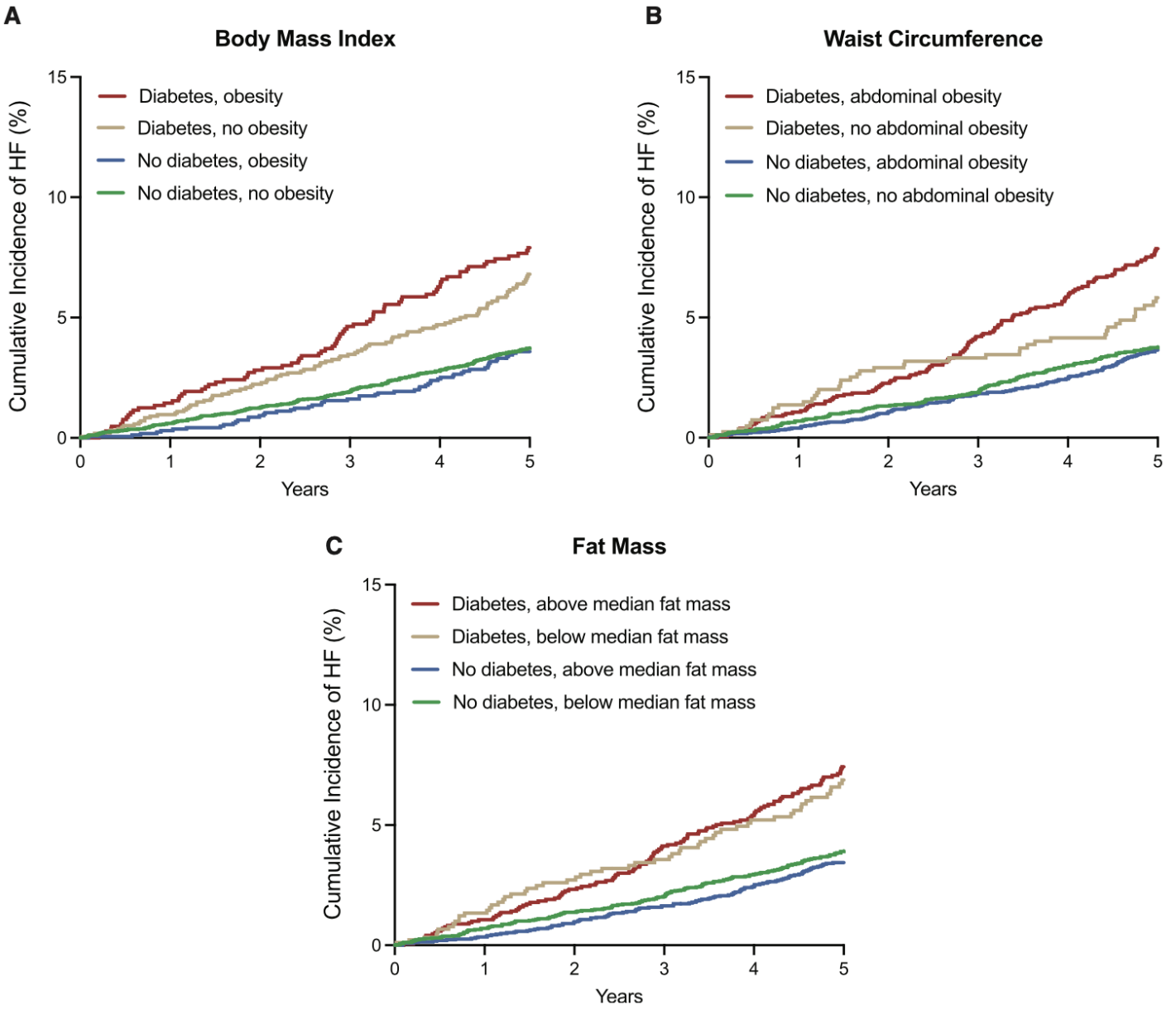
Augmentation du risque d'IC de 5 % pour les H et de 7 % pour les F pour chaque augmentation de 1 de l'IMC

N Engl J Med 2002; 347:305-313

Association Diabète-Obésité

ARIC study (Atherosclerosis Risk in Communities and the CHS (Cardiovascular Health Study)

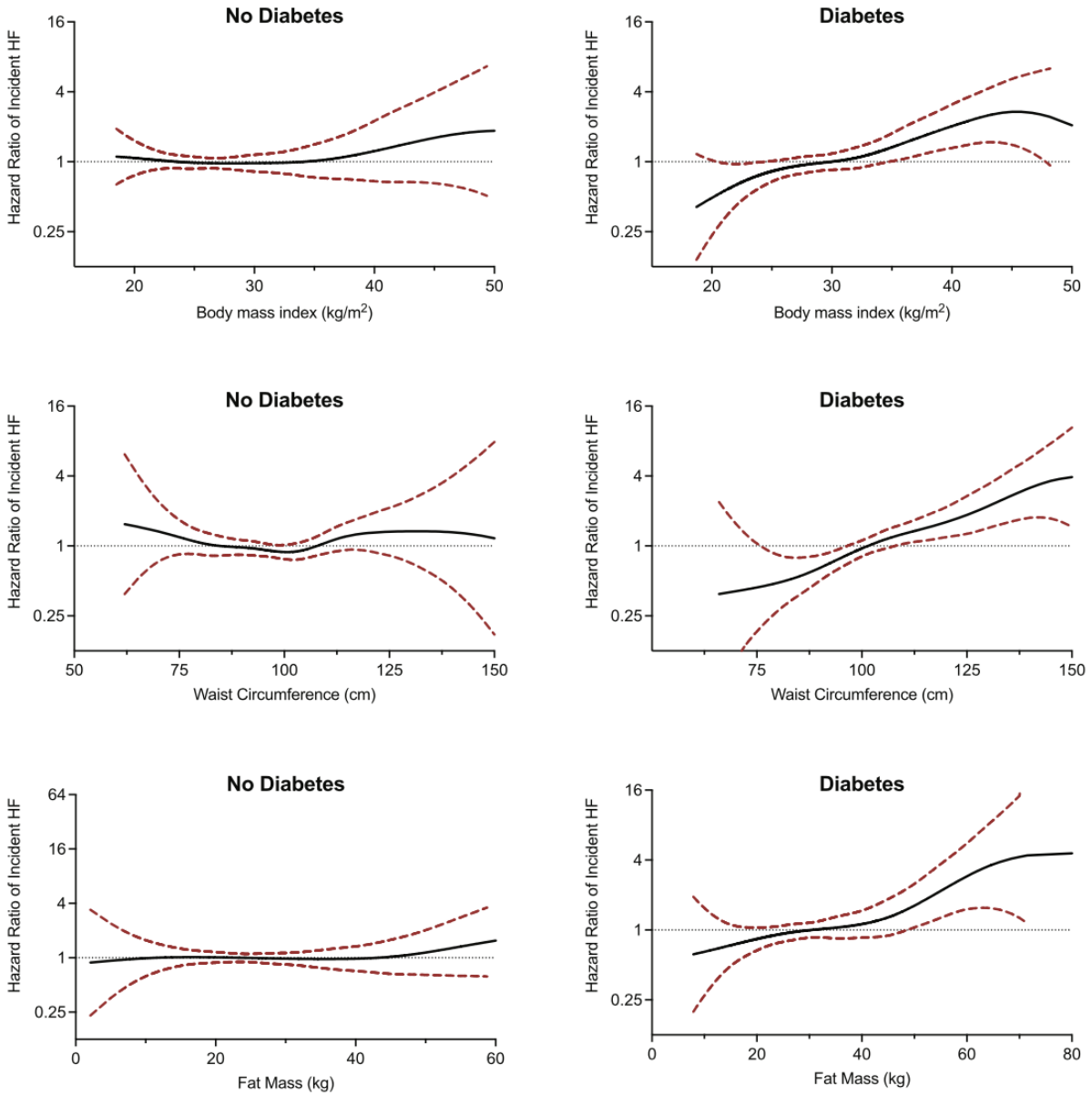
10 387 participants (52.9% ARIC; 25.1% diabetes; median age, 74 years).



