From Non-alcoholic fatty liver disease to Heart Failure with Preserved Ejection Fraction….and Sleep Apnea/COPD

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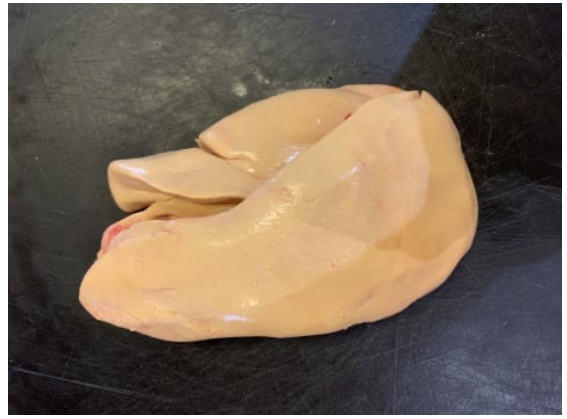
【Non-alcoholic fatty liver disease; NAFLD】

- NAFLD is the hepatic outcome of metabolic abnormalities such as obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia.
- NAFLD encompasses a continuum of the liver disease progressing from steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and finally to cirrhosis.
- The worldwide prevalence of NAFLD is estimated to be about 25 % of the general population.

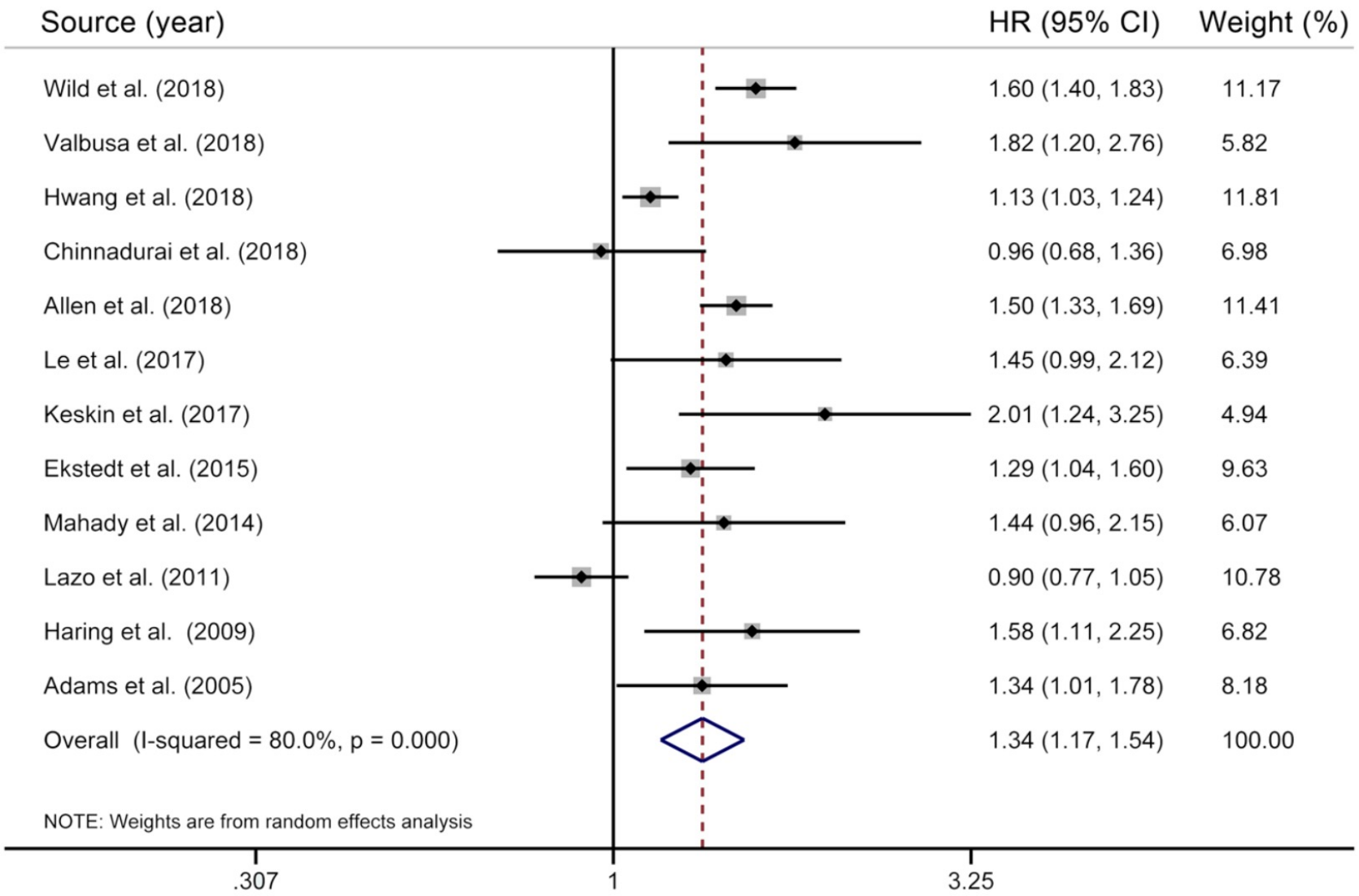


ESC Heart Fail 2021; 8: 789-798
JACC 2019; 73: 948-963
Gastroenterology 2020; 158: 1851-1864

Criteria for Diagnosis of NAFLD	Potential Barriers to Screening for NAFLD
1. Hepatic steatosis on imaging or histology	Limited therapies with sustained benefits
2. Absence of significant history of alcohol consumption	Costs of imaging
3. Absence of competing etiologies for hepatic steatosis	Liver biochemistries can be normal
4. Absence of coexisting causes of chronic liver disease	Inheritability of NAFLD is variable

JACC 2019; 73: 948-963

【NAFLD is the risk of death】

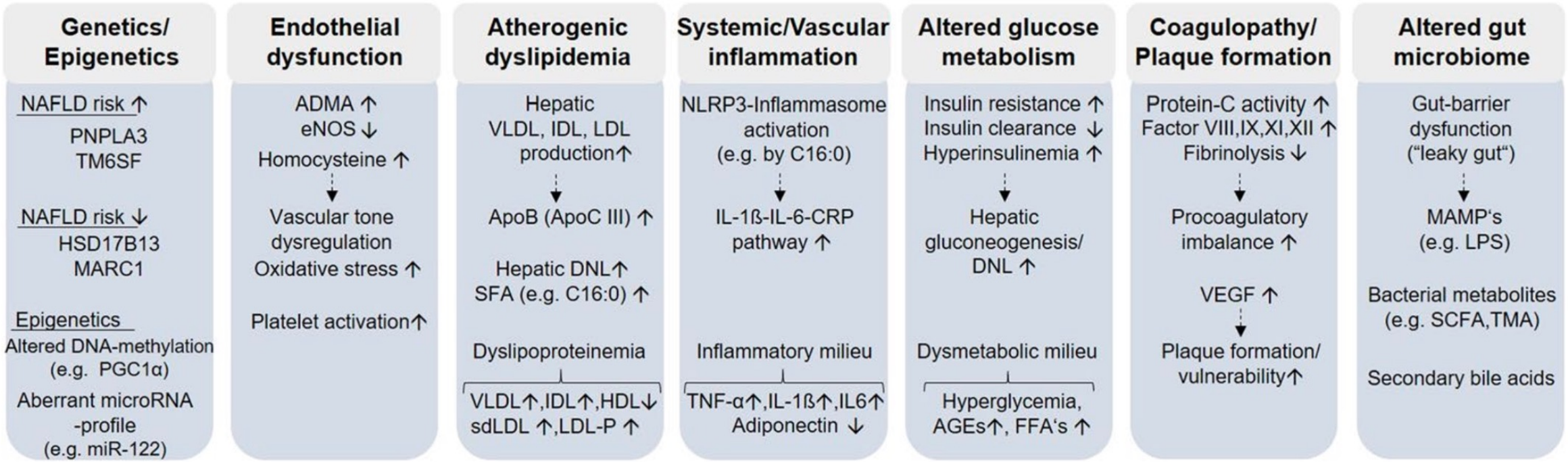


Sci Rep 2019; 9: 11124

【NAFLD and cardiovascular diseases (CVD)】

- Both NAFLD and CVD are manifestations of end-organ damage from **metabolic syndrome.**
- There is **growing evidence that NAFLD is associated with an increased incidence of CVD**.

