CHFS SCIC
Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

@CanHFSociety #HFupdate

Linkages in Obesity, NASH, Diabetes and HFpEF

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Learning Objectives

- Explore the epidemiologic and pathophysiologic conditions which lead to NASH
- Understand the impact of NASH on HFpEF, and vice versa
- Adapt prevention and treatment plans for people with HF and multiorgan metabolic comorbidities

Prevalence of HF

1

Prevalence

750,000

Canadians are living with HF[1]

50%

have EF > 40%[2]

2

Burden

est. 50%

of HF hospitalizations are for HFpEF[3-7]

up to 50%

5-year mortality rate[8]

3

Undetected

>50%

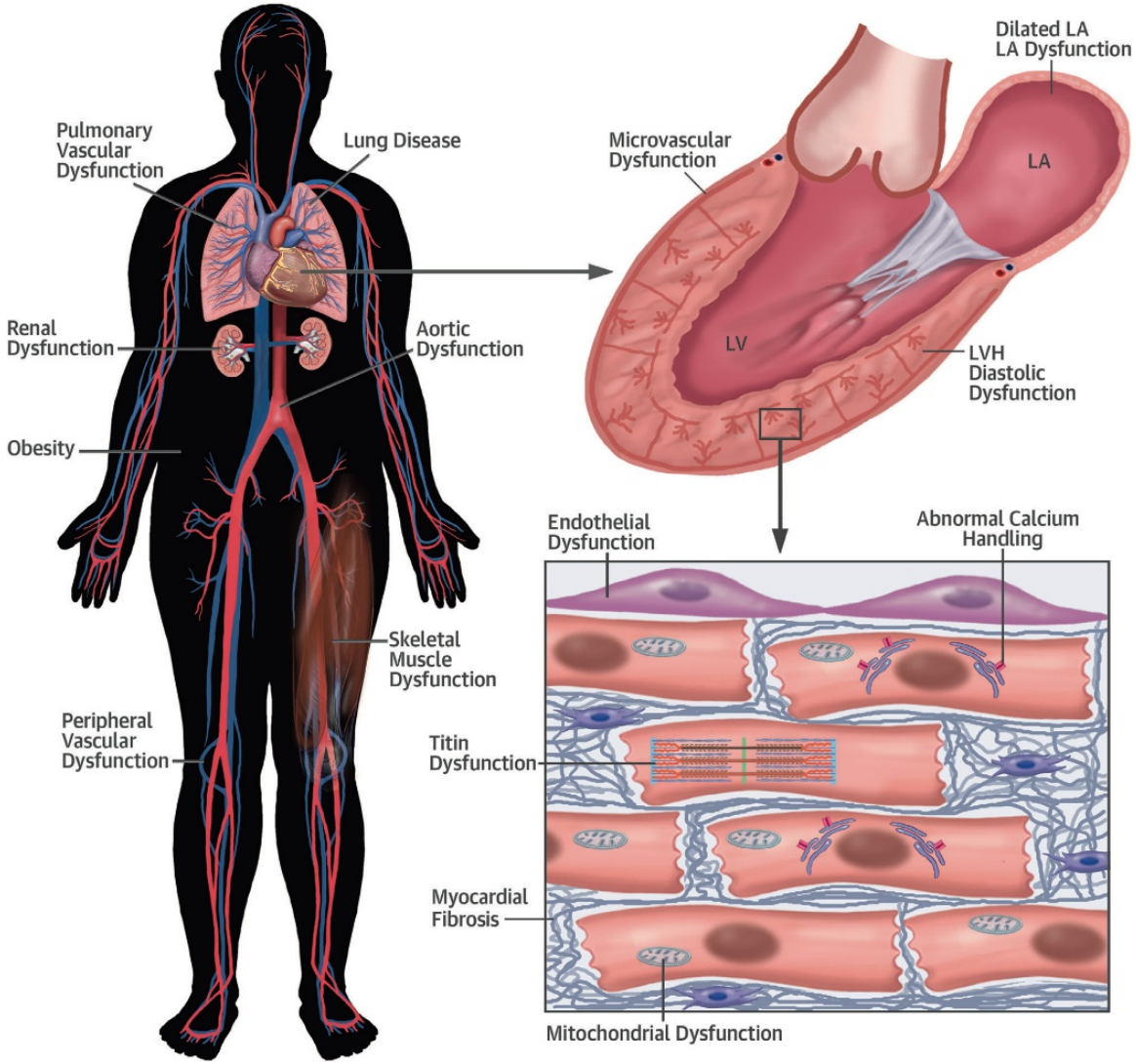
are undiagnosed[9]

