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et la région Aquitaine
Palais des Congrès
du mercredi 15 juin 2022
au vendredi 17 juin 2022

La menace métabolique

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- **Board:** ***Amgen, Sanofi, NovoNordisk***
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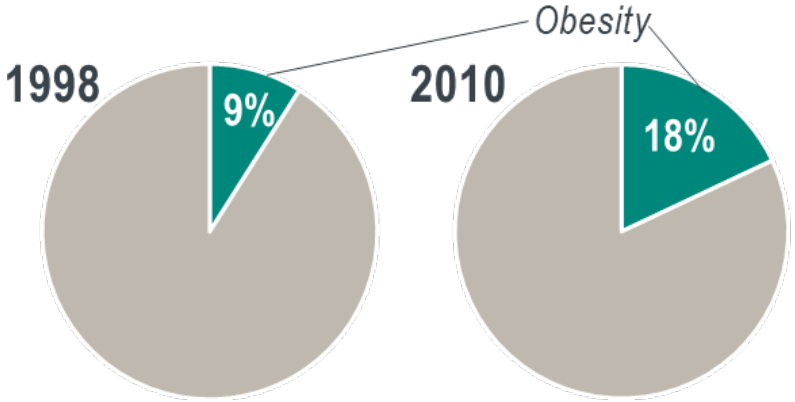
Sommaire

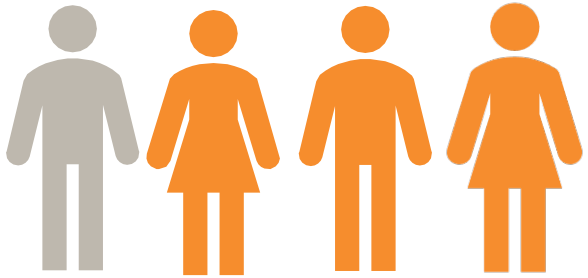
- **Epidemiologie de l'obésité chez les PVIH**
- **Association entre l'obésité, l'insulinorésistance et le diabète**
- **Dyslipidémie de l'obèse**
- **Impact de la graisse ectopique**

L’obésité devient de plus en plus prévalente chez les PVIH

Obesity amongst PLWH increased 2-fold between 1998 and 2010[1]



In 2017-2018, ~74% of adults aged 20 and over in the United States were overweight or obese[2]

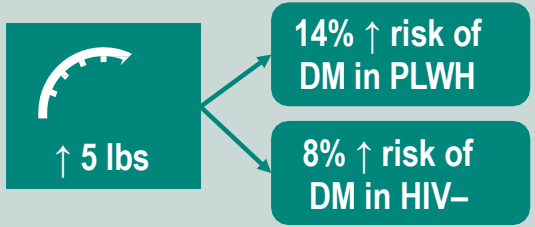


1. *Koethe JR et al. AIDS Res Human Retroviruses. 2016;32(1):50-58.*
2. *CDC. National Center for Health Statistics. Obesity and Overweight. https://www.cdc.gov/nchs/fastats/obesity-overweight.htm*

Les PVIH avec un IMC élevé sont à risque de diabète
Risque du surpoids ET diabète plus important chez PVIH

A study has shown that a higher risk for diabetes with increasing BMI is more pronounced among PLWH compared with HIV-negative controls[1]

BMI (kg/m^2)	Odds Ratio (95% CI)	
	HIV+ (n=3,327)	HIV- (n=3,240)
<20 kg/m^2	1.00	1.00
20 to 24.9 kg/m^2	1.68 (1.04-2.70)	1.20 (0.64-2.24)
25 to 29.9 kg/m^2	2.30 (1.43-3.69)	1.70 (0.93-3.11)
≥30 kg/m^2	5.35 (3.20-8.93)	3.25 (1.78-5.94)



Every 5 lbs of weight gain is associated with:
14% increased risk of DM in PLWH (HR, 1.14; 95% CI, 1.10-1.17) versus an 8% increased risk in HIV negative individuals (HR, 1.08; 95% CI, 1.07-1.10) (*P* <0.01)[2]

DM, diabetes mellitus

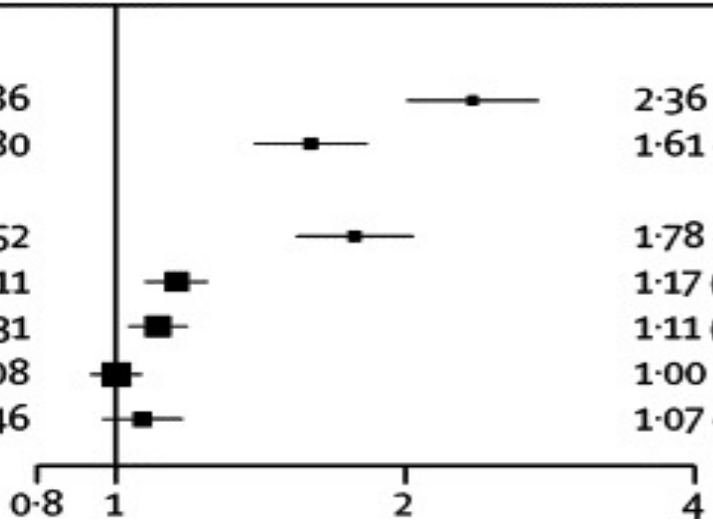
1. Butt AA et al. AIDS. 2009;23(10):1227-1234
2. Herrin M et al. J Acquir Immune Defic Syndr. 2016;73:20:228-236

Obésité, insulinorésistance/diabète et RCV

Le risque de maladie coronaire débute dès une glycémie au-delà de 6.0 mmol/L

Meta-analysis of 102 prospective studies including 698 782 people
(52 765 non-fatal or fatal vascular outcomes; 8·49 million person-years at risk)

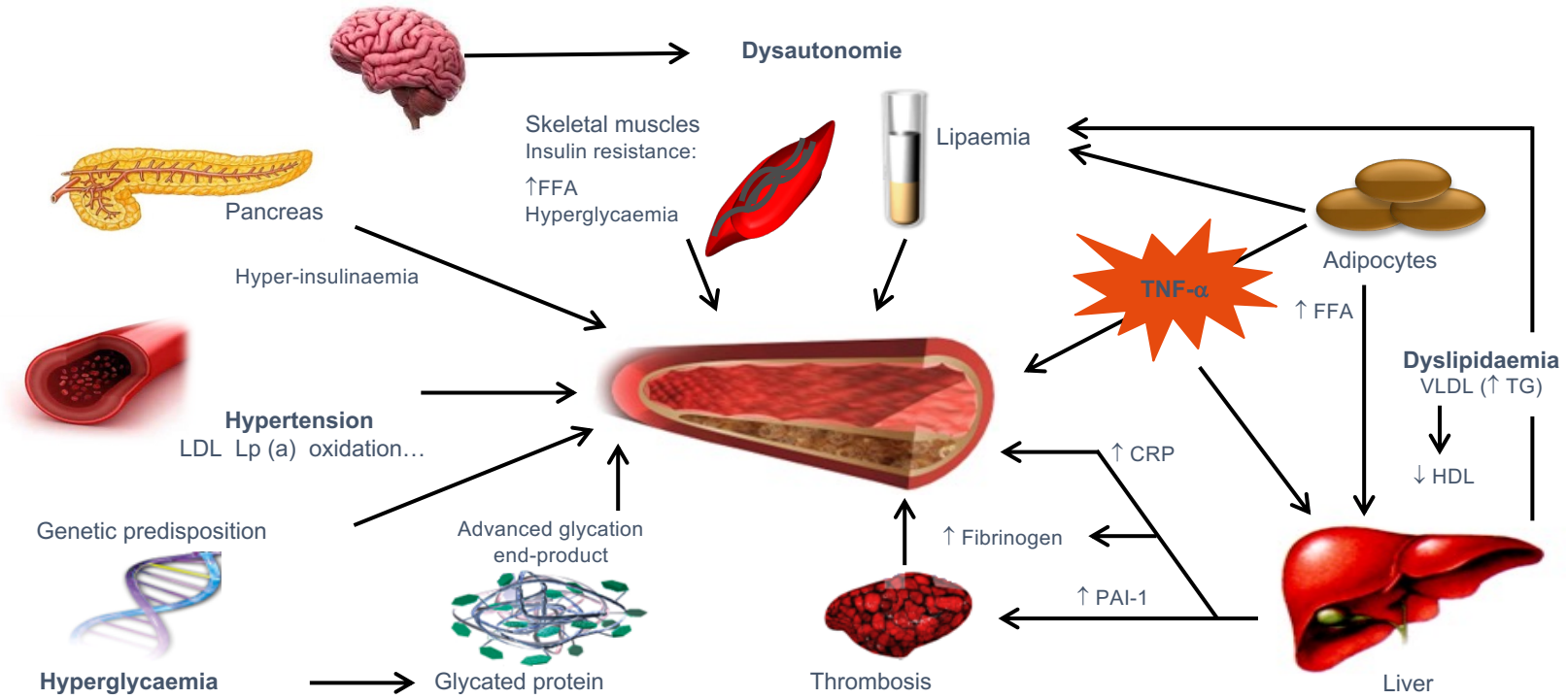
Fasting blood glucose concentration	Number of participants (%)	Number of cases	HR (95% CI)
Known diabetes at baseline			
≥7 mmol/L	13 122 (4·7%)	1186	2·36 (2·02–2·76)
<7 mmol/L	5807 (2·1%)	380	1·61 (1·42–1·82)
No known diabetes at baseline			
≥7 mmol/L	7240 (2·6%)	452	1·78 (1·56–2·03)
6·1 to <7 mmol/L	19 607 (7·0%)	1011	1·17 (1·08–1·26)
5·6 to <6·1 mmol/L	32 008 (11·5%)	1631	1·11 (1·04–1·18)
3·9 to <5·6 mmol/L*	185 590 (66·5%)	9508	1·00 (0·95–1·06)
<3·9 mmol/L	15 916 (5·7%)	646	1·07 (0·97–1·18)



Hazard ratios (HRs) for coronary heart disease by clinically defined categories of baseline fasting blood glucose concentration

The Emerging Risk Factors Collaboration. Lancet 2010;375:2215-2222.