【Pathophysiological mechanisms linking NAFLD and CVD】



Clin Res Cardiol 2021; 110: 921-937

【Summary of studies evaluated the association between NAFLD and ASCVD risk】

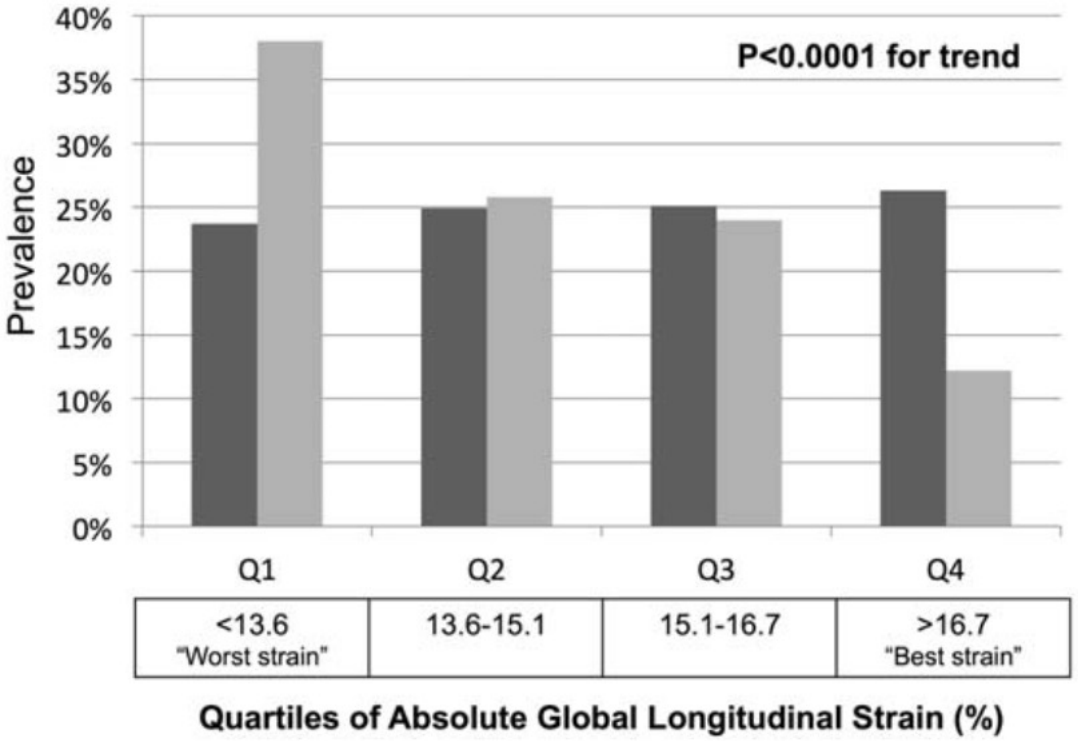
Reference	NAFLD diagnosis	Patients, n	Type of study	Impact of NAFLD on CVD outcomes or ASCVD compared with control subjects after adjustment for risk factor covariates
Jepsen et al,[34] 2003	Ultrasound	1804	Retrospective	OR, 2.1 for CVD mortality
Targher et al,[35] 2007	Ultrasound	2839	Cross-sectional	OR, 1.49 for CAD, PAD, and cerebrovascular disease in type 2 diabetes
Hamaguchi et al,[36] 2007	Ultrasound	1637	Prospective	HR, 4.1 for nonfatal CVD events
Santos et al,[37] 2007	Ultrasound	505	Cross-sectional	OR, 1.73 for coronary calcification
Haring et al,[38] 2009	Ultrasound	4160	Prospective	HR, 6.22 for all-cause and CVD mortality
Assy et al,[39] 2010	CT	61	Cross-sectional	OR, 2.03 for coronary calcification
Chen et al,[40] 2010	Ultrasound/CT	295	Cross-sectional	OR, 2.46 for CAC >100
Wong et al,[41] 2011	Ultrasound	612	Prospective	OR, 2.31 for significant coronary artery disease (>50% obstruction)
Targher et al,[42] 2012	Ultrasound	343	Cross-sectional	OR, 7.6 for CAD, PAD, and cerebrovascular disease in type 1 diabetes
Kim et al,[43] 2012	Ultrasound	4023	Cross-sectional	OR, 1.32 for CAC >10
Zhou et al,[44] 2012	Ultrasound	3543	Prospective	OR, 3.0 for CVD mortality
Stepanova and Younossi,[45] 2012	Ultrasound	20 050	Prospective	OR, 1.23 for CVD events
Ekstedt et al,[46] 2015	Liver biopsy	229	Retrospective	HR, 1.55 for CVD mortality
Mellinger et al,[47] 2015	CT	3014	Cross-sectional	OR, 1.20 for CAC score >90th percentile for age
Mantovani et al,[48] 2016	Ultrasound	286	Retrospective	OR, 6.73 for incident cardiovascular events in type 1 diabetes
Pais et al,[49] 2016	Fatty Liver Index	5671	Retrospective	NAFLD severity correlates with CIMT and carotid plaque severity
Yoshitaka et al,[50] 2017	Ultrasound	1647	Prospective	HR, 10.4 in nonoverweight, 3.1 in overweight for incident cardiovascular events
Mahfood Hadad et al,[51] 2017	Ultrasound	25 837 (11 studies)	Meta-analysis	RR, 1.77 for incident CVD, 1.43 for cardiovascular mortality
Zhou et al,[52] 2018	Ultrasound/CT	8346 (6 studies)	Meta-analysis	OR, 2.20 for incident CVD in patients with diabetes
Kapuria et al,[53] 2018	Ultrasound/CT	42 410 (12 studies)	Meta-analysis	OR, 1.64 for higher CAC scores
Sinn et al,[54] 2019	Ultrasound	111 492	Retrospective	HR, 1.54 for myocardial infarction
Pais et al,[55] 2019	Fatty Liver Index	2554	Retrospective	NAFLD correlated with CIMT, CAC, and carotid plaque