EF, ejection fraction; est, estimated; HF, heart failure; HFpEF, heart failure with preserved ejection fraction.

1. Heart and Stroke Foundation of Canada. Heart Failure. Online at https://www.heartandstroke.ca/heart-disease/conditions/heart-failure. Accessed April 29, 2022;
2. Borlaug BA. Nat Rev Cardiol. 2020 Sep;17(9):559–73; 3. Lenzen MJ et al. Eur Heart J. 2004;25(14): 1214-20; 4. Mavrea AM et al. Clin Interv Aging. 2015;10: 979-90; 5. Crespo-Leiro MG et al. Eur J Heart Fail. 2016;18(6): 613-25; 6. Oktay AA et al. Curr Heart Fail Rep. 2013;10(4):401–10; 7. Fonarow GC al. J Am Coll Cardiol. 2007;50(8):768–77; 8. Shah KS et al. JACC. 2017;70(20):2476–86; 9. Groenewegen A et al. Eur J Heart Fail. 2020;22(8):1342–56.

HFpEF epidemiological associations

- Age
- Female gender
- Hypertension
- **Diabetes**
- Renal failure (~25%)
- Anemia (~20%)
- **Obesity**
- Atrial fibrillation
- Obstructive sleep apnea
- COPD (~22%)
- **NAFLD / NASH ???**



HFpEF: not a 'single' disease

COPD, chronic obstructive pulmonary disease
Lewis et al. JACC 2017.