Circulation. 2022;145:268–278. DOI: 10.1161/CIRCULATIONAHA.121.055830

Association Diabète-Obésité

ARIC study (Atherosclerosis Risk in Communities and the CHS (Cardiovascular Health Study)



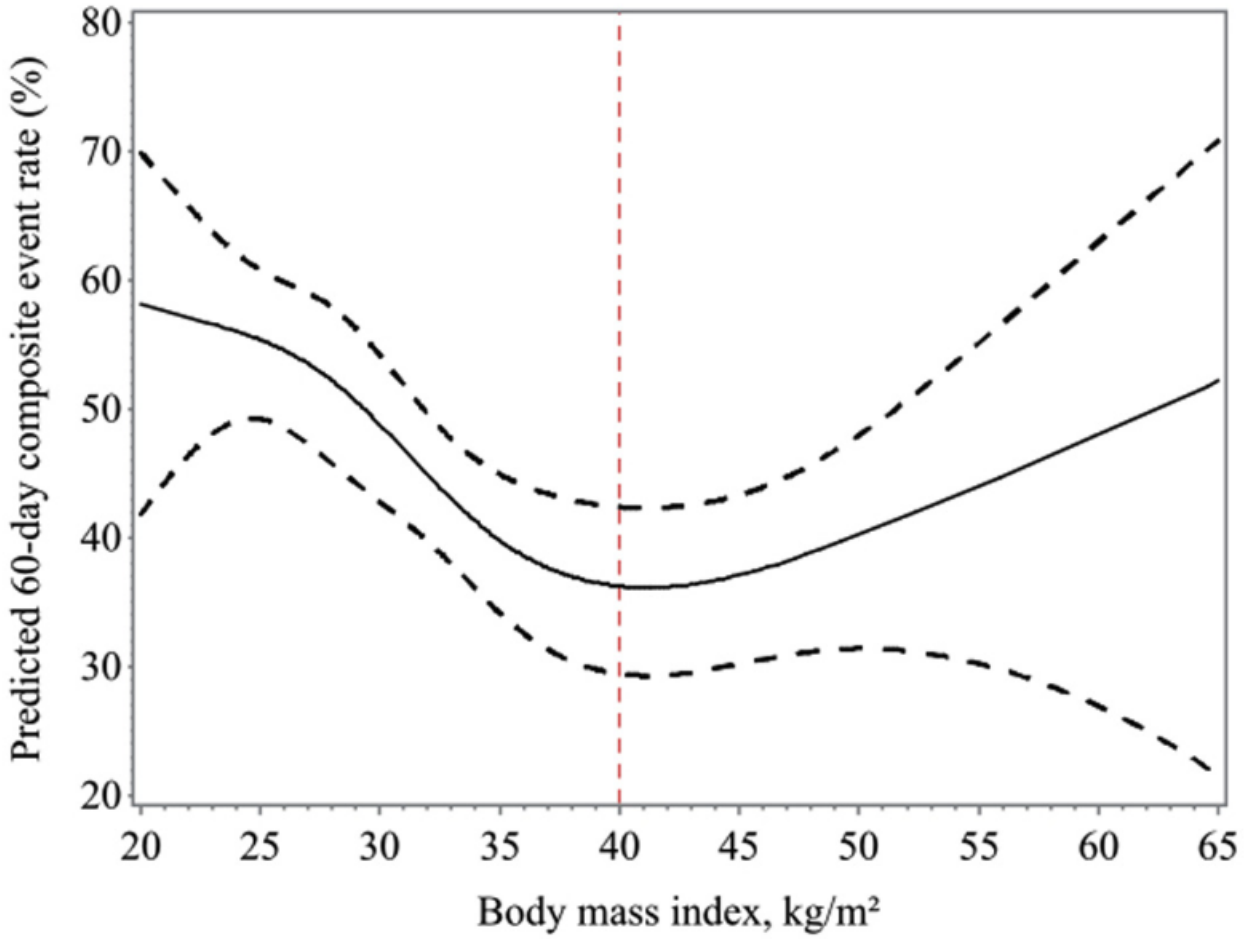
Circulation. 2022;145:268–278. DOI: 10.1161/CIRCULATIONAHA.121.055830

Obésité, IC et mortalité : “Obesity paradox”

3 essais IC
- DOSE [Diuretic Strategies Optimization Evaluation],
- CARRESS-HF [Cardiorenal Rescue Study in Acute Decompensated Heart Failure],
- ROSE [Renal Optimization Strategies Evaluation in Acute Heart Failure]).

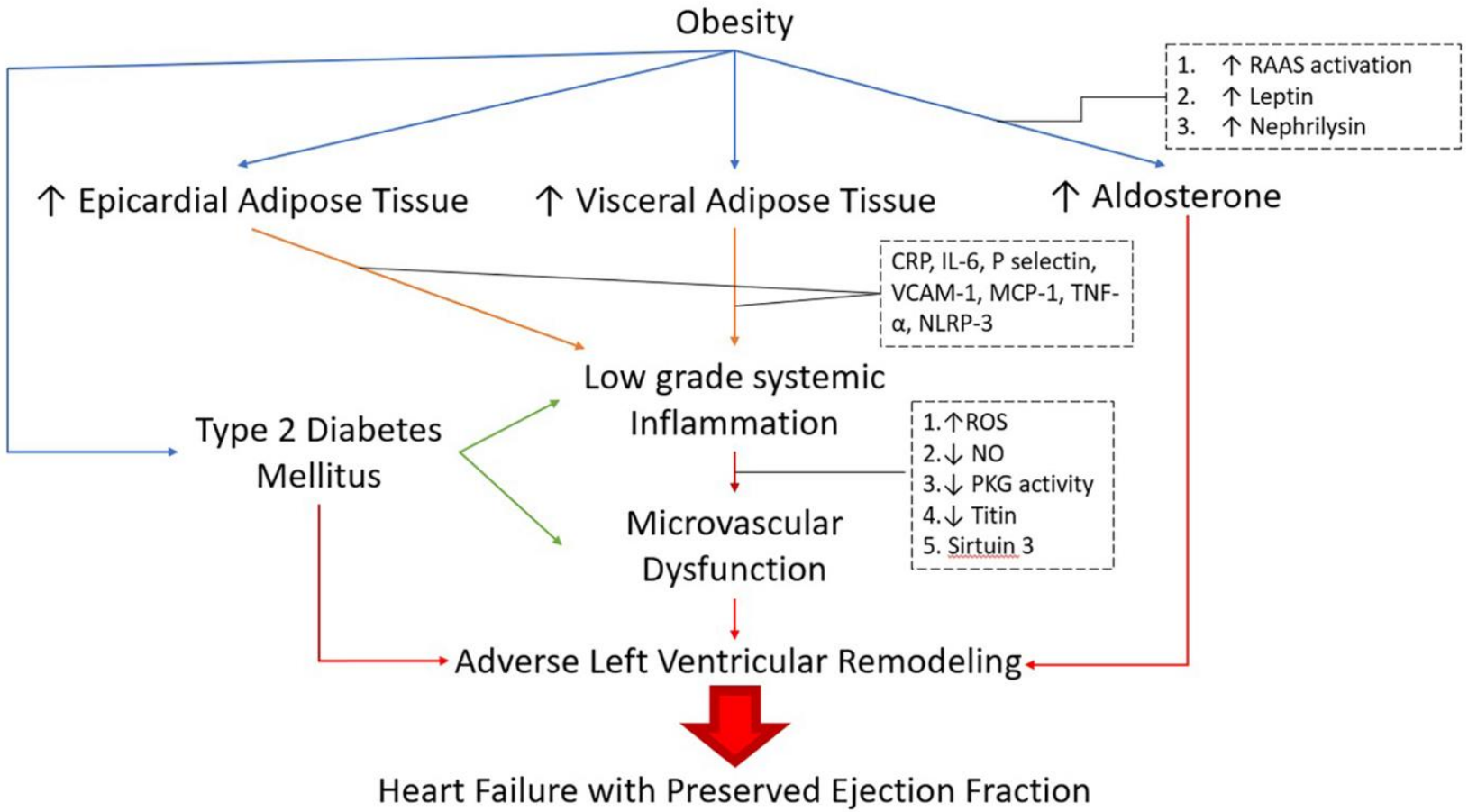
795 participants avec IMC mesuré au moment de l'admission et suivi complet