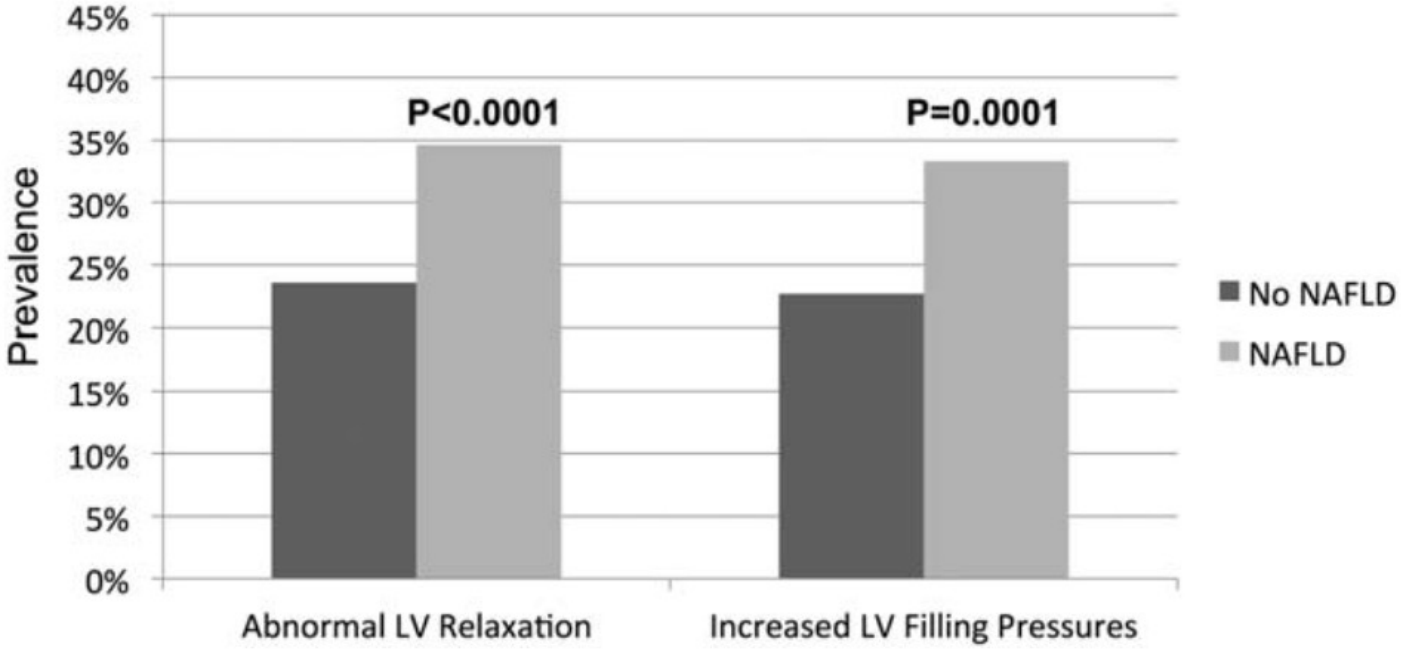
CAD
AMI
PAD
CAC
CVD mortality

Arterioscler Thromb Vasc Biol 2022; 42: e168-e185

【Impact of NAFLD on heart diseases; Myocardial abnormalities】

- NAFLD patients showed significant cardiac dysfunction compared with non-NAFLD patients.





Hepatology 2015; 62: 773-783

【Impact of NAFLD on heart diseases; Myocardial abnormalities】

- Meta-analysis study also showed the adverse structural alterations and cardiac dysfunction in patients with NAFLD.

	Mean difference, 95% CI	I^2	Heterogeneity	p value
Systolic cardiac function				
LVEF, %	−0.30 [−0.91, 0.30]	70%	Moderate	0.33
Diastolic cardiac function				
E, cm/s	−3.63 [−7.56, 0.30]	89%	High	0.07
E/e'	1.05 [0.61, 1.50]	93%	High	**<0.01**
A, cm/s	3.55 [2.70, 4.39]	4%	Insignificant	**<0.01**
E/A	−0.15 [−0.22, −0.08]	94%	High	**<0.01**
Relaxation time, s	10.00 [4.03, 15.97]	84%	High	**<0.01**
Deceleration time, s	13.04 [5.37, 20.71]	89%	High	**<0.01**
Cardiac structure				
LVM, g	47.22 [33.25, 61.18]	92%	High	**<0.01**
LVM/height, $g/m^{2.7d}$	3.82 [1.61, 6.03]	91%	High	**<0.01**
LVM/BSA, g/m^2	7.39 [2.22, 12.56]	86%	High	**<0.01**
LVEDD, mm	1.32 [0.93, 1.70]	38%	Low	**<0.01**
LVEDV, mL	2.23 [−2.09, 6.55]	49%	Low	0.31
LVESD, mm	−0.31 [−1.28, 0.66]	93%	High	0.53
LVESV, mL	1.13 [−1.01, 3.28]	27%	Low	0.30
LAD, mm	2.19 [1.04, 3.35]	95%	High	**<0.01**
LAV/BSA, mL/m^2	1.52 [0.05, 3.00]	32%	Low	**0.04**
Posterior wall thickness, mm	1.14 [0.75, 1.53]	96%	High	**<0.01**
Septum thickness, mm	1.06 [0.67, 1.45]	94%	High	**<0.01**