Effets de l'hyperglycémie chronique (diabète)

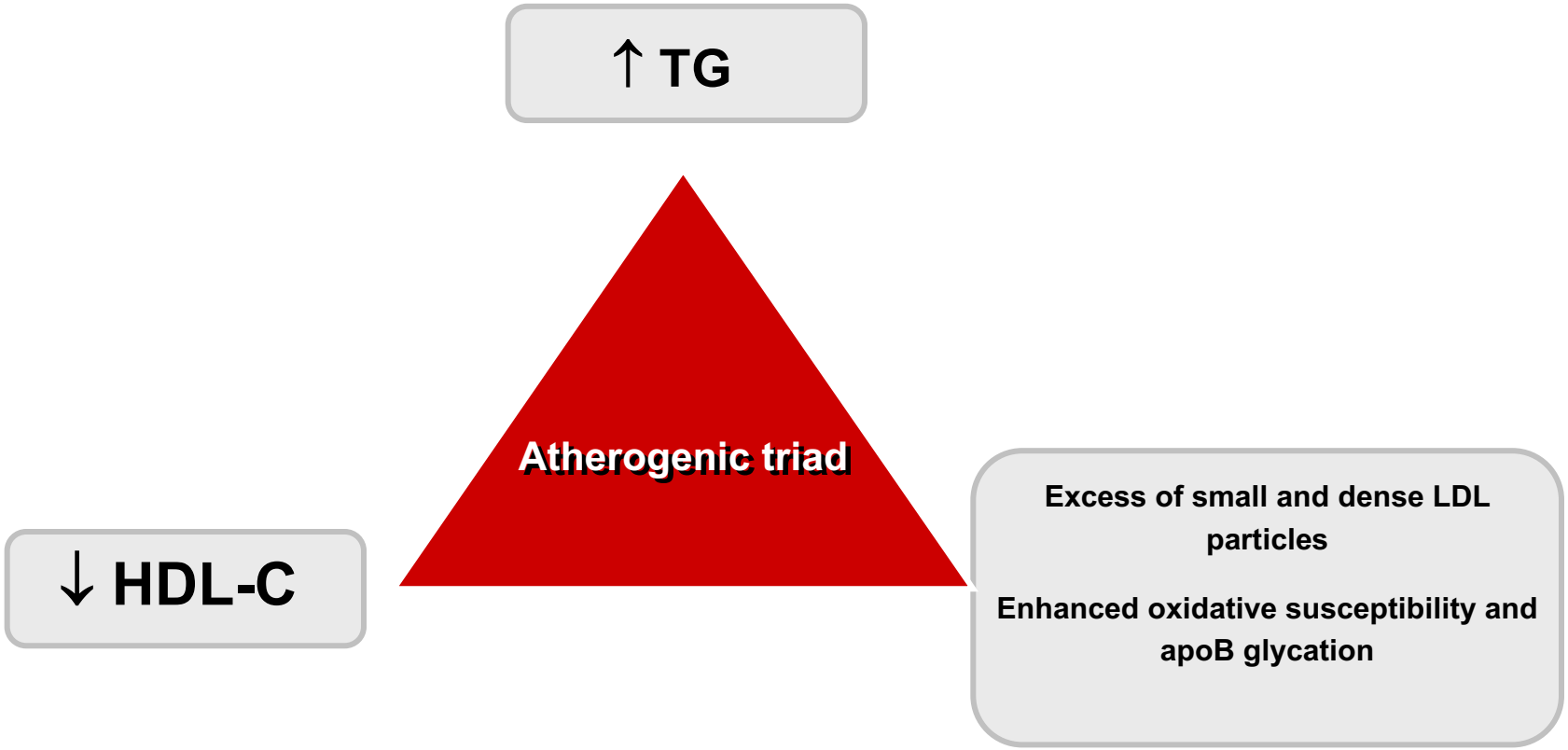


CRP, C-reactive peptide; CV, cardiovascular; FFA, free fatty acid; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; T2D, type 2 diabetes ; TG, triglyceride; TNF-α, tumour necrosis factor-α; VLDL, very low-density lipoprotein.

Libby P, Plutzky J. Circulation 2002;106:2760–2763.

Obésité et profil lipidique

TRIADE ATHEROGENE

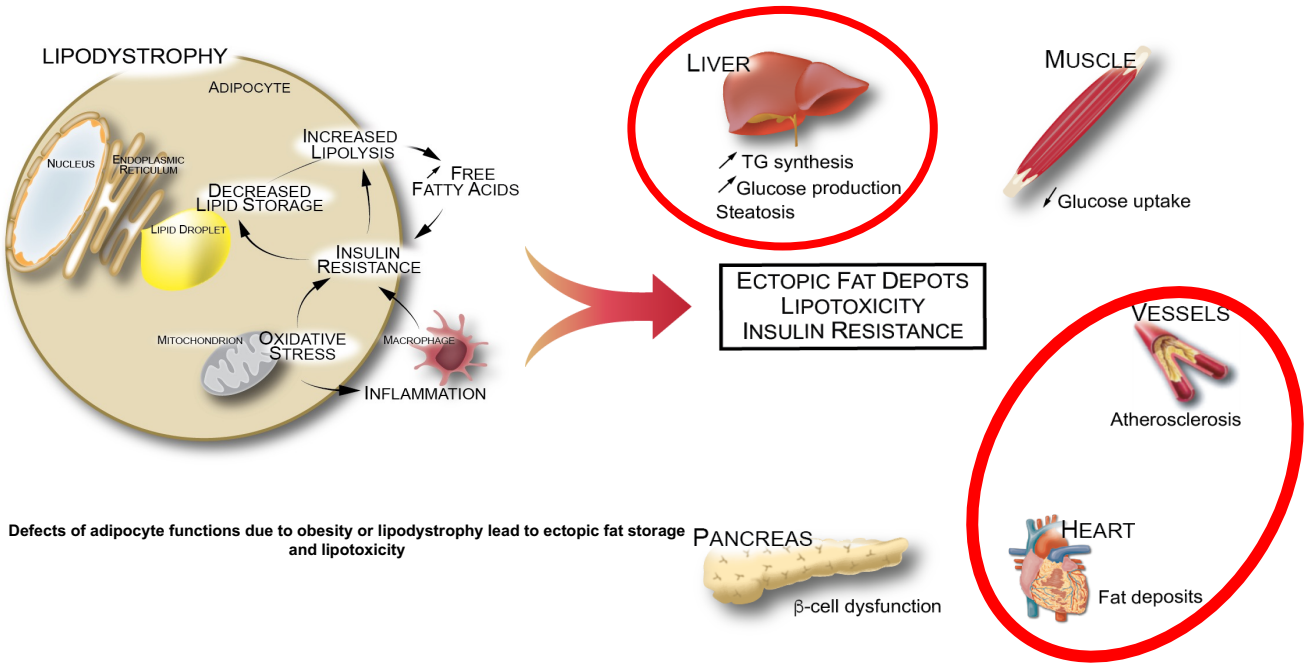


Impact de l’accumulation de la graisse ectopique

Qu’est-ce que la graisse ectopique ?

- Ectopic fat is defined by excess of adipose tissue located outside of classical adipose tissue deposits.

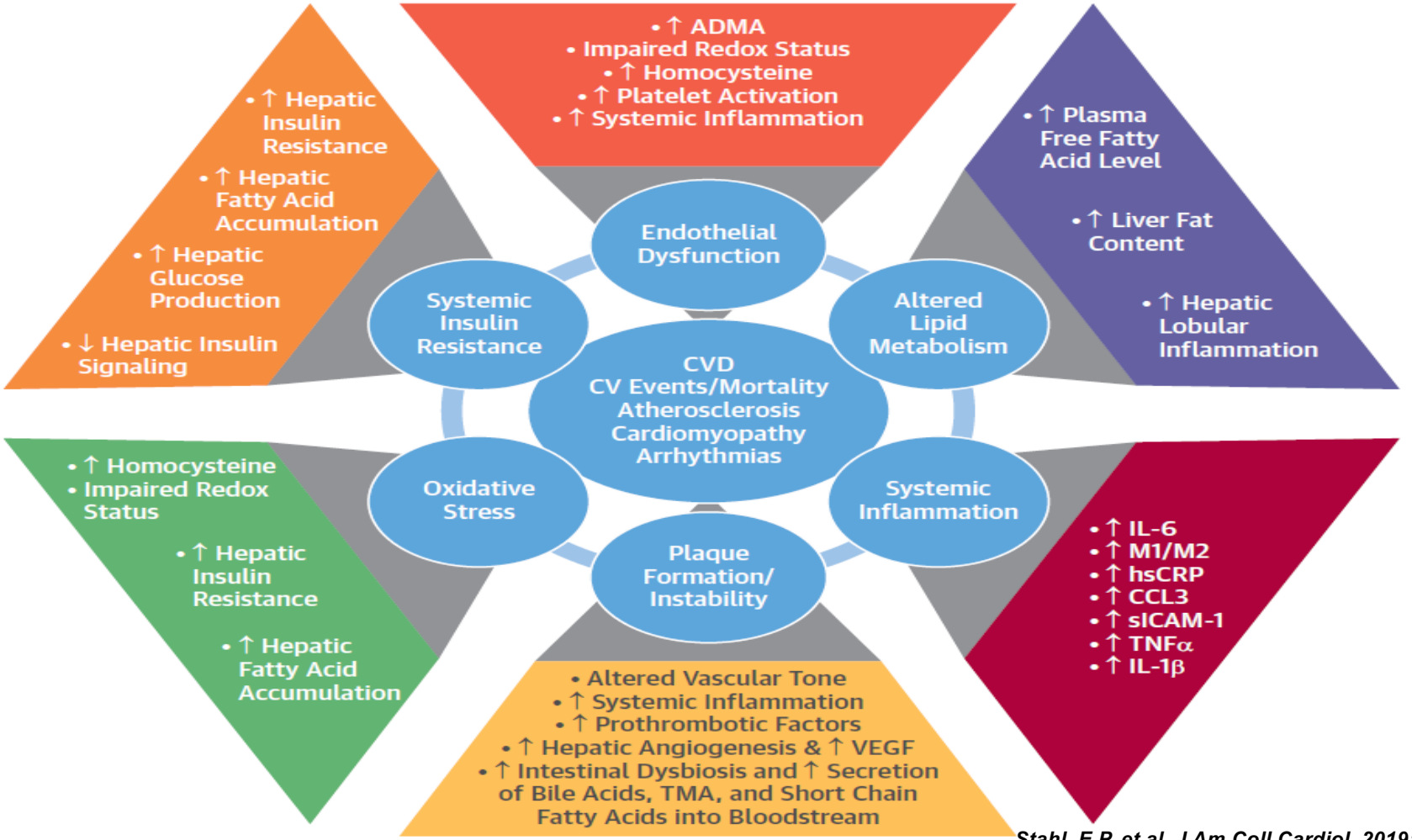
- Subcutaneous to ectopic fat deposition? → multifactorial, involving genetic, epigenetic and environmental factors leading to dysfunctional Epicardial Adipose Tissue characterized by a pro-inflammatory and pro-fibrotic phenotype.