FIGURE 3 Predicted 60-Day Primary Composite Event Rates



J Am Coll Cardiol HF 2016;4:923–31

Diab-Obésité et ICFEP : physiopathologie

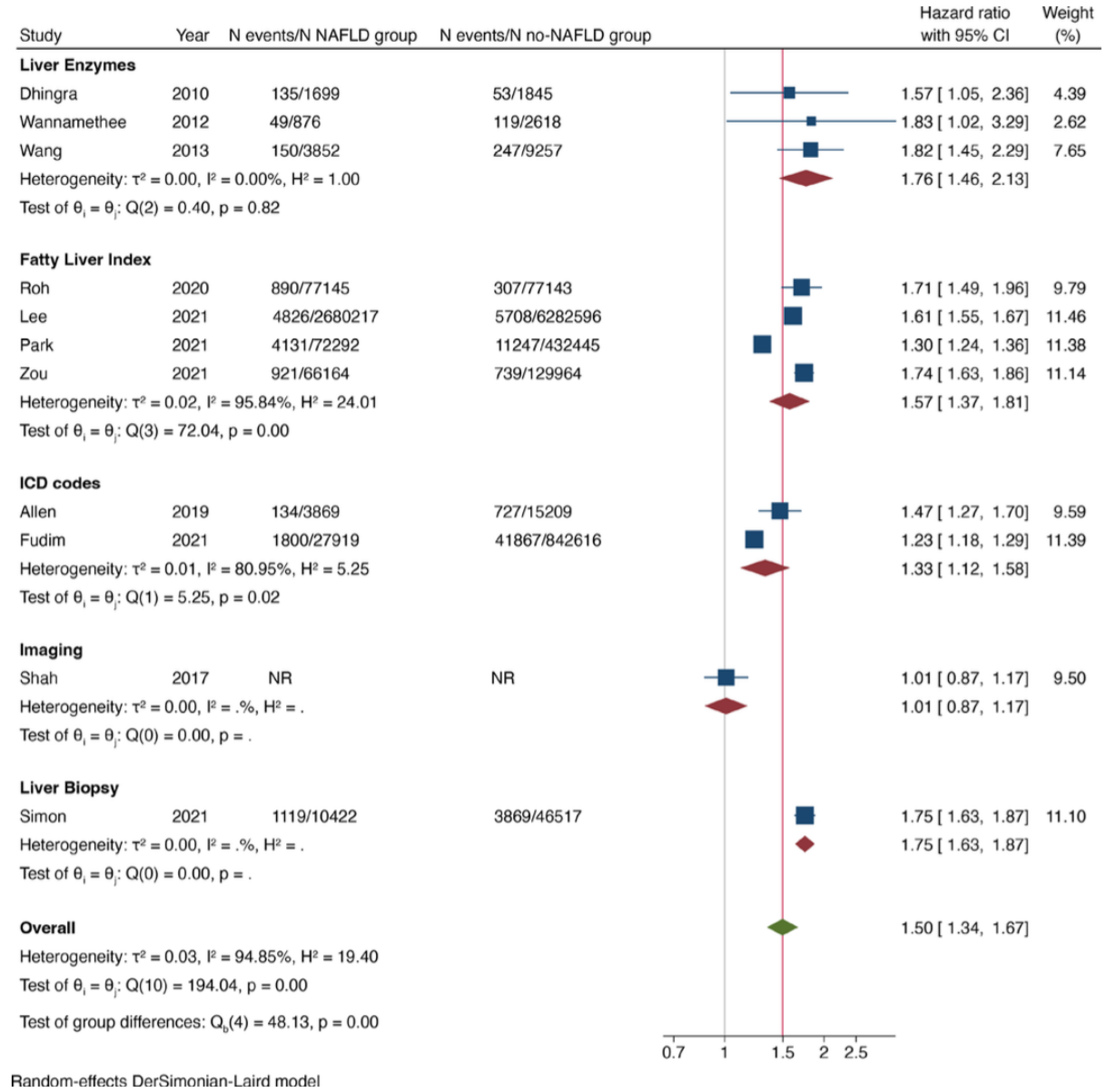


Dhore-patil A et al. 2022, Front. Physiol. 12:785879. doi: 10.3389/fphys.2021.785879