Diastolic dysfunction

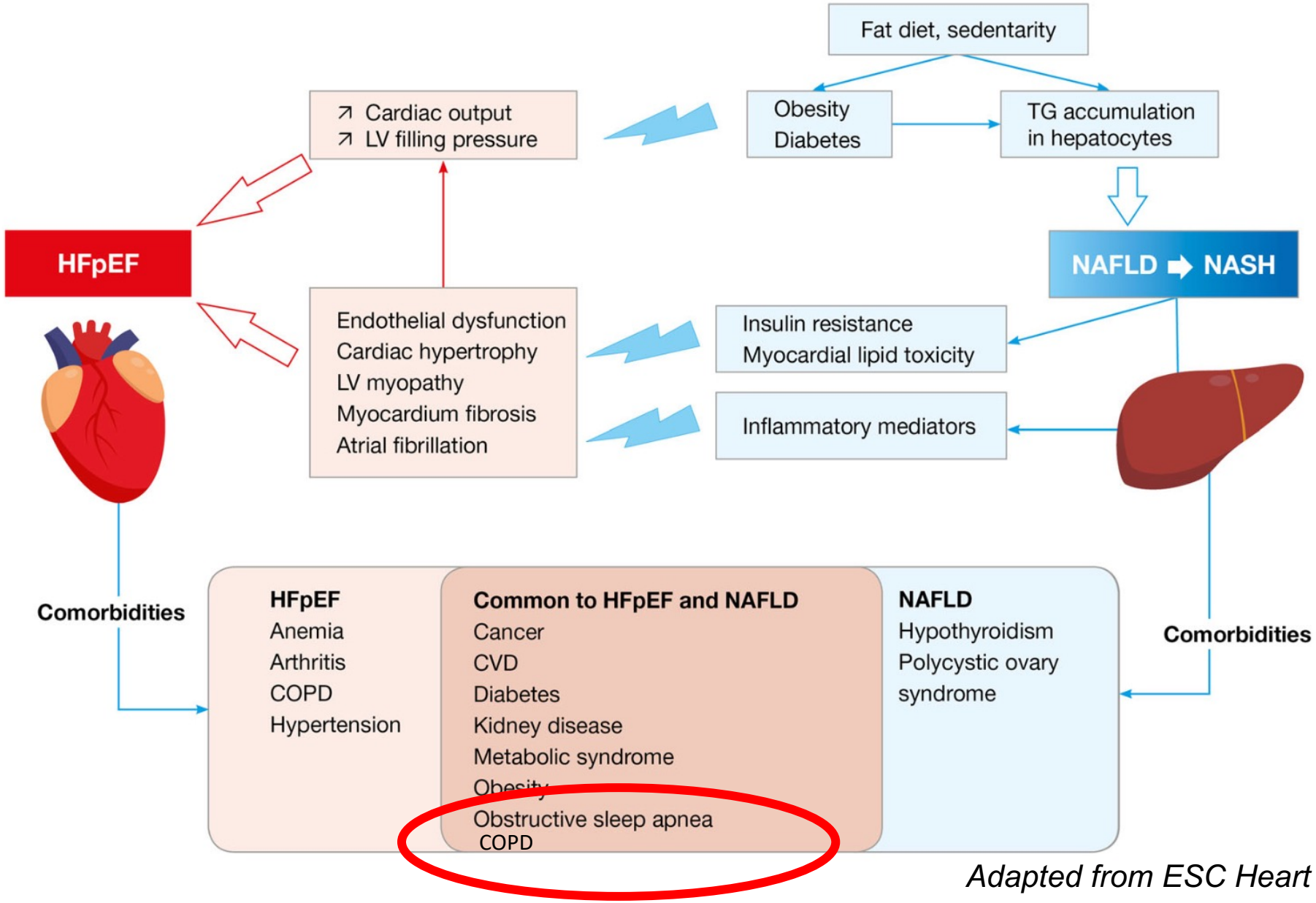
HFpEF definition

LV hypertrophy

LA dilatation

Endocrine 2019; 66: 467-476

【NAFLD and heart failure with preserved ejection fraction (HFpEF)】

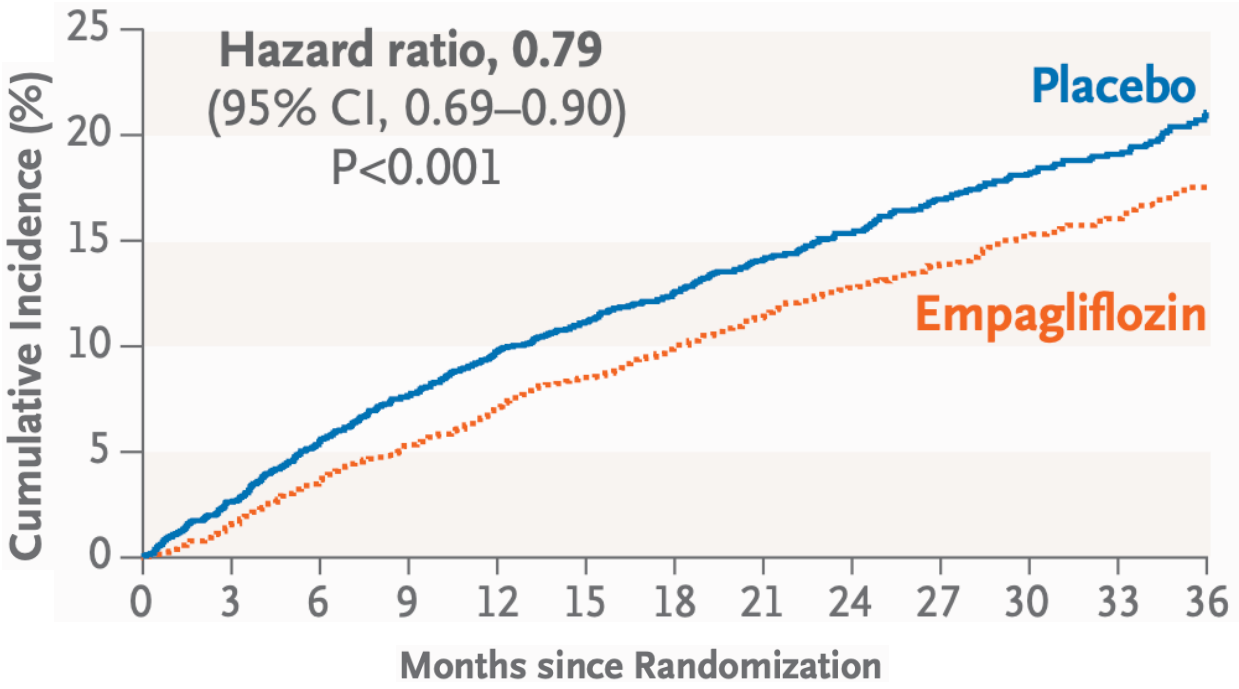


Adapted from ESC Heart Fail 2021; 8: 789-798

【Impact of drugs for CVD on NAFLD: SGLT2 inhibitors】

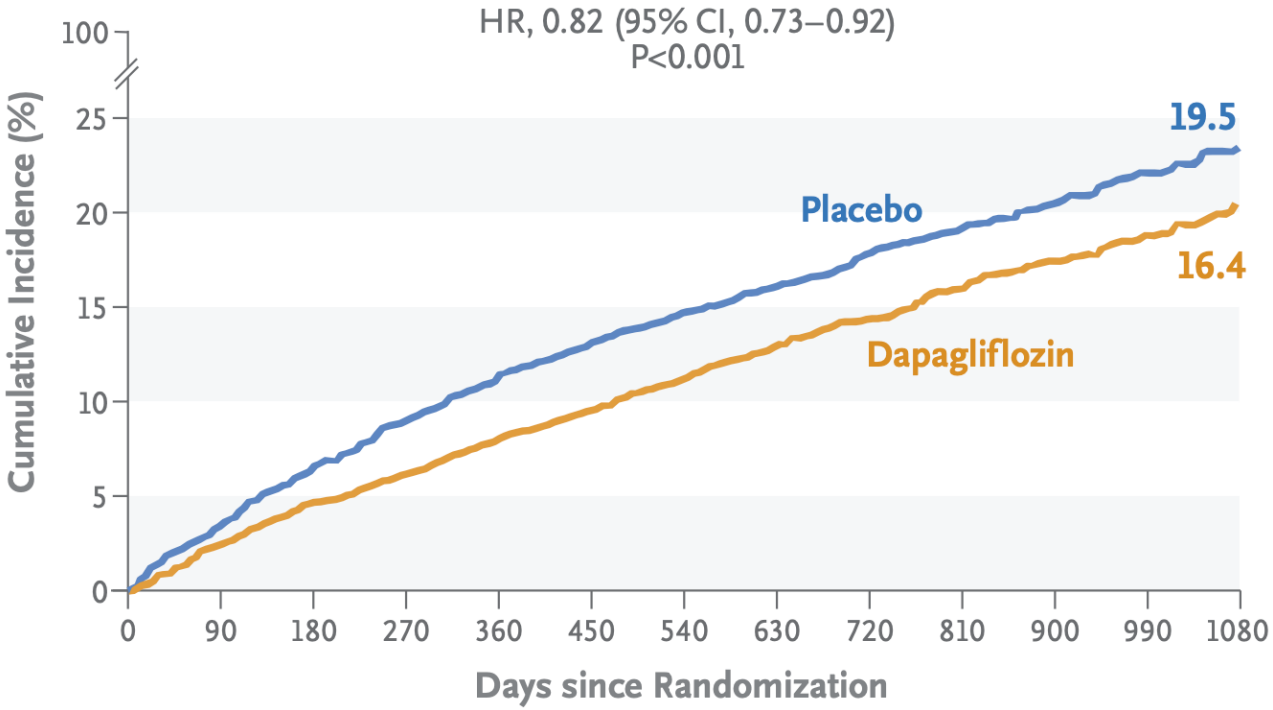
- Two randomized controlled trials demonstrated the effects of the SGLT2 inhibitors on cardiovascular outcomes in HFpEF patients.