Defects of adipocyte functions due to obesity or lipodystrophy lead to ectopic fat storage and lipotoxicity

Adapted from Guénantin et al, Semin Cell Dev Biol 2014

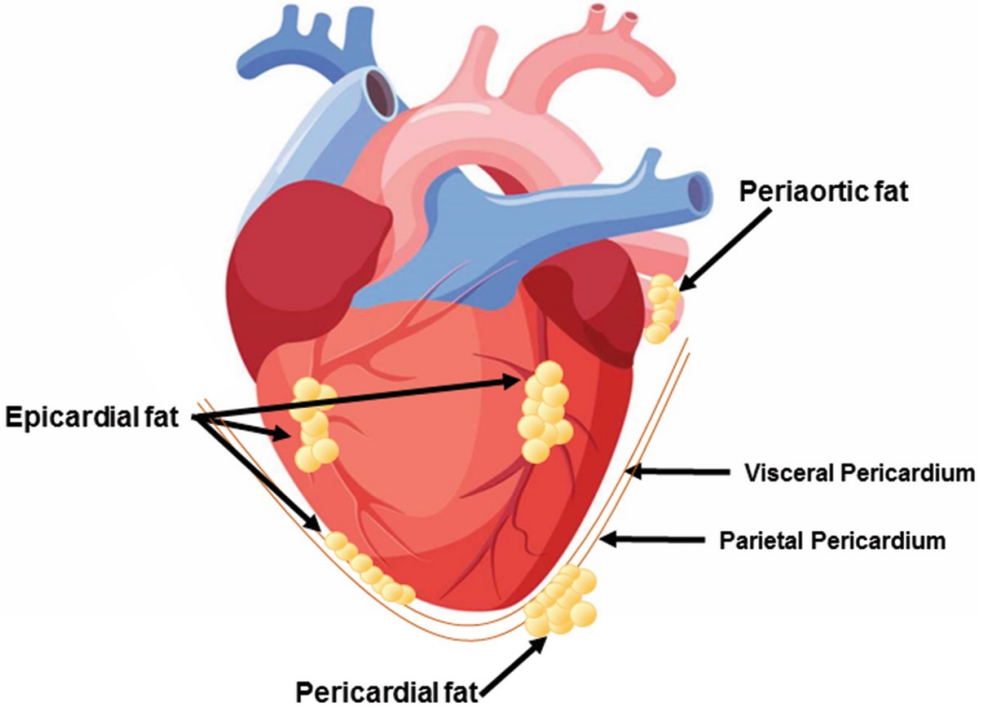
Liens entre stéatose hépatique et risque cardiovasculaire



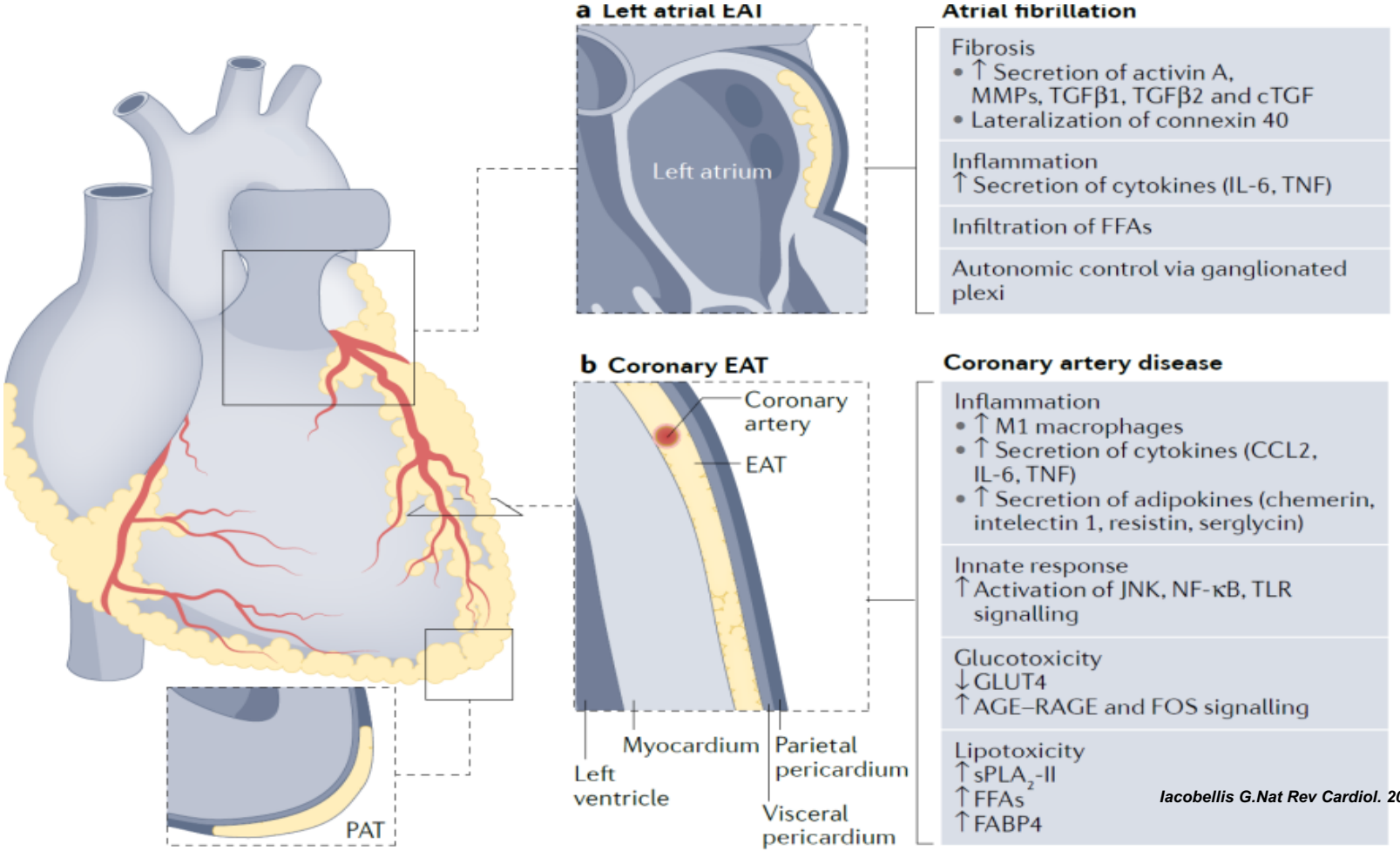
Stahl, E.P. et al. J Am Coll Cardiol. 2019;73:948–63.

Qu’est ce que la graisse épicardique ?

Systemic effects : visceral adipose tissue, intrahepatic and intramuscular fat.
Local activity: kidney and heart.
Heart fat : paracardial and epicardial adipose tissue (EAT)
EAT: fat depots between the myocardium and the visceral pericardium (i.e. pericardial fat, perivascular fat, and myocardial steatosis).



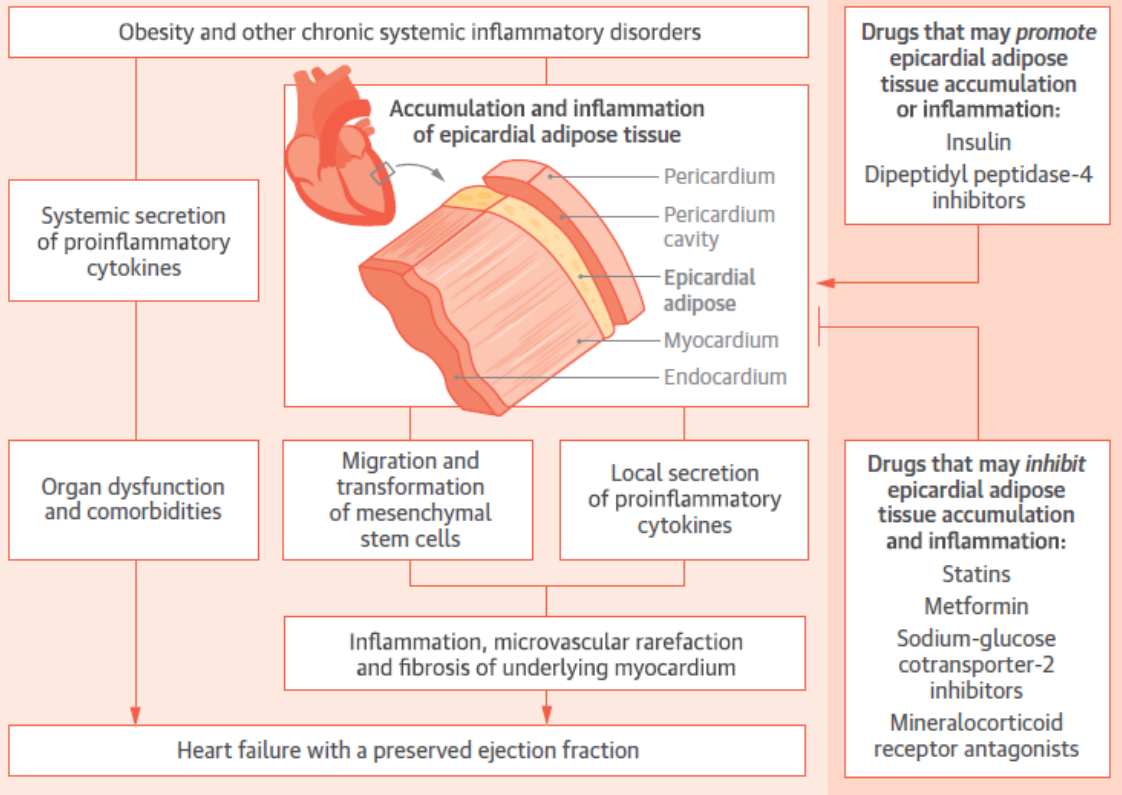
Tissu adipeux épicardique et atteinte cardiovasculaire



Iacobellis G.Nat Rev Cardiol. 2022 Mar 16:1-14.

Liens entre tissu adipeux épicardique et insuffisance cardiaque

- The pro-inflammatory and pro-fibrotic secretome characterizing dysfunctional EAT may impair cardiac structure and function→ pathogenesis of diastolic heart failure and atrial fibrillation.



Packer M. JACC 2018;7:2360-2372.