NAFLD et IC

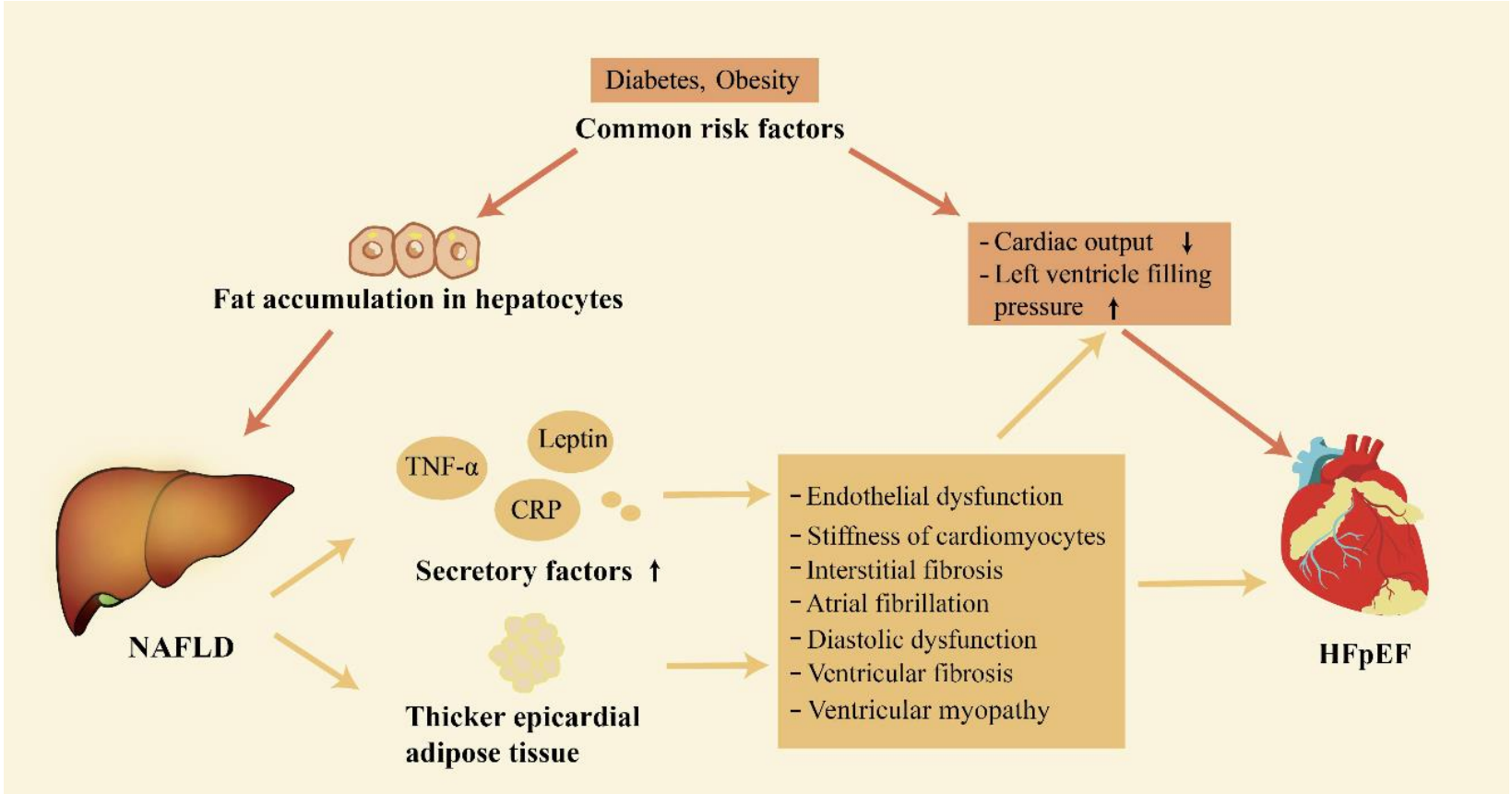
Métaanalyse 2023

Pooled estimates of the effect of NAFLD on the risk of developing new-onset heart failure in 11 eligible cohort studies



Mantovani A, Petracca G, Csermely A, et al. Gut 2023;72:372–380.

Diab-Obésité, NAFLD et ICFEP



Front. Cardiovasc. Med. 9:1120085. doi: 10.3389/fcvm.2022.1120085

Bénéfices des traitements de l’IC et maladies métaboliques

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

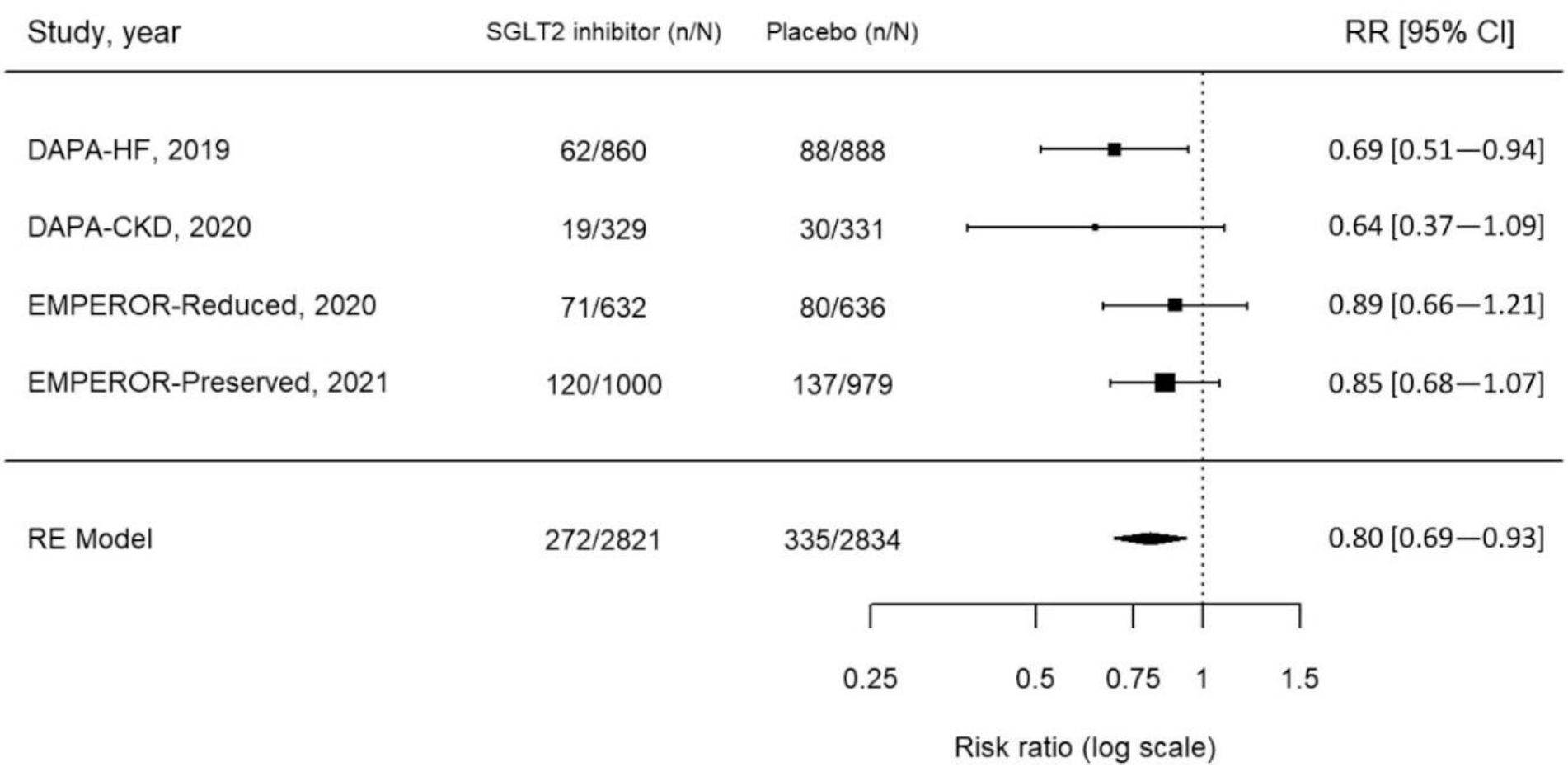
Paul A. Heidenreich, Biykem Bozkurt, David Aguilar, Larry A. Allen, Joni J. Byun, Monica M. Colvin, Anita Deswal, Mark H. Drazner, Shannon M. Dunlay, Linda R. Evers, James C. Fang, Savitri E. Fedson, Gregg C. Fonarow, Salim S. Hayek, Adrian F. Hernandez, Prateeti Khazanie, Michelle M. Kittleson, Christopher S. Lee, Mark S. Link, Carmelo A. Milano, ... See all authors

Originally published 1 Apr 2022 | https://doi.org/10.1161/CIR.0000000000001063 | Circulation. 2022;145:e895–e1032

Top 10 Take-Home Messages

- Guideline-directed medical therapy (GDMT) for heart failure (HF) with reduced ejection fraction (HFrEF) now includes 4 medication classes that include sodium-glucose cotransporter-2 inhibitors (SGLT2i).
- SGLT2i have a Class of Recommendation 2a in HF with mildly reduced ejection fraction (HFmrEF). Weaker recommendations (Class of Recommendation 2b) are made for ARNi, ACEi, ARB, MRA, and beta blockers in this population.
- New recommendations for HFpEF are made for SGLT2i (Class of Recommendation 2a), MRAs (Class of Recommendation 2b), and ARNi (Class of Recommendation 2b). Several prior recommendations have been renewed including treatment of hypertension (Class of Recommendation 1), treatment of atrial fibrillation (Class of Recommendation 2a), use of ARBs (Class of Recommendation 2b), and avoidance of routine use of nitrates or phosphodiesterase-5 inhibitors (Class of Recommendation 3: No Benefit).
- Improved LVEF is used to refer to those patients with previous HFrEF who now have an LVEF >40%. These patients should continue their HFrEF treatment.
- Value statements were created for select recommendations where high-quality, cost-effectiveness studies of the intervention have been published.
- Amyloid heart disease has new recommendations for treatment including screening for serum and urine monoclonal light chains, bone scintigraphy, genetic sequencing, tetramer stabilizer therapy, and anticoagulation.
- Evidence supporting increased filling pressures is important for the diagnosis of HF if the LVEF is >40%. Evidence for increased filling pressures can be obtained from noninvasive (eg, natriuretic peptide, diastolic function on imaging) or invasive testing (eg, hemodynamic measurement).
- Patients with advanced HF who wish to prolong survival should be referred to a team specializing in HF. A HF specialty team reviews HF management, assesses suitability for advanced HF therapies, and uses palliative care including palliative inotropes where consistent with the patient's goals of care.
- Primary prevention is important for those at risk for HF (stage A) or pre-HF (stage B). Stages of HF were revised to emphasize the new terminologies of "at risk" for HF for stage A and pre-HF for stage B.
- Recommendations are provided for select patients with HF and iron deficiency, anemia, hypertension, sleep disorders, type 2 diabetes, atrial fibrillation, coronary artery disease, and malignancy.