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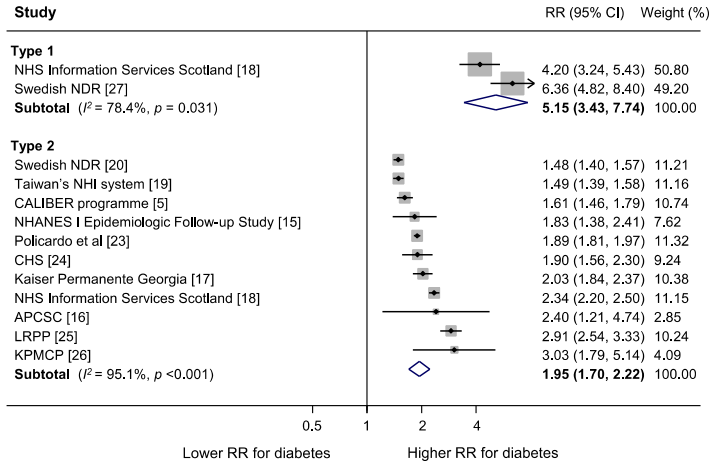
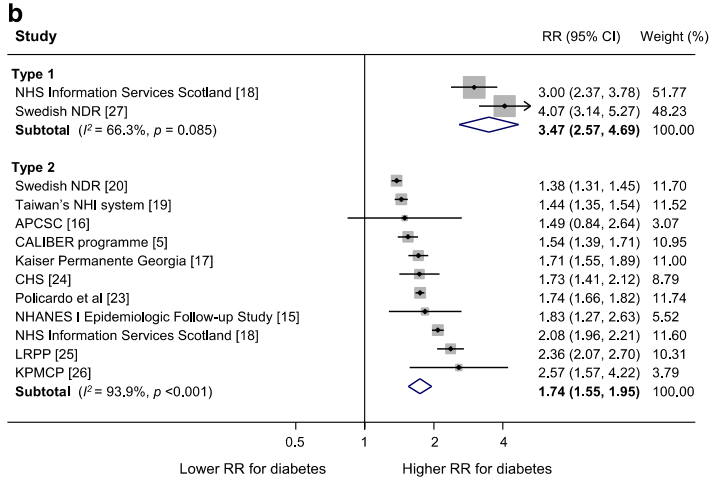
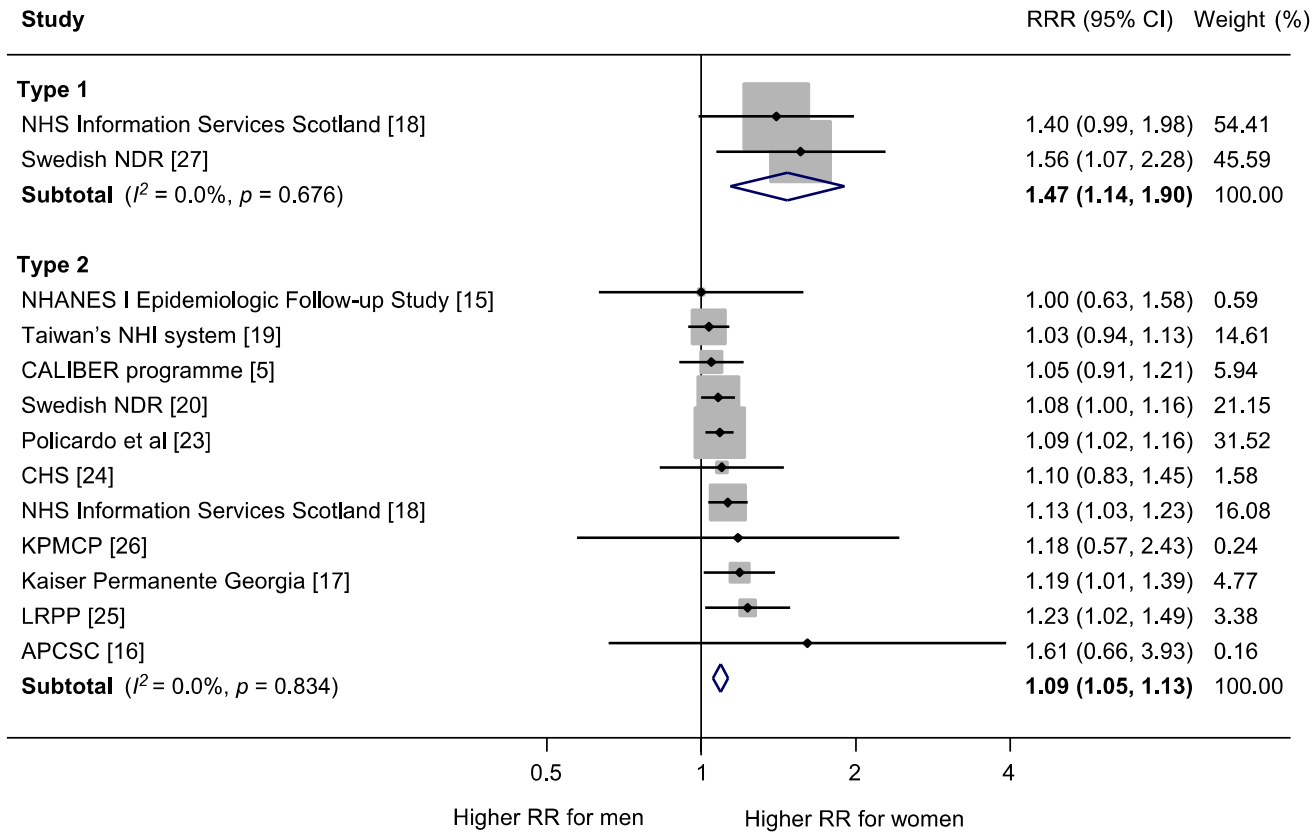
1. Diabetes and HFpEF