Quantification of EAT and future advances

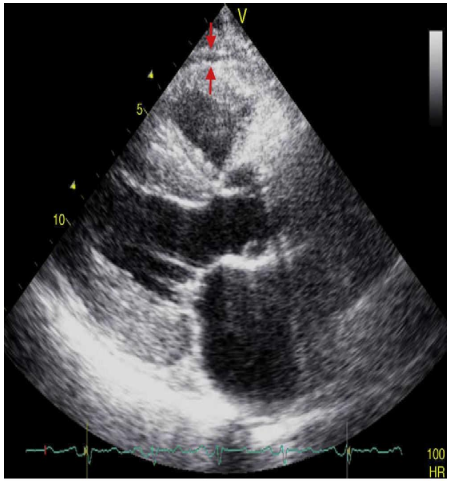
- **Two-dimensional trans-thoracic echocardiography (TTE) is the most accessible and safe procedure. > 5mm abnormal. Low reproducibility**

- **CT scan : quantification of volume**

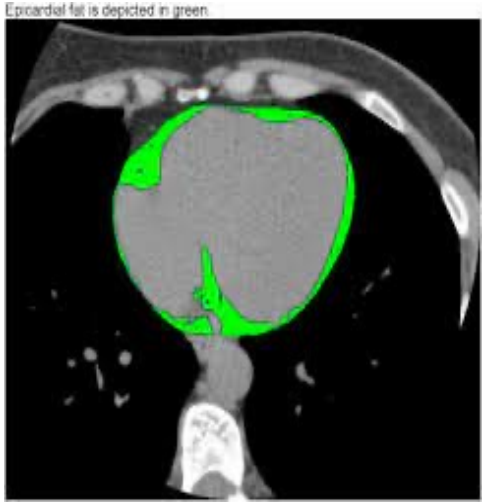
- **Cardiac Magnetic Resonance (CMR) = *gold standard* for EAT quantification:**

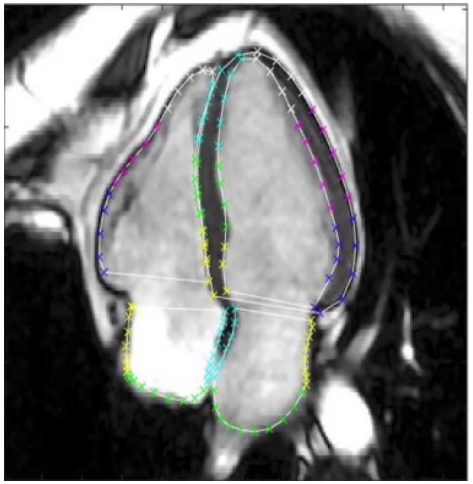
→ Both thickness and volume *(high costs and high time expenditure → limiting the routinely use of CMR in clinical practice*).

TTE **CT** **CMR**



Endocrinol Nutr. 2013;60:320–8

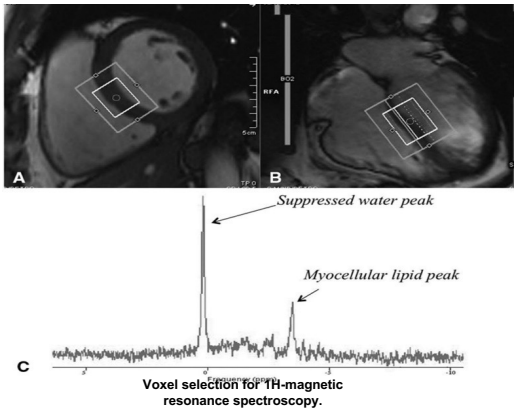




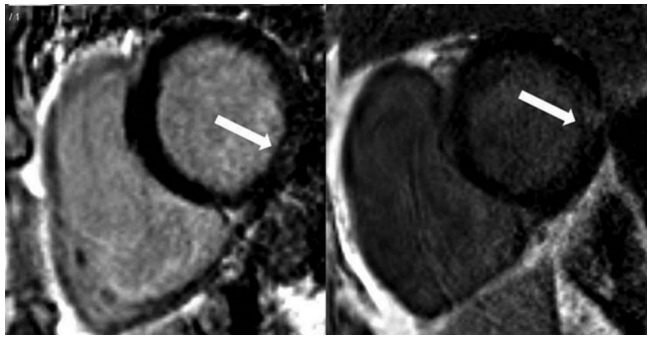
Stéatose ou fibrose cardiaque chez PVIH?

90 HIV+ *vs.* 30 HIV- controls underwent Cardiac MRI and spectroscopy
Cardiac function, cardiac fibrosis and lipid content

HIV+ had: 47% higher median myocardial lipid levels ($p < 0.003$)
74% higher median plasma triglyceride levels ($p<0.001$)
Myocardial fibrosis 76% vs 13% of control subjects ($p<0.001$)
Lower peak myocardial systolic and diastolic longitudinal strain



Voxel selection for 1H-magnetic resonance spectroscopy.



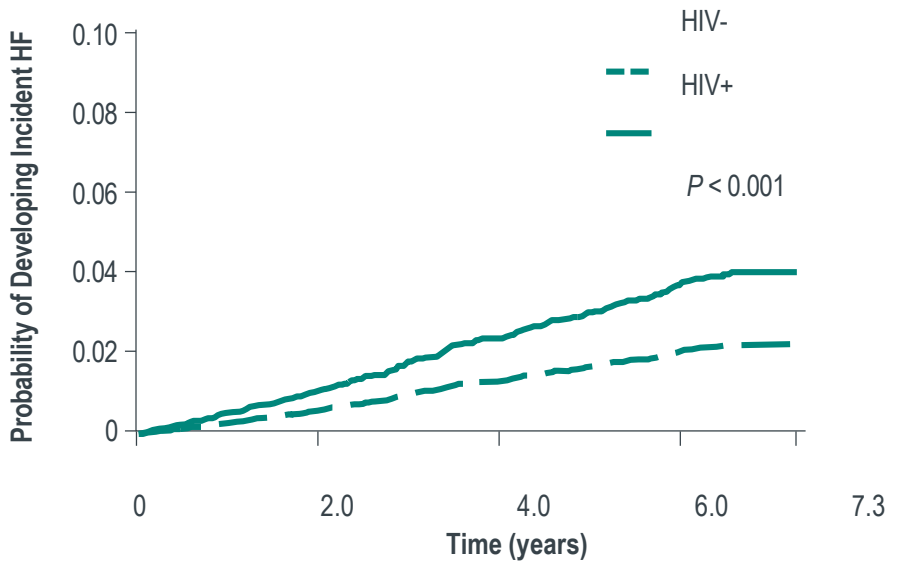
Holloway CJ et al. Circulation. 2013;128:814-822

Similar to patients with generalized lipodystrophy. The lipotoxicity hypothesis.
Nelson M et al. AJC 2013

Plusieurs cohortes nord-américaines observent un sur-risque d'insuffisance cardiaque chez PVIH

- Large observational cohorts of HIV-infected U.S. Veterans (VACS-VC) and the general U.S. adult population (NA-ACCORD) demonstrated that:
  - **VACS-VC:** HIV-infected women (n=710) had a 2.8-fold higher risk of CVD vs HIV-negative women (n=1477) (HR, 2.8; 95% CI, 1.7, 4.6)[1]
  - **VACS-VC:** PLWH had a 1.8-fold higher risk of heart failure (HR, 1.8; 95% CI, 1.39, 2.36) (as shown)[2]
  - **NA-ACCORD:** PLWH (n=29,169) had a 1.2-fold increased risk of MI (aIRR 1.21; 95% CI, 1.02, 1.45) compared to the general population (n=14,308)[3]

***Risk of Heart Failure Among Veterans Without CHD or Alcohol Abuse/Dependence Prior to Incident Heart Failure Event*[2]**

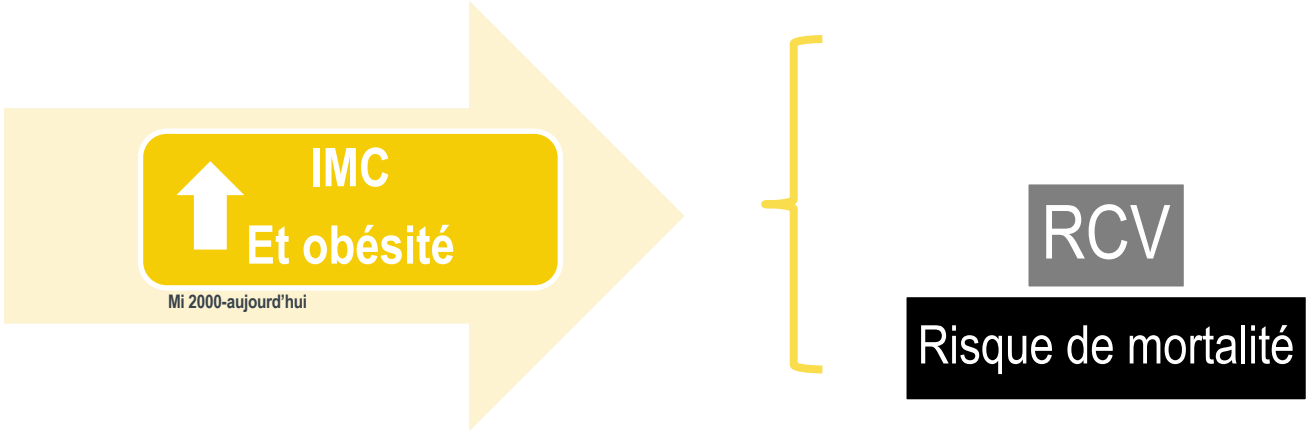


*The broader tern CVD includes heart failure and myocardial infarction.

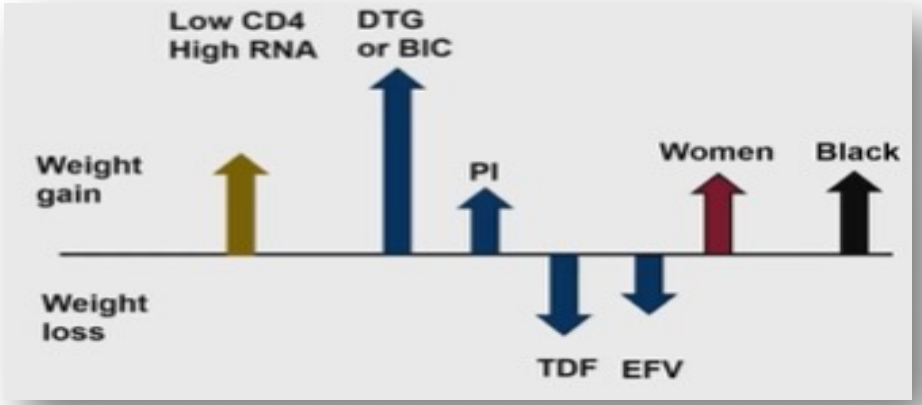
aIRR, adjusted incidence rate ratio; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; VACS-VC: Veterans Aging Cohort Study-Virtual Cohort, NA-ACCORD: North American AIDS Cohort Collaboration on Research and Design

1. Womack JA et al. *J Am Heart Assoc.* 2014;3:e001035.
2. Butt AA et al. *Arch Intern Med.* 2011;171(8):737-43.
3. Drozd DR et al. *J Acquir Immune Defic Syndr* 2017;75(5):568-576.