iSGLT2 et Prévention du DT2



The Journal of Clinical Endocrinology & Metabolism, 2023, **108**, 221–231

iSGLT2 et Obésité

DECLARE–TIMI 58 trial

DECLARE
N=17160
Patients DT2
Multiples facteurs de risque CV OU
antécédants de pathologies athéromateuses

randomisation 1:1
Suivi médian: 4,2 ans

DAPA 10 mg | **Placebo**

Critère principal

MACE 3points
Composite des décès CV
ou hospitalization pour IC

Critères secondaires

- Déclin chronique ≥40% du DFGe, diminution du DFG < à 60ml/min/1,73m²
- Mortalité toutes causes

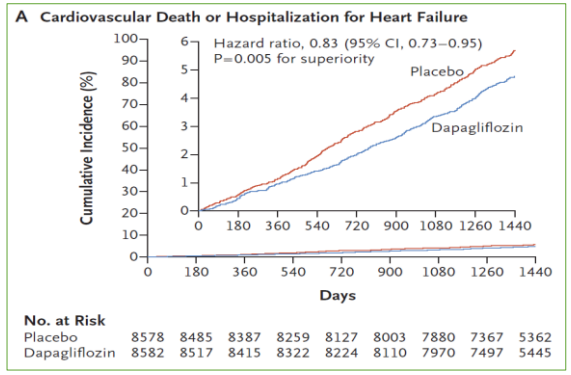
Characteristiques à l'initiation

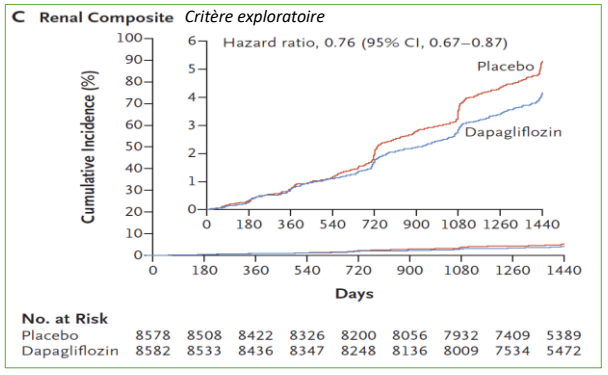
32
kg/m² d'IMC

10%
Insuffisance cardiaque

8,3%
D'HbA1c

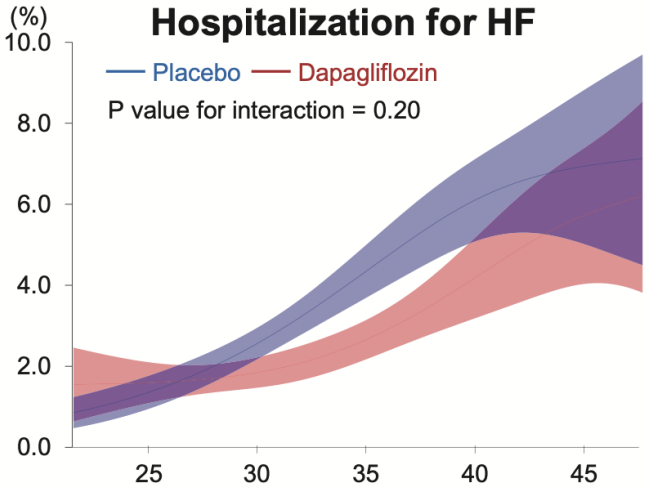
85
mL/min/1.73 m²
DFGe moyen





Wiviott S.D. et al., N Engl J Med 2019; 380:347-57

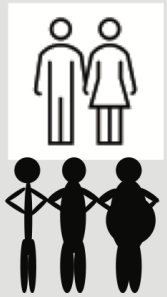
Event/BMI Subgroup	Adjusted HR (95% CI)	P value for trend
Hospitalization for HF		
Normal (18.5-<25)	Ref.	<0.001
Overweight (25-<30)	1.26 (0.63-2.52)	
Moderately obese (30-<35)	1.95 (0.99-3.86)	
Severely obese (35-<40)	2.87 (1.42-5.76)	
Very severely obese (≥40)	3.93 (1.92-8.08)	



European Heart Journal (2022) **43**, 2958–2967

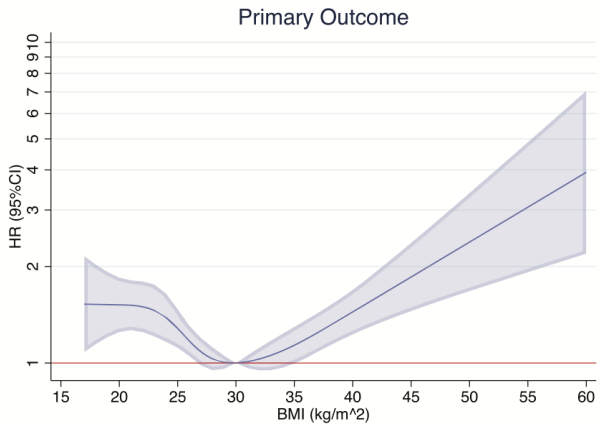
iSGLT2 et Obésité

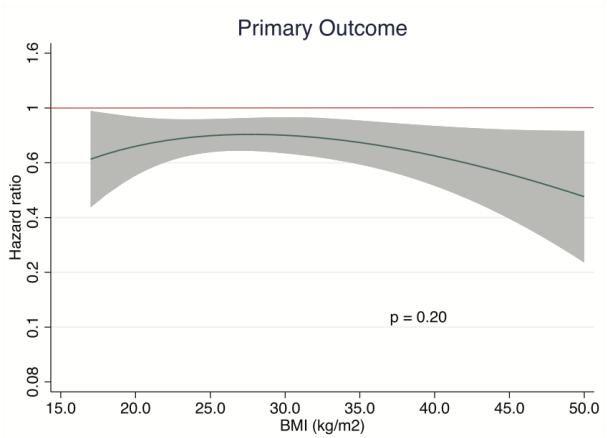
DAPA-HF

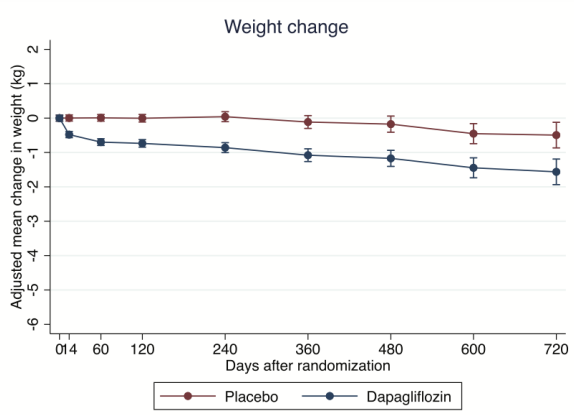


Population: 4742 adults with HFrEF enrolled in DAPA-HF trial

Questions: How does risk of adverse outcome vary by baseline BMI?
Does the effect of dapagliflozin vary according to baseline BMI?
What was the effect of dapagliflozin on weight?