【EMPEROR-Preserved】



N Engl J Med 2021; 385: 1451-1461

【DELIVER】



N Engl J Med 2022; 387: 1089-1098

【Impact of drugs for CVD on NAFLD: SGLT2 inhibitors】

- **A lot of clinical studies have highlighted the benefit of SGLT2 inhibitors in patients with NAFLD and T2DM**.

- Not only insulin resistance amelioration but also the antioxidant effects of SGLT2 inhibitors may contribute to NAFLD improvement.

Free-radical production mechanism	Effects of SGLT2i
Pro-oxidant enzymes	Decrease in Nox, eNOS, and xanthine oxidase function
AGEs–AGE/RAGE crosstalk	Lowering AGEs generation, reduction in the AGE–RAGE interaction
Proinflammatory cytokines	Lowering proinflammatory cytokine expression
Insulin resistance	Improving insulin sensitivity
Hemodynamic modification	Altering/normalizing hemodynamic state
Mitochondrial dysfunction	Improving mitochondrial function
Renin–angiotensin system (RAS)	Amelioration of RAS components activity

AGEs, advanced glycation end products
eNOS, endothelial nitric oxide synthase
RAGE, receptor for advanced glycation end product

J Cell Physiol 2019; 234: 3231-3237

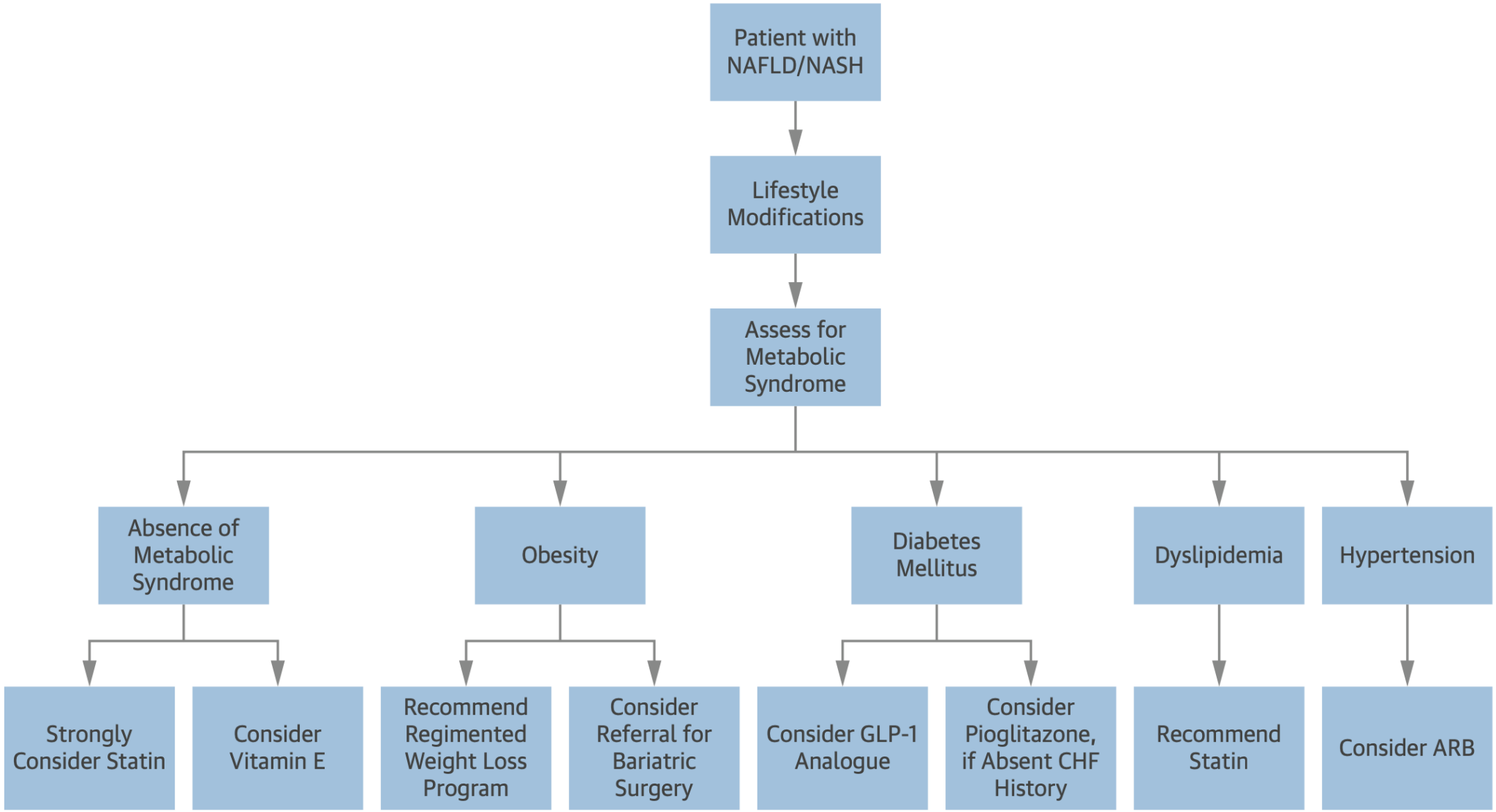
【Perspective of specific therapy for NAFLD】

Drugs	Mechanisms of action	Stage of development and main outcomes	
Inflammatory/fibrosis modulators			
Cenicriviroc	CCR2/CCR5 antagonist	Phase III (CENTAUR)	Significant antifibrotic effect
Selonsertib	ASK-1 inhibitor	Phase III (STELLAR)	Primary endpoint (fibrosis improvement) not met
Belapectin	Galectin-3 inhibitor	Phase IIb	Primary endpoint (no reduction in HVPG) not met
Metabolic modulators			
Elafibranor	Dual PPAR-α/δ agonist	Phase III (RESOLVE-IT)	Primary endpoint (NASH resolution without fibrosis worsening) not met
Multimodal drugs			
Obeticholic acid	FXR agonist	Phase III (REGENERATE)	Histological improvement—clinical assessment ongoing
Cilofexor	FXR agonist	Phase II	Reductions in hepatic steatosis and liver biochemistry
Combination-based therapies			
Cilofexor + selonsertib		Phase II (ATLAS)	Primary endpoint (fibrosis improvement) not met
Cilofexor + firsocostat[a]		Phase II (ATLAS)	Primary endpoint (fibrosis improvement) not met
Selonsertib + firsocostat[a]		Phase II (ATLAS)	Primary endpoint (fibrosis improvement) not met
Cenicriviroc + tropifexor		Phase IIb (TANDEM)	Ongoing—primary endpoint: safety and tolerability
Tropifexor + licogliflozin		Phase II (ELIVATE)	Ongoing—NASH resolution + no fibrosis worsening, or fibrosis improvement
Semaglutide[b] + cilofexor		Phase II	Ongoing—primary endpoint: safety and tolerability
Semaglutide[b] + firsocostat[a]		Phase II	Ongoing—primary endpoint: safety and tolerability