a

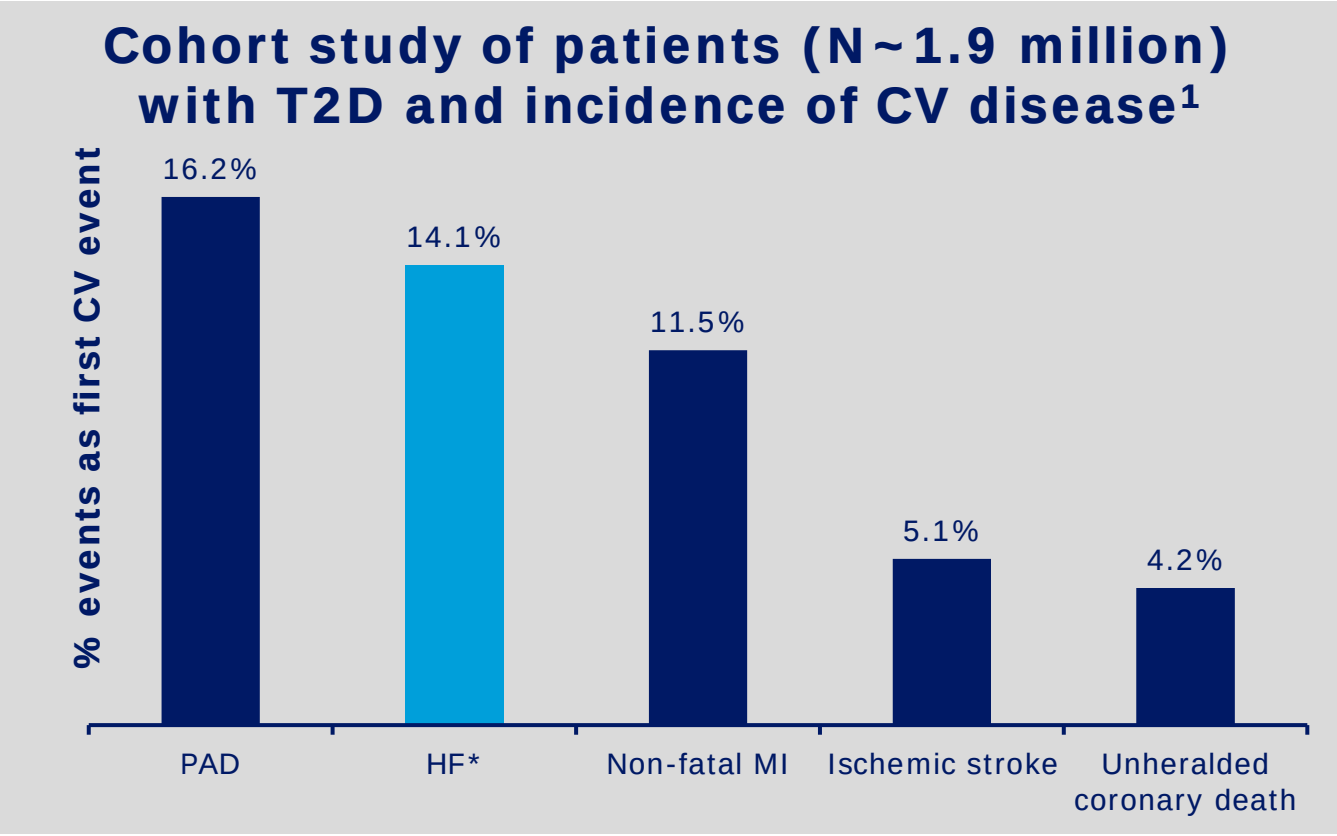

Study
RR (95% CI) Weight (%)
Type 1
NHS Information Services Scotland [18] 4.20 (3.24, 5.43) 50.80
Swedish NDR [27] 6.36 (4.82, 8.40) 49.20
Subtotal (I^2 = 78.4%, p = 0.031) 5.15 (3.43, 7.74) 100.00
Type 2
Swedish NDR [20] 1.48 (1.40, 1.57) 11.21
Taiwan's NHI system [19] 1.49 (1.39, 1.58) 11.16
CALIBER programme [5] 1.61 (1.46, 1.79) 10.74
NHANES I Epidemiologic Follow-up Study [15] 1.83 (1.38, 2.41) 7.62
Policardo et al [23] 1.89 (1.81, 1.97) 11.32
CHS [24] 1.90 (1.56, 2.30) 9.24
Kaiser Permanente Georgia [17] 2.03 (1.84, 2.37) 10.38
NHS Information Services Scotland [18] 2.34 (2.20, 2.50) 11.15
APCSC [16] 2.40 (1.21, 4.74) 2.85
LRPP [25] 2.91 (2.54, 3.33) 10.24
KPMCP [26] 3.03 (1.79, 5.14) 4.09
Subtotal (I^2 = 95.1%, p <0.001) 1.95 (1.70, 2.22) 100.00
0.5
1
2
4
Lower RR for diabetes
Higher RR for diabetes