The lowest risk patients were those in obesity class I (BMI 30.0-34.9 Kg/m^2), consistent with the “obesity paradox”

Dapagliflozin was beneficial across the range of baseline BMI, with no safety concerns

Dapagliflozin led to a modest decrease in weight (0.9 [0.7 – 1.1] kg at 8 months) compared with placebo. Baseline BMI did not modify the effect of dapagliflozin on weight (p = 0.69)

European Journal of Heart Failure (2021) 23, 1662–1672

iSGLT2 et Obésité

DELIVER

Dapagliflozin for heart failure according to body mass index: A prespecified analysis of the DELIVER trial

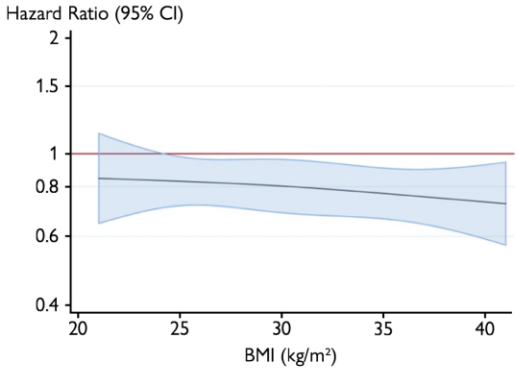
6257 patients in DELIVER trial with a recorded BMI measurement at baseline

- HFpEF or HFmrEF
- Randomized to dapagliflozin or matched placebo

- 45% patients were obese
- 78% were obese or overweight

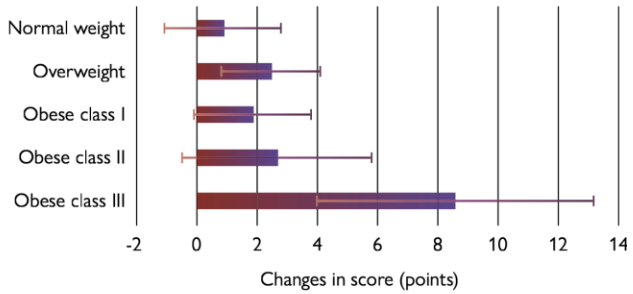
Prespecified analysis by baseline BMI

Primary outcome (worsening HF or CV death)



Dapagliflozin reduced the incidence of primary outcome, regardless of baseline BMI

Mean change in KCCQ-TSS from baseline to 8 months according to BMI category

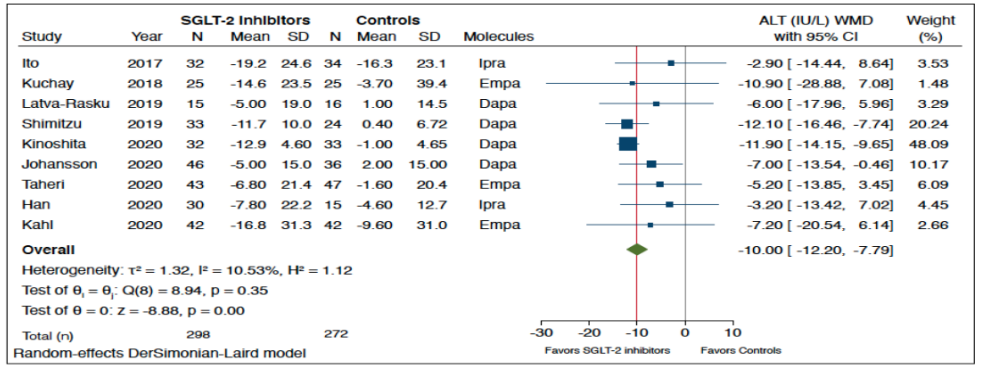


Larger increases (improvement) in KCCQ-TSS were seen in patients with obesity

European Heart Journal (2022) 43, 4406–4417

iSGLT2 et Enzymes Hépatiques

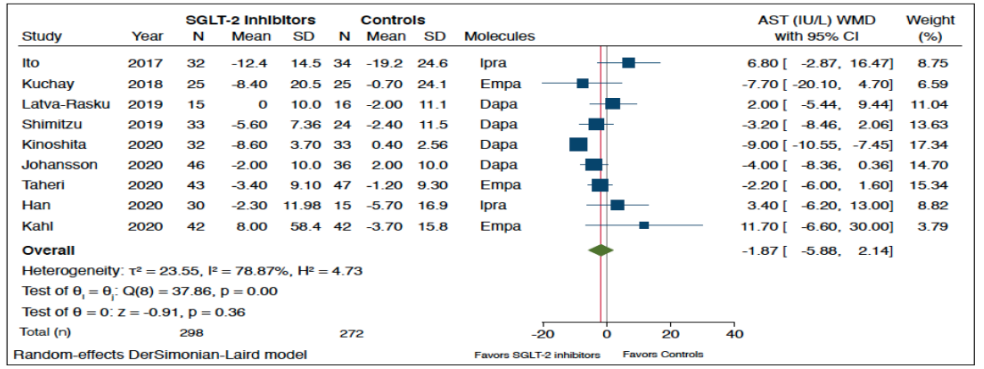
Panel A



Study	Year	SGLT-2 Inhibitors N	Mean	SD	Controls N	Mean	SD	Molecules	ALT (IU/L) WMD with 95% CI	Weight (%)
Ito	2017	32	-19.2	24.6	34	-16.3	23.1	Ipra	-2.90 [-14.44, 8.64]	3.53
Kuchay	2018	25	-14.6	23.5	25	-3.70	39.4	Empa	-10.90 [-28.88, 7.08]	1.48
Latva-Rasku	2019	15	-5.00	19.0	16	1.00	14.5	Dapa	-6.00 [-17.96, 5.96]	3.29
Shimitzu	2019	33	-11.7	10.0	24	0.40	6.72	Dapa	-12.10 [-16.46, -7.74]	20.24
Kinoshita	2020	32	-12.9	4.60	33	-1.00	4.65	Dapa	-11.90 [-14.15, -9.65]	48.09
Johansson	2020	46	-5.00	15.0	36	2.00	15.00	Dapa	-7.00 [-13.54, -0.46]	10.17
Taheri	2020	43	-6.80	21.4	47	-1.60	20.4	Empa	-5.20 [-13.85, 3.45]	6.09
Han	2020	30	-7.80	22.2	15	-4.60	12.7	Ipra	-3.20 [-13.42, 7.02]	4.45
Kahl	2020	42	-16.8	31.3	42	-9.60	31.0	Empa	-7.20 [-20.54, 6.14]	2.66
Overall									-10.00 [-12.20, -7.79]	
Heterogeneity: $\tau^2 = 1.32$, $I^2 = 10.53\%$, $H^2 = 1.12$										
Test of $\theta_i = \theta_j$: Q(8) = 8.94, p = 0.35										
Test of $\theta = 0$: z = -8.88, p = 0.00										
Total (n)		298			272					