ASK-1, apoptosis signal-regulating kinase 1
FXR, farnesoid X nuclear receptor
PPAR, peroxisome proliferator activated receptor

ESC Heart Fail 2021; 8: 789-798

【Therapeutic approach to NAFLD to reduce the risk of CVD】



SGLT2-i

JACC 2019; 73: 948-963

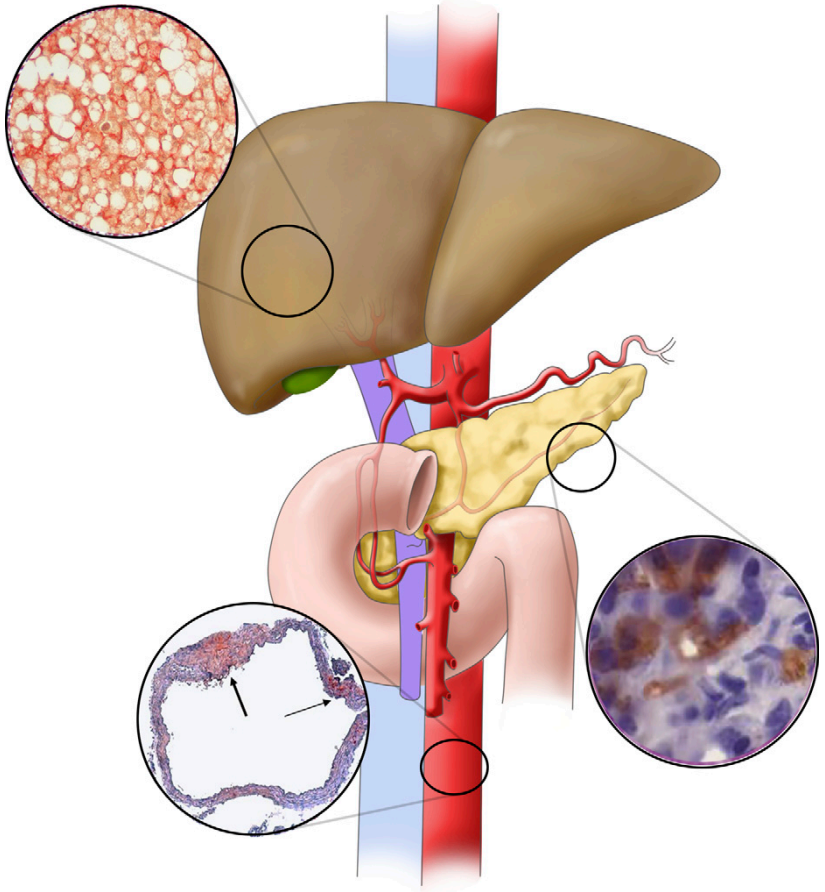
【Obstructive Sleep Apnea, Hypoxia, and NAFLD】

CONCISE TRANSLATIONAL REVIEW

Obstructive Sleep Apnea, Hypoxia, and Nonalcoholic Fatty Liver Disease

Omar A. Mesarwi[1], Rohit Loomba[2,3], and Atul Malhotra[1]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, [2]Division of Gastroenterology, Department of Medicine, and [3]Department of Family Medicine and Public Health, University of California San Diego School of Medicine, La Jolla, California



Mechanisms by which intermittent hypoxia in obstructive sleep apnea may result in metabolic dysfunction in nonalcoholic fatty liver disease : oxidative stress, mitochondrial dysfunction, inflammation, and overactivation of the sympathetic nervous system …

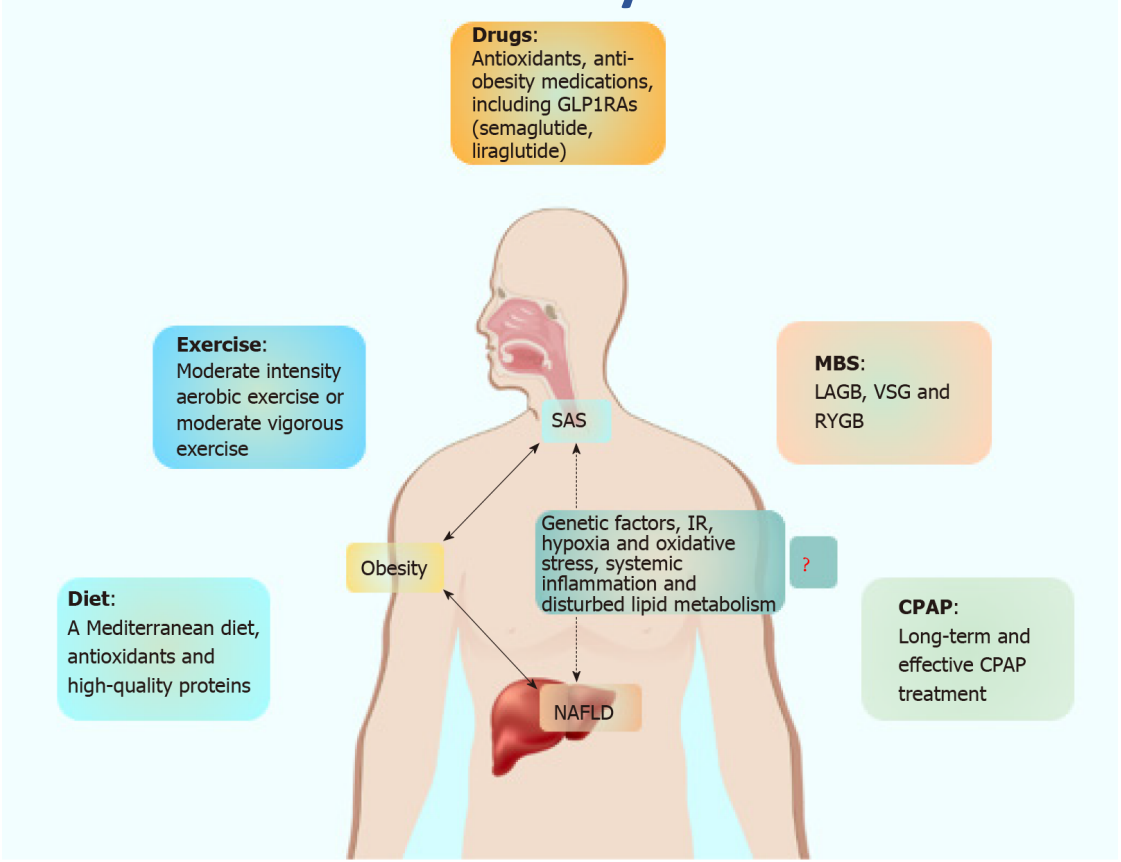
The question is: how aggressively should the clinician screen for NAFLD in patients with OSA, and vice versa?

Am J Respir Crit Care Med. 2019 Apr 1;199(7):830-841

【Obstructive Sleep Apnea, Hypoxia, and NAFLD】

Sheng W *et al*. Management of NAFLD and SAS

Management of nonalcoholic fatty liver disease with sleep apnea syndrome



DOI: 10.3748/wjg.v28.i43.6099

Figure 1 Management of nonalcoholic fatty liver disease with sleep apnea syndrome. Healthy lifestyle management remains the current first-line recommendation for nonalcoholic fatty liver disease (NAFLD) with sleep apnea syndrome (SAS), including diet, exercise, and weight loss. For patients with obesity and type 2 diabetes, drug intervention should also include anti-obesity medications and insulin-sensitizing drugs. Metabolic bariatric surgery can be considered when lifestyle changes and medical interventions are not effective. In addition, continuous positive airway pressure therapy may improve both intermittent hypoxia and liver injury in patients with NAFLD and SAS. MBS: Metabolic bariatric surgery; CPAP: Continuous positive airway pressure; IR: Insulin resistance; LAGB: Laparoscopic adjustable gastric banding; VSG: Vertical sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass; SAS: Sleep apnea syndrome; NAFLD: Nonalcoholic fatty liver disease.