Challenge de la menace métabolique/prise de poids chez PVIH



Factors associated with weight gain

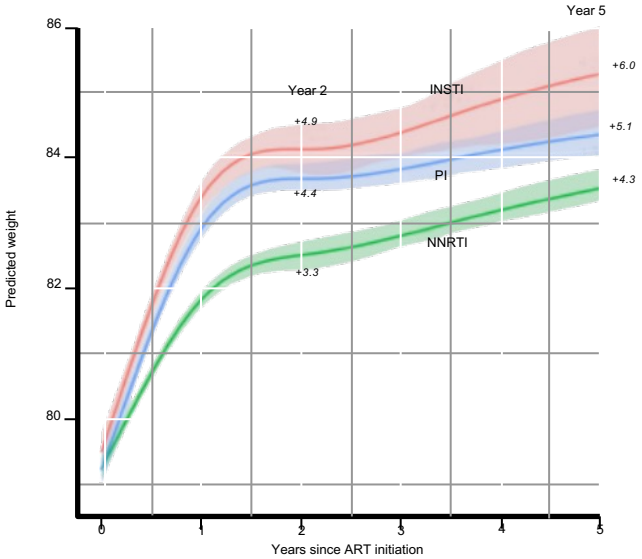


O'Halloran JA *et al.*, Presented at: CROI; March 4-7, 2019; Seattle, Washington
Hill et al., EACS 2019

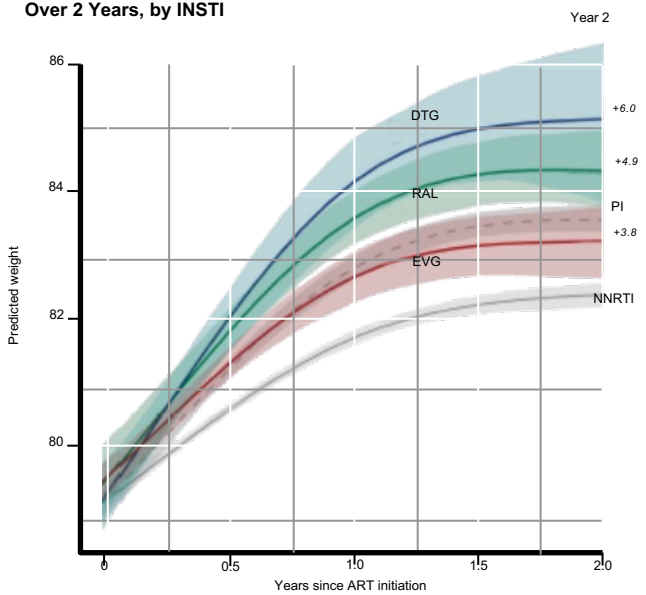
Prise de poids chez les patients naïfs (NA-ACCORD)

24001 patients naifs initiant un traitement à base de NNRTI-, PI- ou INSTI entre 2007 et 2016
NNRTI: n = 11,825
PI: n = 7,436
INSTI: n = 4,740
Méthode: modèle linéraire à effets mixtes (multivariés) utilisé pour adjuster et estimer la prise de poids au cours du temps*

Predicted Weight Changes Over 5 Years, by Class of ART



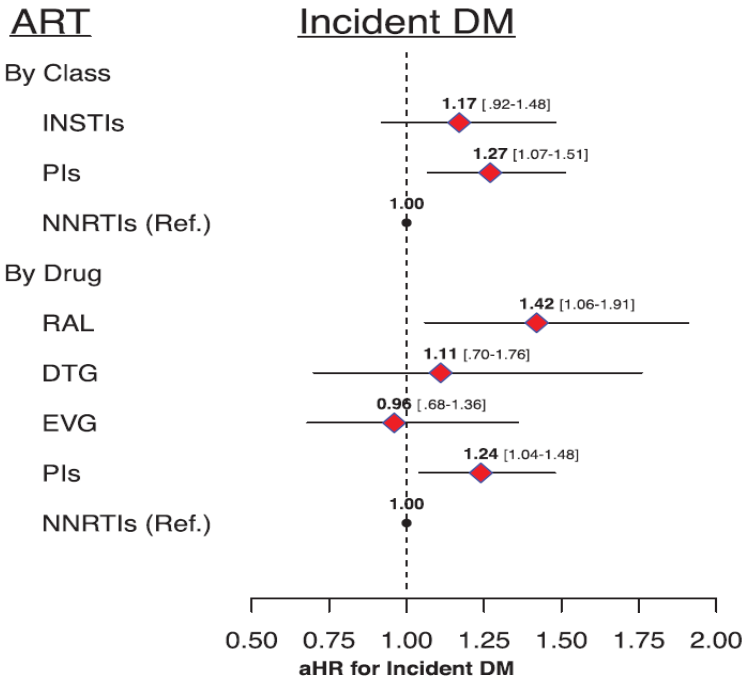
Predicted Weight Changes Over 2 Years, by INSTI



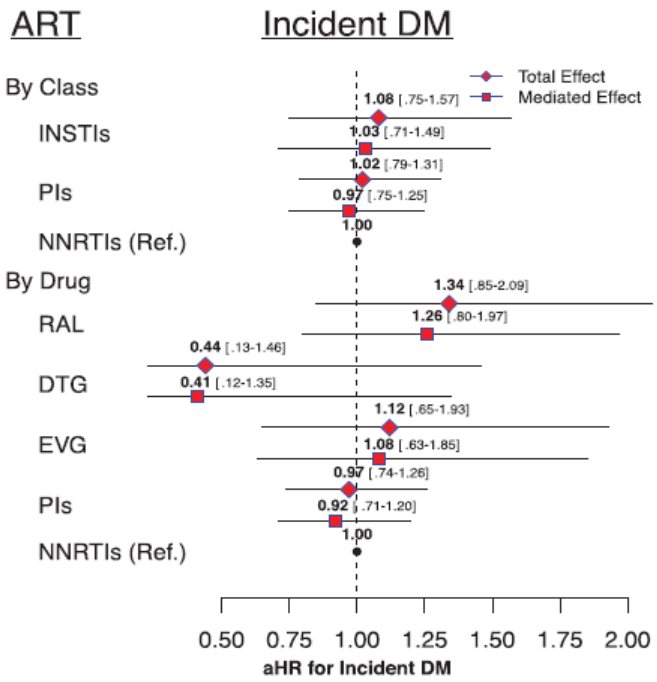
*Adjusted for age, sex, race, cohort site, HIV acquisition mode, ART initiation year, and baseline weight, HIV-1 RNA, and CD4+ cell count.

Adapted from Bourgi K, et al. Presented at CROI 2019; Poster #670

Incidence du diabète NA ACCORD associé à INSTI et prise de poids



HR ajusté pour l'incidence du diabète chez des sjts de la cohort NA-ACCORD nord-américain ayant débuté cART entre 2007 et 2016.



HR ajusté effet total et direct avec mesure de poids disponible à M12 initiation cART.

PWH (US and Canada), incident DM 10.7 cases per 1000 persons/year over a decade. 2-fold higher than in the general US population

Rebeiro PF et al. CID 2021;73:e2234-e2242

Questions en suspens

- **Prise de poids avec les anti-intégrases (études observationnelles et essais randomisés). Incidence plus élevée chez la femme d'Afrique sub-saharienne.**

- **S'agit-il d'un retour à un état normal chez les PVIH naïfs?**

- **TAF + dolutegravir augmentent la graisse tronculaire (ADVANCE trial) mais le dolutegravir n'augmente pas le risque de diabète incident (NAMSAL trial)→ quelle drogue est responsable?**
- **RESPOND cohort : comparé à lamivudine; Dolu, ralte et TAF significativement associés >7% ↗ IMC, idem pour IMC faible préART (2·10, 1·91–2·31) et ethnie noire (1·61, 1·47–1·76).**

- **Quelle définition de la prise de poids chez PVIH? 7% ↗ IMC idem pop gal? (ex antipsychotiques)**

Bansi-Matharu L et al. Lancet HIV 2021; 8: e711–22.

CONCLUSIONS

- La prise de poids est une menace métabolique pouvant entrainer une hypertension, une dyslipidémie et un état d'insulinorésistance

- La prise de poids et/ou l'augmentation de la graisse viscérale > 5% est associé à une augmentation du risque métabolique (HTA, baisse HDLc, insulinorésistance et élévation des TG)