Random-effects DerSimonian-Laird model

Panel B



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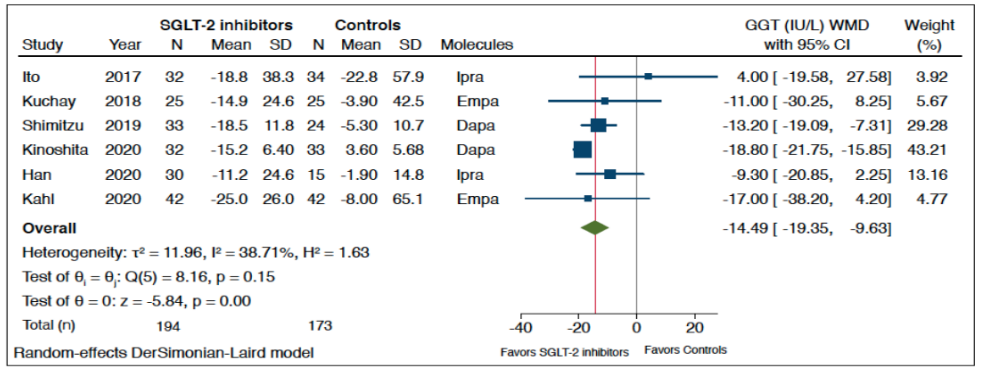
Ito	2017	32	-12.4	14.5	34	-19.2	24.6	Ipra	6.80 [-2.87, 16.47]	8.75
Kuchay	2018	25	-8.40	20.5	25	-0.70	24.1	Empa	-7.70 [-20.10, 4.70]	6.59
Latva-Rasku	2019	15	0	10.0	16	-2.00	11.1	Dapa	2.00 [-5.44, 9.44]	11.04
Shimitzu	2019	33	-5.60	7.36	24	-2.40	11.5	Dapa	-3.20 [-8.46, 2.06]	13.63
Kinoshita	2020	32	-8.60	3.70	33	0.40	2.56	Dapa	-9.00 [-10.55, -7.45]	17.34
Johansson	2020	46	-2.00	10.0	36	2.00	10.0	Dapa	-4.00 [-8.36, 0.36]	14.70
Taheri	2020	43	-3.40	9.10	47	-1.20	9.30	Empa	-2.20 [-6.00, 1.60]	15.34
Han	2020	30	-2.30	11.98	15	-5.70	16.9	Ipra	3.40 [-6.20, 13.00]	8.82
Kahl	2020	42	8.00	58.4	42	-3.70	15.8	Empa	11.70 [-6.60, 30.00]	3.79
Overall									-1.87 [-5.88, 2.14]	
Heterogeneity: $\tau^2 = 23.55$, $I^2 = 78.87\%$, $H^2 = 4.73$										
Test of $\theta_i = \theta_j$: Q(8) = 37.86, p = 0.00										
Test of $\theta = 0$: z = -0.91, p = 0.36										
Total (n)		298			272					

Random-effects DerSimonian-Laird model

Panel C



Study	Year	SGLT-2 inhibitors N	Mean	SD	Controls N	Mean	SD	Molecules	GGT (IU/L) WMD with 95% CI	Weight (%)
Ito	2017	32	-18.8	38.3	34	-22.8	57.9	Ipra	4.00 [-19.58, 27.58]	3.92
Kuchay	2018	25	-14.9	24.6	25	-3.90	42.5	Empa	-11.00 [-30.25, 8.25]	5.67
Shimitzu	2019	33	-18.5	11.8	24	-5.30	10.7	Dapa	-13.20 [-19.09, -7.31]	29.28
Kinoshita	2020	32	-15.2	6.40	33	3.60	5.68	Dapa	-18.80 [-21.75, -15.85]	43.21
Han	2020	30	-11.2	24.6	15	-1.90	14.8	Ipra	-9.30 [-20.85, 2.25]	13.16
Kahl	2020	42	-25.0	26.0	42	-8.00	65.1	Empa	-17.00 [-38.20, 4.20]	4.77
Overall									-14.49 [-19.35, -9.63]	
Heterogeneity: $\tau^2 = 11.96$, $I^2 = 38.71\%$, $H^2 = 1.63$										
Test of $\theta_i = \theta_j$: Q(5) = 8.16, p = 0.15										
Test of $\theta = 0$: z = -5.84, p = 0.00										
Total (n)		194			173					