【Obstructive Sleep Apnea, Hypoxia, and COPD】

Nonalcoholic fatty liver disease in chronic obstructive pulmonary disease

Damien Viglino[1,2,9], Ingrid Jullian-Desayes[1,3,9], Mélanie Minoves[1,3], Judith Aron-Wisnewsky[4,5,6], Vincent Leroy[7,8], Jean-Pierre Zarski[7,8], Renaud Tamisier[1,3], Marie Joyeux-Faure[1,3,10] and Jean-Louis Pépin[1,3,10]

1- The prevalence in COPD patients of steatosis, NASH and fibrosis was 41%, 37% and 61%, respectively.

2- Liver steatosis, NASH and fibrosis were primarily linked with the metabolic comorbidities of COPD (i.e. obesity and insulin resistance) and systemic inflammation.

3- Insulin resistance, systemic inflammation and CIH seem to play a role in the development of NAFLD in COPD patients.

4- As physical activity is the first-line treatment of NAFLD, pulmonary rehabilitation could be expected to have a positive effect on NAFLD in COPD patients.

5- In the obese inflamed COPD phenotype, lifestyle intervention with cautious weight loss might also improve NAFLD.

Eur Respir J 2017; 49: 1601923

【Obstructive Sleep Apnea, Hypoxia, and COPD】

Nonalcoholic fatty liver disease and COPD: is it time to cross the diaphragm?

Amedeo Lonardo[1], Fabio Nascimbeni[1,2] and Maurizio Ponz de Leon[1,2]

Affiliations: [1]Operating Unit of Internal Medicine, OCSAE, Modena, Italy. [2]University of Modena and Reggio Emilia, Modena, Italy.

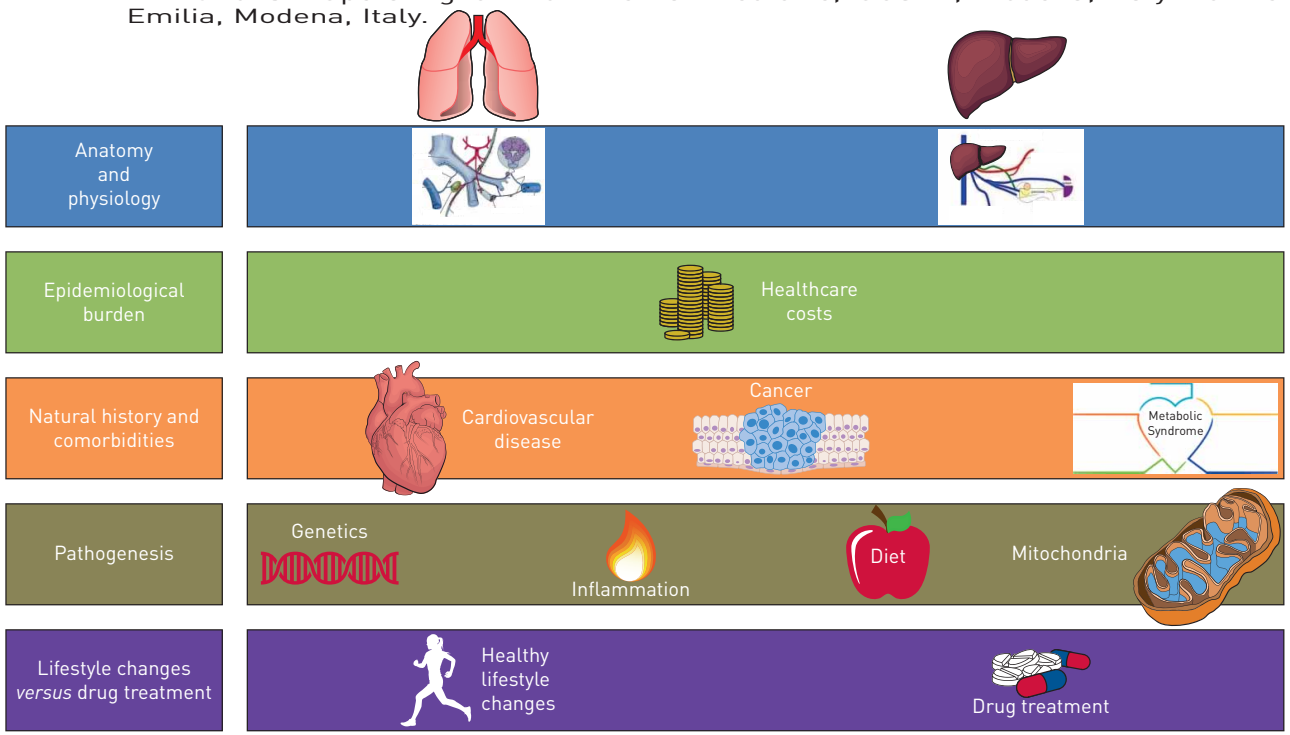


FIGURE 1 The spectrum of analogies linking chronic obstructive pulmonary disease (COPD) and nonalcoholic fatty liver disease (NAFLD). Both the lung and liver are highly vascularised organs with a dual blood supply, are involved in antigen processing and are master regulators of energy homeostasis. Based on their high prevalence and dangerous outcomes, COPD and NAFLD claim a high health and economic toll. Accordingly, more liberal screening policies have been advocated in individuals at high risk of COPD and NAFLD. COPD and NAFLD are increasingly recognised as multisystem diseases with high comorbidity rate, mainly clustered in the metabolic, cardiovascular and neoplastic area. Both COPD and NAFLD are complex noncommunicable diseases determined by environmental factors (unhealthy lifestyle habits) and genetic predisposition. Principles of treatment of COPD and NAFLD include lifestyle changes (smoking cessation, diet and physical activity) as a first step.

Eur Respir J 2017; 49: 1700546

【Take home message - Conclusion】

- NAFLD and HFpEF share most of the same comorbidities
- Early detection of NAFLD so it can be managed with approved non-specific strategies associated with heart failure treatment.
- Practical clinical trials to determine the impact of heart failure treatment on NAFLD.
- **Similarly, sleep Apnea and COPD have the same relationship with NAFLD than HF.**

ESC HEART FAILURE
ESC Heart Failure (2021)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13222

REVIEW

Non-alcoholic fatty liver disease and heart failure with preserved ejection fraction: from pathophysiology to practical issues

Romain Itier[1], Maeva Guillaume[2], Jean-Etienne Ricci[3], François Roubille[4], Nicolas Delarche[5], François Picard[6], Michel Galinier[1] and Jérôme Roncalli[1]*

[1]*Department of Cardiology, Institute CARDIOMET, CHU-Toulouse, Toulouse, France;* [2]*Department of Gastroenterology and Hepatology, Clinique Pasteur, Toulouse, France;* [3]*Department of Cardiology, CHU-Nimes, Nimes, France;* [4]*INSERM, CNRS, Cardiology Department, PhyMedExp, Université de Montpellier, CHU-Montpellier, Montpellier, France;* [5]*Department of Cardiology, CH-Pau, Pau, France;* [6]*Department of Cardiology, CHU-Bordeaux, Bordeaux, France*