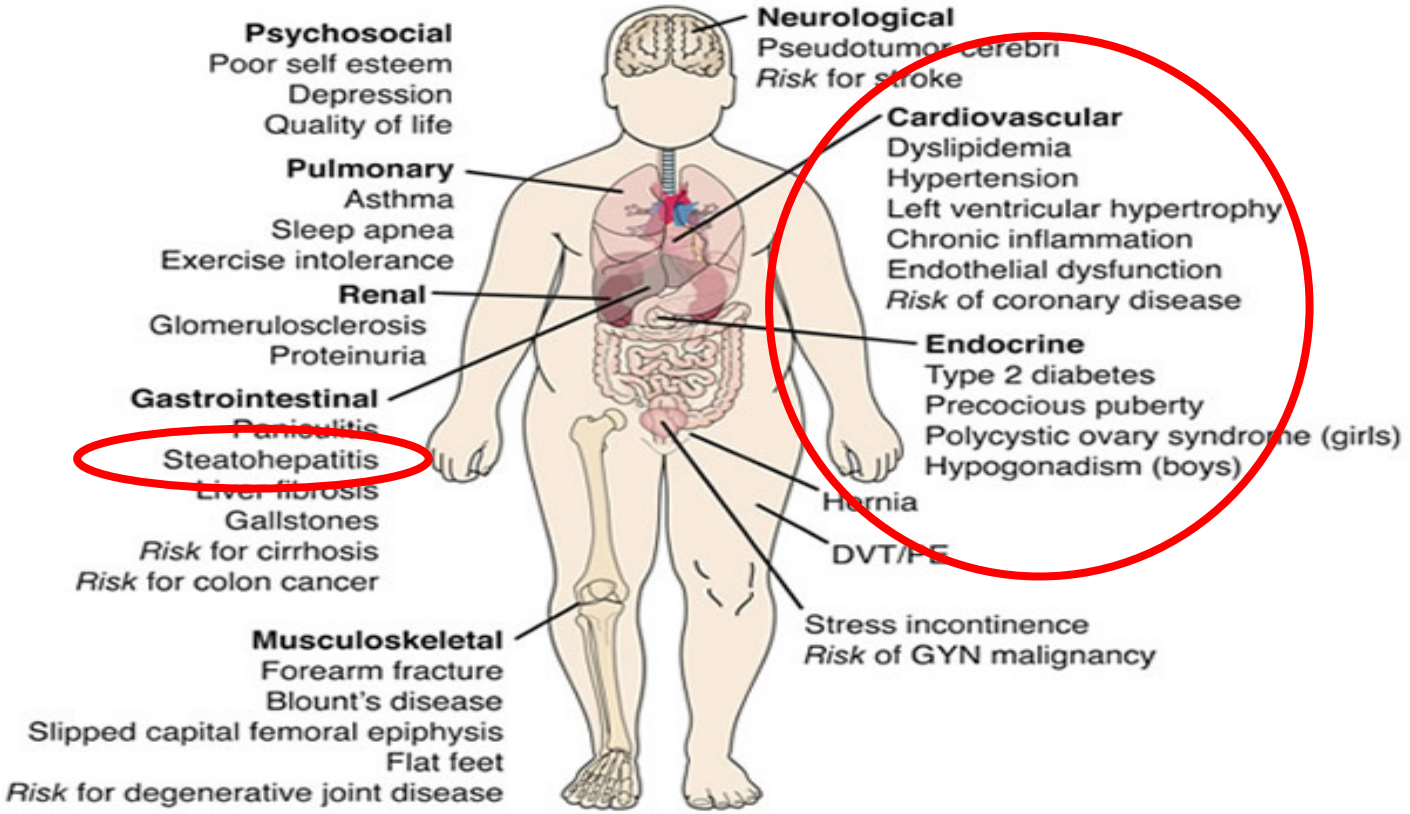
- La stéatose hépatique et le dysfonctionnement du tissu adipeux épicardique ont un rôle important de développement des maladies CV (athérosclérose, insuffisance cardiaque et troubles du rythme). Mécanismes non élucidés.

- Le dysfonction du TA chez PVIH est complexe; pas seulement un pb de quantité mais surtout de qualité (activité immune du TA, inflammation chronique du TA)

Thank you

Fernando Botero
Dancers 1987

Complications of Childhood Obesity



Macleods Clinical examination 13th Ed. (2013)

EAT and CAD

- A growing body of evidence supports the role of EAT as a promoter of atherosclerotic plaque progression and vulnerability.

BIO

- Integrative miRNA and whole genome analyses identified the signature of miRNAs in EAT of CAD patients, by focusing on miR-103-3p downregulation as prominent features.
- The typical secretome of dysfunctional EAT is also associated with VSMC migration and activation.
- Relationship between EAT and different features of plaque vulnerability: thin-cap of the fibroatheromas, high percentage of necrosis, elevated endoluminal stenosis and presence of calcification.

Epidemio

- Two meta-analyses confirmed this association independently of CAD definition: obstructive or significant coronary stenosis, coronary artery calcification (CAC) or myocardial ischemia.
- Predictive role of dysfunctional EAT towards the occurrence of major adverse cardiovascular events (i.e. CV death, myocardial infarction [MI], unstable angina, intra-stent re-stenosis).

Ansaldo AM et al. IJC 2019;279:254–260.
Nerlekar N. et al. J. Am. Heart Assoc. 2017
Mancio J et al. Eur. Heart J. Cardiovasc. Imaging 2018;19:490–497.
Mahabadi AA et al. JACC. 2013;31 1388–1395.

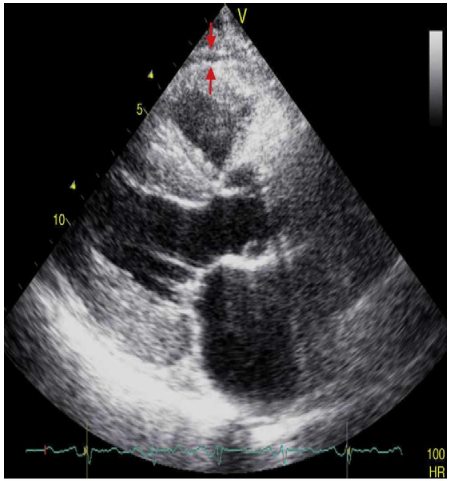
- Two-dimensional trans-thoracic echocardiography (TTE) is the most accessible and safe procedure. > 5mm abnormal. Low reproducibility

- CT scan : quantification of volume

- Cardiac Magnetic Resonance (CMR) = *gold standard* for EAT quantification:

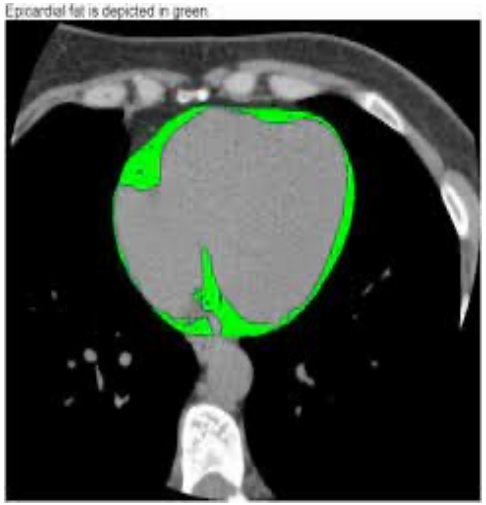
→ Both thickness and volume *(high costs and high time expenditure → limiting the routinely use of CMR in clinical practice*).

TTE

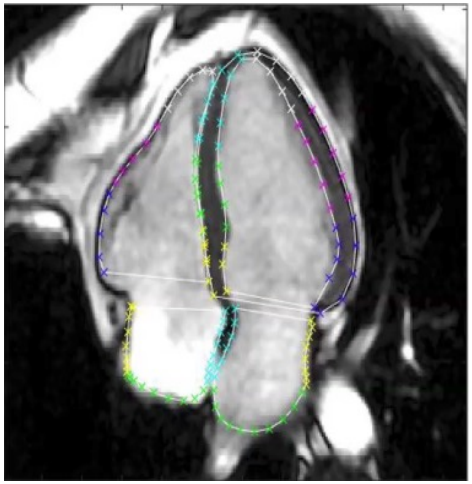


Endocrinol Nutr. 2013;60:320-8

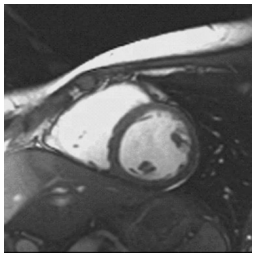
CT

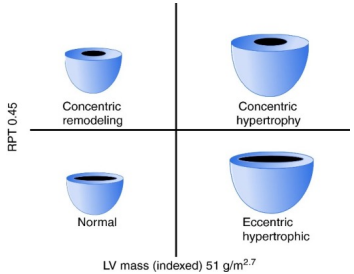


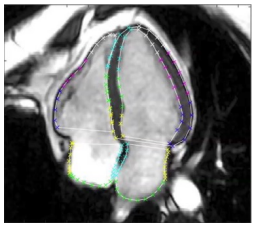
CMR

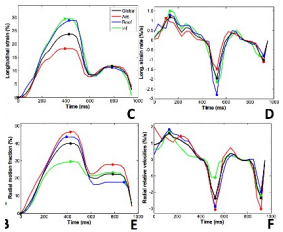


SSFP



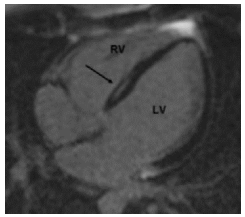




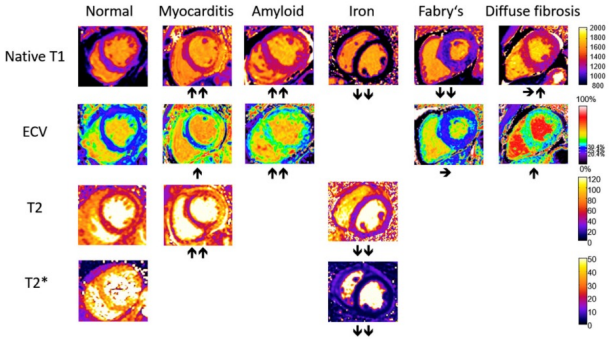


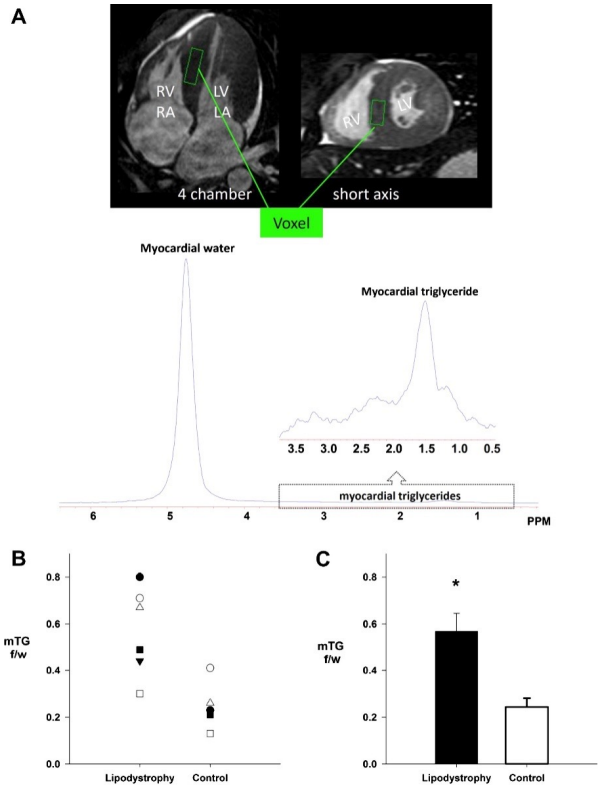
Whole Heart FT-MRI

LGE in LMNA CMP



Quantitative Myocardial Relaxometry Mapping





Am J Cardiol. 2013 October 1; 112(7): 1019–1024. doi:10.1016/j.amjcard.2013.05.036.