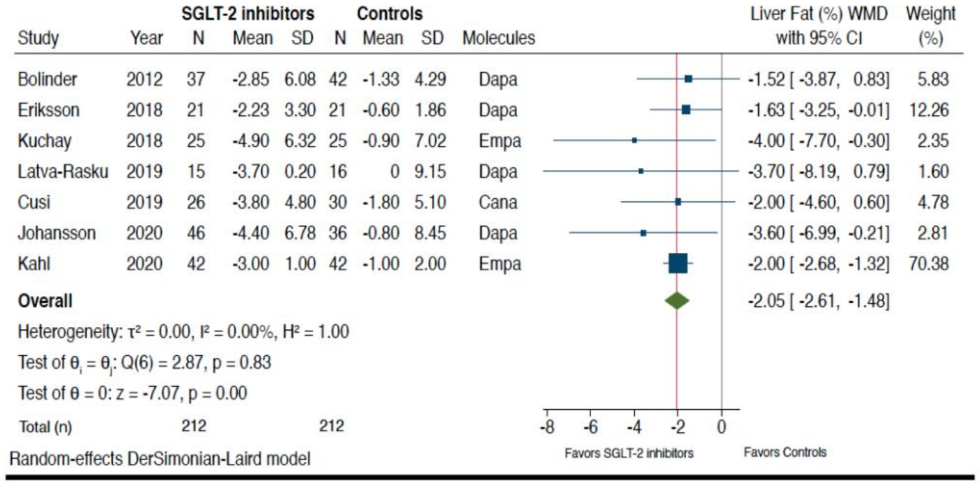
Random-effects DerSimonian-Laird model

Metabolites 2021, 11, 22. https://doi.org/10.3390/metabo 11010022

iSGLT2 et Graisse Intrahépatique

Méta-analyse des essais randomisés contrôlés

RMN

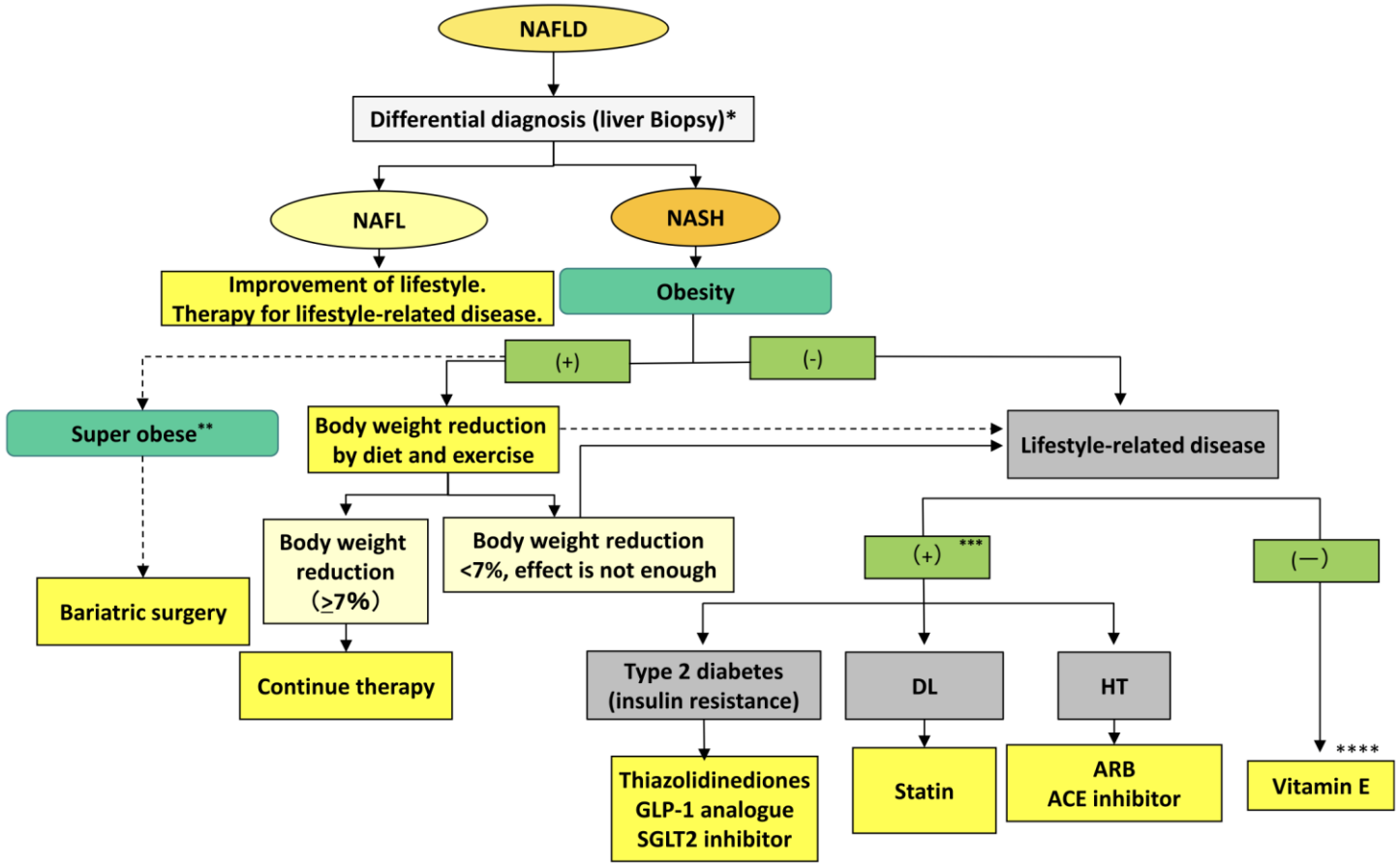


	WMD (95%CI)	Test *Z* for Overall Effect	Number of RCTs Included	Number of Subjects Assigned to Placebo or Reference Therapy	Number of Subjects Assigned to SGLT-2 Inhibitors	Heterogeneity I^2
Liver fat content						
MRI-PDFF or MRS (%)	−2.05 (−2.61–−1.48)	$Z = 7.07$, $p < 0.0001$	7	212	212	0.0%
Controlled attenuation parameter (dB/m)	−13.9 (−30.1–+2.20)	$Z = 1.69$, $p = 0.089$	3	86	106	43.7%
CT-Liver-to-spleen attenuation ratio	+0.10 (−0.06–+0.23)	$Z = 1.14$, $p = 0.256$	2	67	64	86.2%
Liver stiffness on Fibroscan®						
Liver stiffness measurement (kPa)	− 0.65 (−1.48–+0.20)	$Z = 1.48$, $p = 0.097$	2	71	76	14.0%

Metabolites 2021, 11, 22. https://doi.org/10.3390/metabo 11010022

iSGLT2 et NAFLD/ NASH ?

Practical guidelines for NAFLD/NASH, Japanese Society of Gastroenterology & the Japan Society of Hepatology



*When hepatic fibrosis is suspected in NAFLD, it should be treated as NASH.
**Adaptive insurance;① BMI over 35 kg/m^2 in spite of medical treatment, and ②Positive for at least one of DM HT, DL and sleep apnea.
***Add vitamin E in addition to therapy for lifestyle-related diseases.
****In Japan, vitamin E is not adaptive for insurance for NAFLD/NASH.

J Gastroenterol (2021) 56:951–963

Non validées par les Autorités de Santé à ce jour

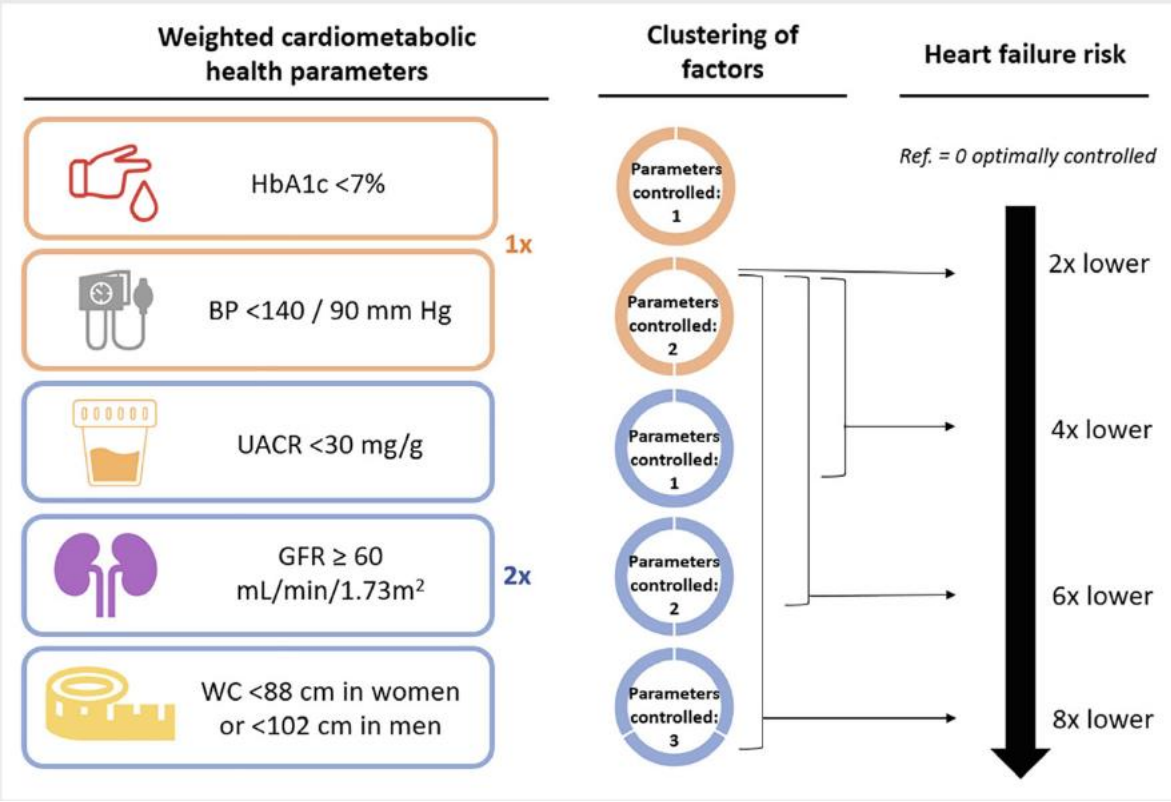
Pour Conclure

Approche Globale de la Prévention IC

Look AHEAD Essai Randomisé Contrôlé sur les effets CV d'une intervention intensive sur le mode de vie (perte de poids et augmentation de l'AP) par rapport au soutien et à l'éducation au diabète parmi 5145 participants âgés de 45 à 76 ans atteints de DT2 et de surpoids ou d'obésité

Table 1 **Cardiometabolic health parameters, their optimal target levels, associations, and weighted contribution to the cardiometabolic health score for heart failure**

Cardiometabolic health parameter	Optimal target level	HR (95% CI) (optimal vs. non-optimal control)	*p*-value	Cardiometabolic health score
WC	<88 cm (women) or <102 cm (men)	0.40 (0.18–0.90)	0.03	2
UACR	<30 mg/g	0.41 (0.31–0.54)	<0.001	2
GFR	≥60 ml/min/1.73 m^2	0.44 (0.30–0.64)	<0.001	2
HbA1c	<7%	0.63 (0.48–0.82)	0.001	1
Blood pressure	Systolic BP <140 mmHg and diastolic BP <90 mmHg	0.69 (0.53–0.89)	0.005	1
Smoking status	Non-current smoker	0.80 (0.46–1.42)	0.45	0
HDL-cholesterol	≥50 mg/dl (women) or ≥40 mg/dl (men)	0.83 (0.63–1.10)	0.19	0
Triglycerides	<150 mg/dl	0.93 (0.71–1.22)	0.59	0
Maximum score				8



European Journal of Heart Failure (2022) 24, 2037–2047

A Retenir

- Forte prévalence de l'IC dans la population diabétique
- Surmortalité de l'IC dans la population diabétique
- Effet péjoratif de l'association obésité-diabète sur l'incidence de l'IC
- « Obesity Paradox » : meilleur pronostic de l'IC en présence d'une obésité (IMC < 40 kg/m^2)
- Effet péjoratif de la stéatose hépatique sur l'incidence de l'IC
- iSGLT2
  - Font partie du traitement de base de l'IC (avec ou sans diabète)
  - Réduisent l'incidence du diabète dans la population IC*
  - Efficaces à tous les niveaux d'IMC
  - Effet favorable suggéré sur les paramètres hépatiques*

* Indications Non validées par les Autorités de Santé à ce jour