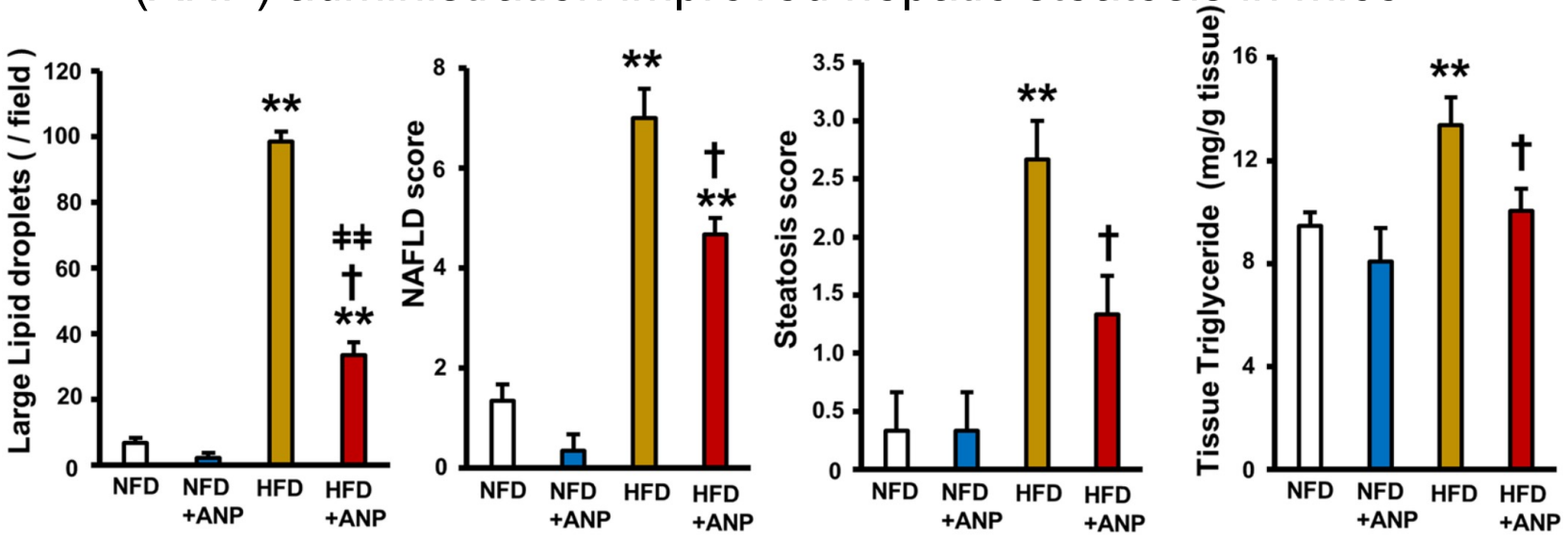
Thank you

Back-up slides

【Impact of drugs for CVD on NAFLD: Natriuretic peptides】

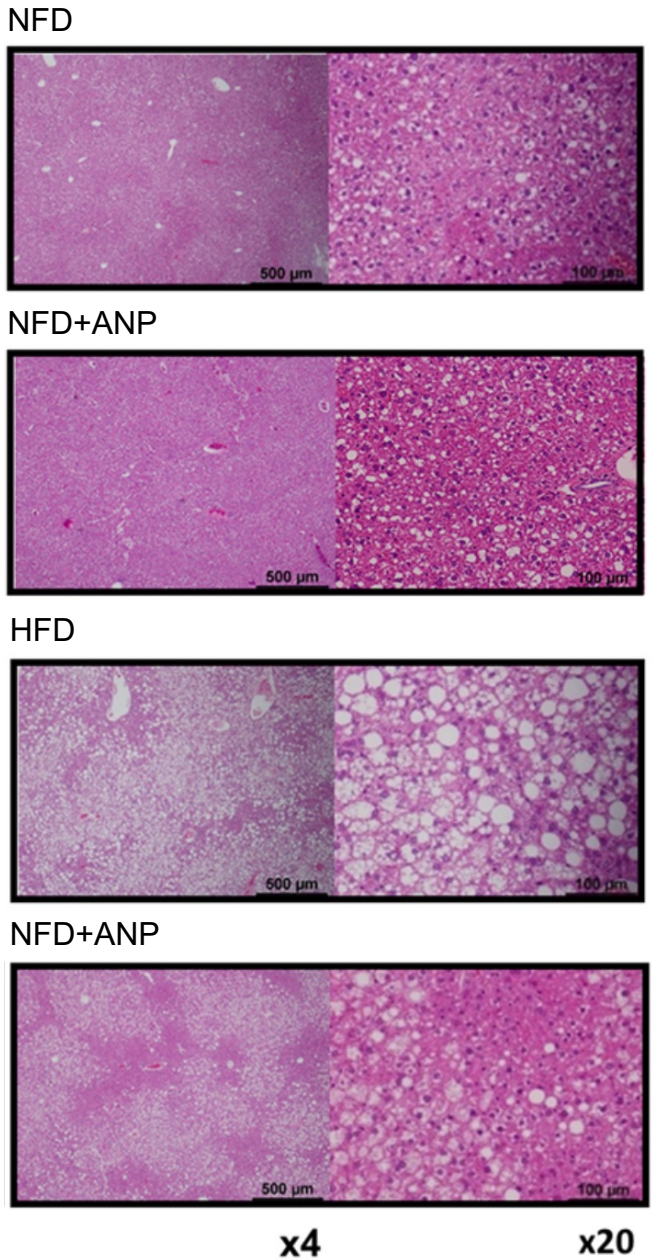
- *ARNI, which reduced the risk of death and hospitalization in HFrEF patients in the PARADIGM-HF trial, did not show positive effects in HFpEF patients in the PARAGON-HF trial (but FDA approved).*

- A basic study demonstrated that atrial natriuretic peptide (ANP) administration improved hepatic steatosis in mice.



NFD, normal-fat-diet
HFD, high-fat-diet

Sci Rep 2021; 11: 17466



【New proposal of HFpEF phenotype associated with NAFLD】

HFpEF Phenotype	Pathophysiology	Characteristics	Proposed Treatment
Obstructive HFpEF phenotype	Increase in the resistance across hepatic sinusoids leading to impairment venous return to the heart, thus limiting preload reserve	• High-normal cardiac output state at rest • Impaired cardiac output augmentation with activity • Low natriuretic peptides levels	• Weight loss • SGLT2 inhibitors • GLP-1 receptor agonists • RAAS inhibitors • ARNIs • Loop diuretic agents
Metabolic HFpEF phenotype	Chronic low-grade inflammatory process	• Metabolic syndrome • Excess visceral adipose tissue	• Weight loss • SGLT2 inhibitors • GLP-1 receptor agonists • RAAS inhibitors • ARNIs • Loop diuretic agents
Advanced liver disease/ cirrhosis HFpEF phenotype	Formation of spontaneous portosystemic and arteriovenous shunts	• Increased arterial blood flow and decreased systemic vascular resistance resulting in high cardiac output at rest • Impaired cardiac output augmentation with activity	• Loop diuretic agents

JACC Basic Transl Sci 2021; 6: 918-932