Cardiac Steatosis and Left Ventricular Hypertrophy in Patients with Generalized Lipodystrophy as Determined by Magnetic Resonance Spectroscopy and Imaging

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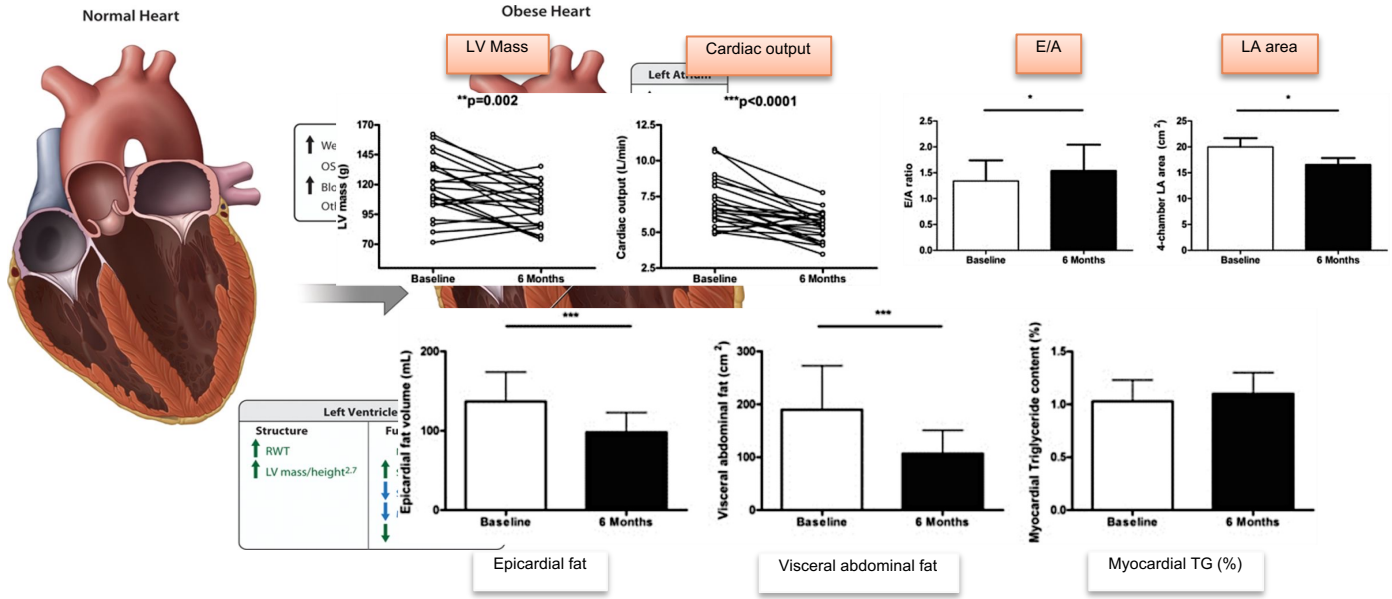
- N=6 vs 6 controls
- LVH independent of BP, exercise, no obesity, pericardial fat
- Relation to cardiac steatosis ?
- Transgenic mouse models, cardiac-specific overexpression of fatty acid transport proteins, or enzymes involved in triglyceride synthesis, produce severe cardiac steatosis, with the excess fatty acid causing concentric LV hypertrophy



Aurigemma G P et al. Circ Cardiovasc Imaging. 2013

Gaborit, Clément et al. JACC

- **Yes**

→ **Many large population-based cohorts.**

- **No**

→ **In contrast, some studies did not.**

After controlling for DM and BMI, NALFD is no more an independent risk factor (70-75% DM have NAFLD)

Haring R, et al. Hepatology 2009;50:1403–11.
Zhou YJ, et al. J Dig Dis 2012;13:153–60.
Treeprasertsuk S, et al. Liver Int 2012;32:945–50.
Pisto P, et al. BMJ Open 2014
Jepsen P, et al. Hepato- Gastroenterology 2003;50:2101–4.

Disparities : How NAFLD is diagnosed in those studies? What are the CVD endpoints?

Studies	N	Non fatal and fatal CVD events	Severity of NAFLD or NASH	CVD Mortality
Meta-analysis of Targher (2016)	n= 34 043 16 studies*	**OR: 1.64** 95% CI: 1.26 to 2.13	**OR: 2.58** 95% CI: 1.78 to 3.75	No association
Meta-analysis of Haddad (2017)	n= 25 837 6 studies) NAFLD (diagnosed via ultrasound)	Clinical CVD evts **RR: 1.77** 95% CI: 1.26 to 2.48	NR	NR
Meta-analysis of Wu (2016)	n= 165 000 34 studies NAFLD was defined by ultrasound, CT, histology, or liver enzymes	**OR: 1.81** 95% CI: 1.23 to 2.66 Incident CVD **HR: 1.37** 95% CI: 1.10 to 1.72	**HR: 2.97** 95% CI: 1.03 to 8.52	No association with either overall mortality or CVD mortality in both NAFLD and NASH.

*NAFLD by imaging/by histology in one study

Targher G, et al. J Hepatol 2016;65:589–600.
Mahfood Haddad T, et al. Diabetes Metab Syndr 2017
Wu S, et al. Sci Rep 2016

- NAFLD is independently associated with increased CIMT and CAC.

- Meta-analysis (n=85 395 with 29 493 NAFLD) increased risk of subclinical atherosclerosis compared with individuals without NAFLD

(OR: 1.60; 95% CI: 1.45 to 1.78)

CIMT (OR: 1.74; 95% CI: 1.47 to 2.06)

Arterial stiffness (OR: 1.56; 95% CI: 1.24 to 1.96)

CAC (OR: 1.40; 95% CI: 1.22 to 1.60)

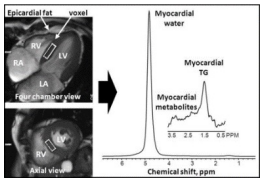
Endothelial dysfunction (FMD) (OR: 3.73; 95% CI: 0.99 to 14.09).

- Longitudinal study (n=8,020, FU 8 years)

Regression of CIMT in those with regression of NAFLD compared with those with persistent NAFLD was HR 0.82 (95% CI: 0.69 to 0.96; p= 0.013)

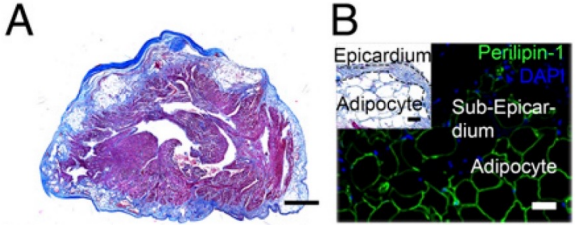
Kim D, et al. Hepatology 2012;56:13.
Zhou YY, et al. Hepatology communications 2018;2:376–92.
Sinn DH et al. Gastroenterology 2016; 151:481–8.e1.

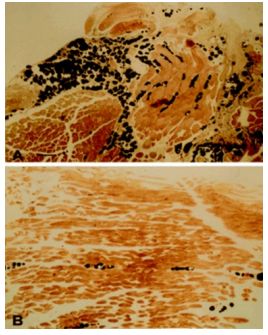
- Increased left ventricular wall thickness and myocardial mass
- lower early diastolic relaxation velocity (and worse absolute global longitudinal strain
- NAFLD independently associated with valvular heart disease, specifically aortic valve sclerosis (AVS) and mitral annulus calcification
- NAFLD (n= 180 D) associated with increased risk of AVS (adjusted OR: 3.04; 95% CI: 1.3to 7.3).
- Increased Epicardial adipose tissue



Trovato FM et al. Int J Cardiol 2016;221:275–9.
Markus MR et al. Arterioscl Biol Vasc Biol 2013;33:1690–5.

- NAFLD is a marker of ectopic fat accumulation in other organs, including the myocardium and pericardium→ left atrial remodeling
- Adipocytes from epicardial, retrosternal or abdominal adipose tissues may modulate the electrophysiological properties and ion currents, causing higher arrhythmogenesis (ANS dysfunction)
- NAFLD may release a variety of pro-inflammatory and pro-coagulant mediators and other inflammatory cytokines possibly inducing structural and/or electrical remodelling of the atria





Jmaly S et al, JACC 2016

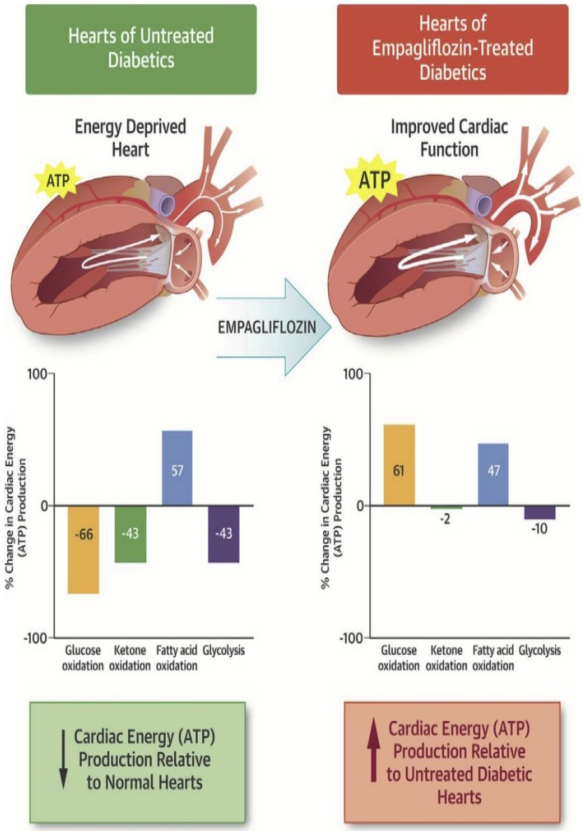
- Statins + effects both CVD, EAT and NAFLD
- Aspirin ?
- Metformin: limited efficacy in NAFLD
- Pioglitazone: decrease hepatic fat content; increase hepatic insulin sensitivity; decrease serum ALT levels; and improve fibrosis, steatosis, inflammation, and ballooning necrosis (concern with HF)
- Liraglutide (GLP-1 analogue) reduces NASH (LEAN: weight loss dependant)
- Empaglifozine (SGLT2i) reduces EAT….
- Angiotensin II receptor blockers (ARBs) weak proof
- Vitamin E no CV effect
- Bariatric surgery

- Future: Ongoing Phase III clinical trials with Farnesoid X receptors (FXRs) agonist : Obeticholic Acid (LDLc increased), Elafibranor (dual PPAR-α/delta agonist)
- Phase IIb: Cenicriviroc is an antagonist of C-C motif chemokine receptor (CCR) types 2 and 5 : decreases fibrosis in NASH

ATTEMPT study. Arch Med Sci 2011;7:796–805.
ACC/AHA guidelines. J Am Coll Cardiol 2014;63:2889–934.
N Engl J Med 2010;362:1675–85.
JAMA Intern Med 2017;177:633–40.

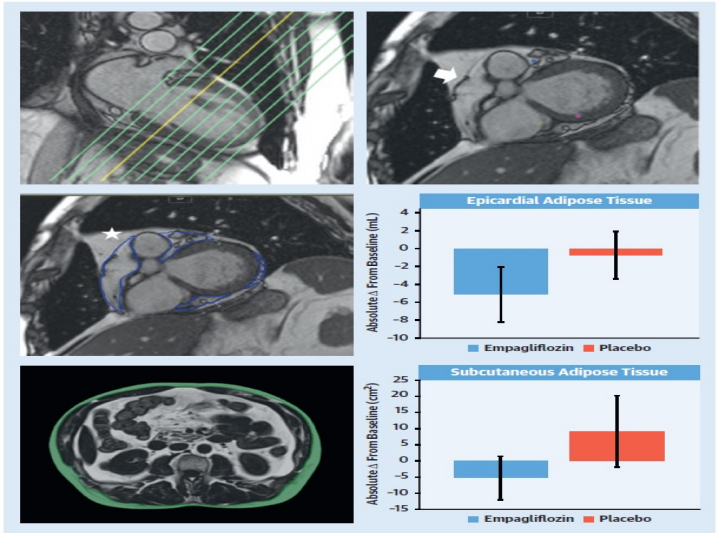
Changes in Epicardial Fat May Drive SGLT2 Inhibitor Benefits

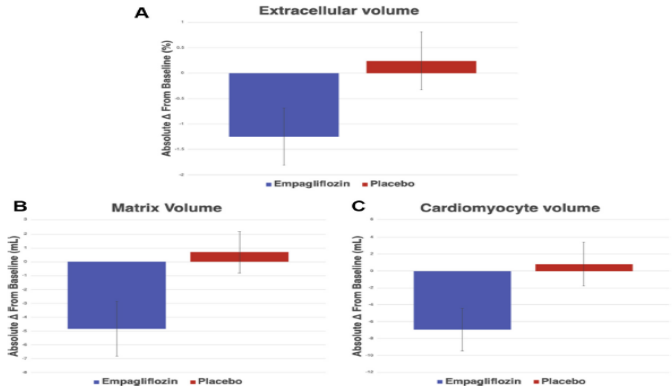
DIABETICS



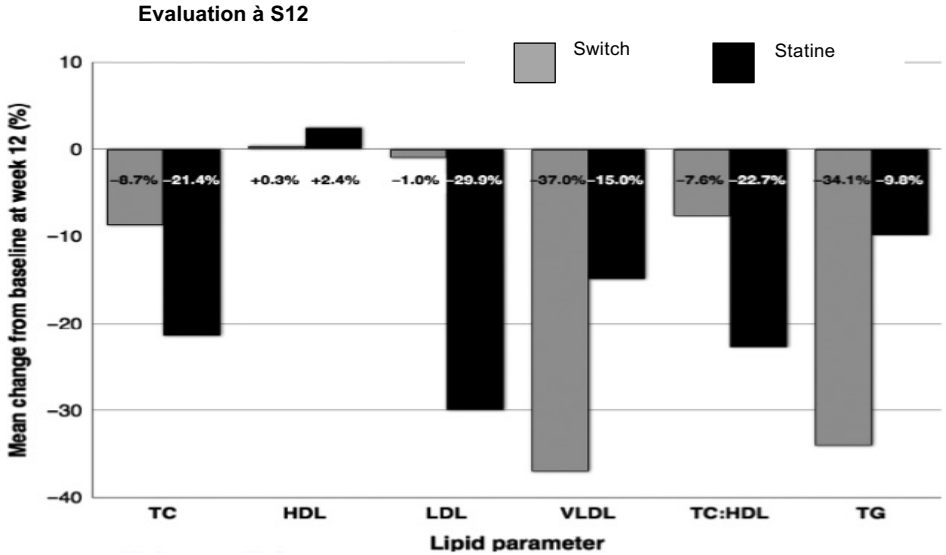
NON DIABETICS with HFrEF

EMPA-TROPISM trial.





Requena-Ibáñez JA et al, JACC Heart Fail 2021;9:578-589.



- Patients VIH < 50 cp/mL, chol total ≥ 5.5 mmol/L et risque CV élevé (score Framingham ≥ 8% ou diabète or antécédents familiaux)
- Randomisation sous rosuvastatin 10 mg/j (n=23) ou switch d'IP/r (n=20: principalement RAL (45%) et RPV (20%)
- En baseline: LPV/r: 51%, ATZ/r: 28% et DRV/r: 21%.

- ***Calza et al., Inf Dis 2017***: Même constat à 48S chez patients VIH < 50 cp/mL avec hyperlipidémie randomisés sous rosuvastatine 10mg/j (n=47) ou switchés d'IP/r vers NVP (n=43) ou RAL (n=46).

- **Impact positif du switch d'IPs sur le VLDL et les TG**
- **Diminution significativement + importante du LDL dans le bras statine**

- L’obésité et ses conséquences métaboliques; l’insulinorésistance et le diabète sont des facteurs de risques indépendants de maladies athérosclérotiques

- Les années passées en surpoids sont associées au risque de décès

- Les mécanismes associés à ce sur-risque sont complexes (inflammation, stress oxydant, dysfonction endothéliale, dyslipidméie athérogène, atteinte multiorgane foie, rein, micro et macrocirculation, T. Adipeux), thrombopathie

- Réduction de l’IMC est associée à une amélioration de la survie

- Prise en charge individualisée (exercice, diététique, dépistage précoce IR et diabète, HTA)

- Prise en charge médicamenteuse discuter switch ARV et/ou statine en fonction du niveau de RCV et historique de la dyslipidémie

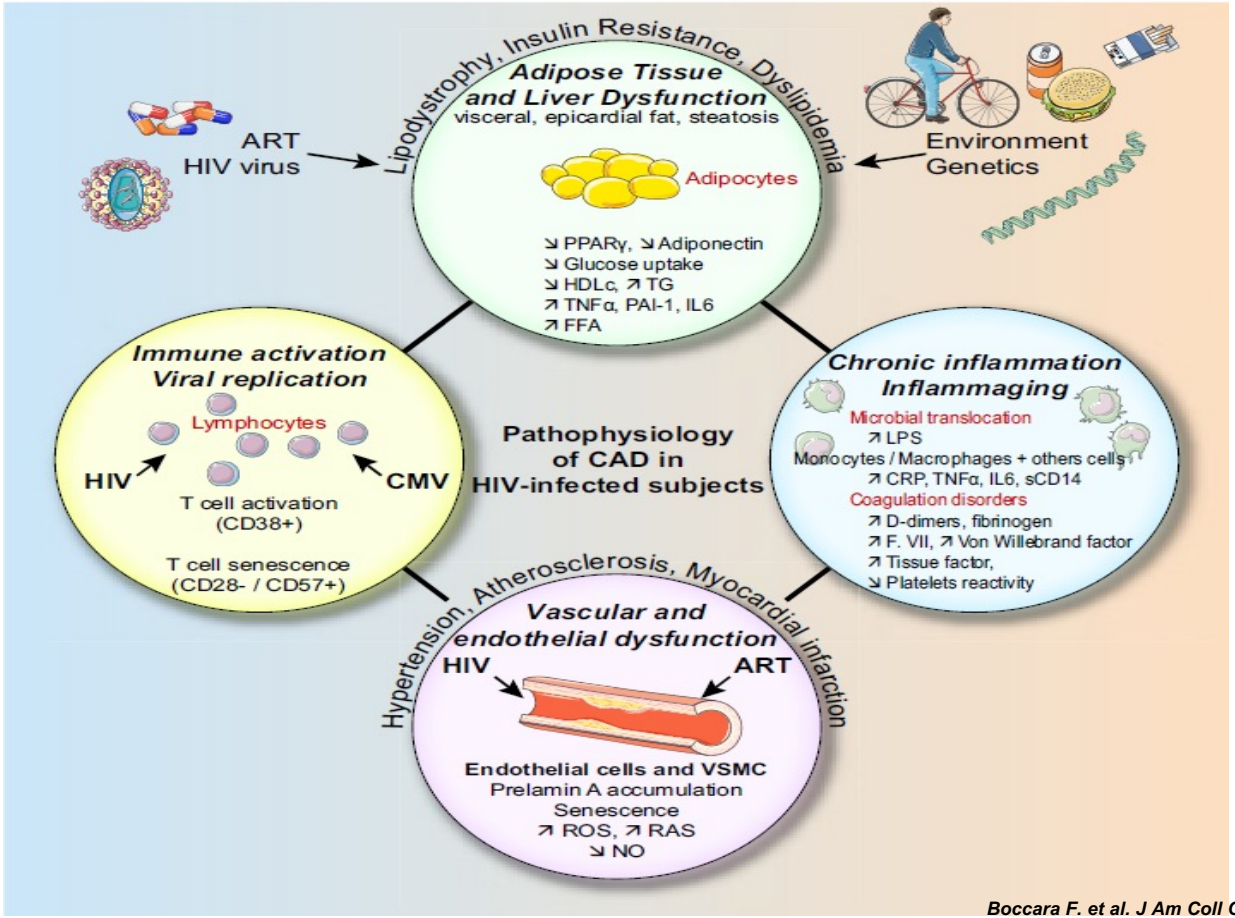
- **Pharmacological treatments. Glucagon-like peptide 1 (GLP-1) receptor are expressed in EAT and their pharmacological activation leads to EAT reduction in a weight loss-dependent way**

- **SGLT2i: improved adiposity, interstitial myocardial fibrosis, aortic stiffness, and inflammatory markers in nondiabetic patients (empaglifozine)**

- **Intensive statin treatment has been described to reduce EAT volume independently of the degree of lipid lowering. It has been then suggested that anti-inflammatory pleiotropic activities of statins might have a role in EAT reduction.**

- **The candidate medications under study for NAFLD should be thoroughly evaluated using cardiovascular endpoints and subclinical CVD.**

Modification of the adipose tissue in PLHIV is part of the increased atherogenic process



Boccara F. et al. J Am Coll Cardiol. 2013;61:511-23.