b


Study
RR (95% CI) Weight (%)
Type 1
NHS Information Services Scotland [18] 3.00 (2.37, 3.78) 51.77
Swedish NDR [27] 4.07 (3.14, 5.27) 48.23
Subtotal (I^2 = 66.3%, p = 0.085) 3.47 (2.57, 4.69) 100.00
Type 2
Swedish NDR [20] 1.38 (1.31, 1.45) 11.70
Taiwan's NHI system [19] 1.44 (1.35, 1.54) 11.52
APCSC [16] 1.49 (0.84, 2.64) 3.07
CALIBER programme [5] 1.54 (1.39, 1.71) 10.95
Kaiser Permanente Georgia [17] 1.71 (1.55, 1.89) 11.00
CHS [24] 1.73 (1.41, 2.12) 8.79
Policardo et al [23] 1.74 (1.66, 1.82) 11.74
NHANES I Epidemiologic Follow-up Study [15] 1.83 (1.27, 2.63) 5.52
NHS Information Services Scotland [18] 2.08 (1.96, 2.21) 11.60
LRPP [25] 2.36 (2.07, 2.70) 10.31
KPMCP [26] 2.57 (1.57, 4.22) 3.79
Subtotal (I^2 = 93.9%, p <0.001) 1.74 (1.55, 1.95) 100.00
0.5
1
2
4
Lower RR for diabetes
Higher RR for diabetes


Study
RRR (95% CI) Weight (%)
Type 1
NHS Information Services Scotland [18] 1.40 (0.99, 1.98) 54.41
Swedish NDR [27] 1.56 (1.07, 2.28) 45.59
Subtotal (I^2 = 0.0%, p = 0.676) 1.47 (1.14, 1.90) 100.00
Type 2
NHANES I Epidemiologic Follow-up Study [15] 1.00 (0.63, 1.58) 0.59
Taiwan's NHI system [19] 1.03 (0.94, 1.13) 14.61
CALIBER programme [5] 1.05 (0.91, 1.21) 5.94
Swedish NDR [20] 1.08 (1.00, 1.16) 21.15
Policardo et al [23] 1.09 (1.02, 1.16) 31.52
CHS [24] 1.10 (0.83, 1.45) 1.58
NHS Information Services Scotland [18] 1.13 (1.03, 1.23) 16.08
KPMCP [26] 1.18 (0.57, 2.43) 0.24
Kaiser Permanente Georgia [17] 1.19 (1.01, 1.39) 4.77
LRPP [25] 1.23 (1.02, 1.49) 3.38
APCSC [16] 1.61 (0.66, 3.93) 0.16
Subtotal (I^2 = 0.0%, p = 0.834) 1.09 (1.05, 1.13) 100.00
0.5
1
2
4
Higher RR for men
Higher RR for women

HF is one of the first manifestations of T2D-related CVD



T2D and HF often coexist[2]

- T2D trials: HF prevalence 10% to 30%
- Chronic HF trials: T2D prevalence ~30%

*Heart failure post MI was not included in this definition of HF
CV, cardiovascular; HF, heart failure; MI, myocardial infarction; PAD, peripheral arterial disease; T2D, type 2 diabetes.
1. Shah AD et al. Article and appendix. Lancet Diabetes Endocrinol. 2015;3:105-113; 2. Seferović PM et al. Eur J Heart Fail. 2018;20:853-872

Diabetes and Heart Failure

REACH Registry (4-year follow-up)

By 4 years, ~1 in 10 in North America with diabetes were HHF

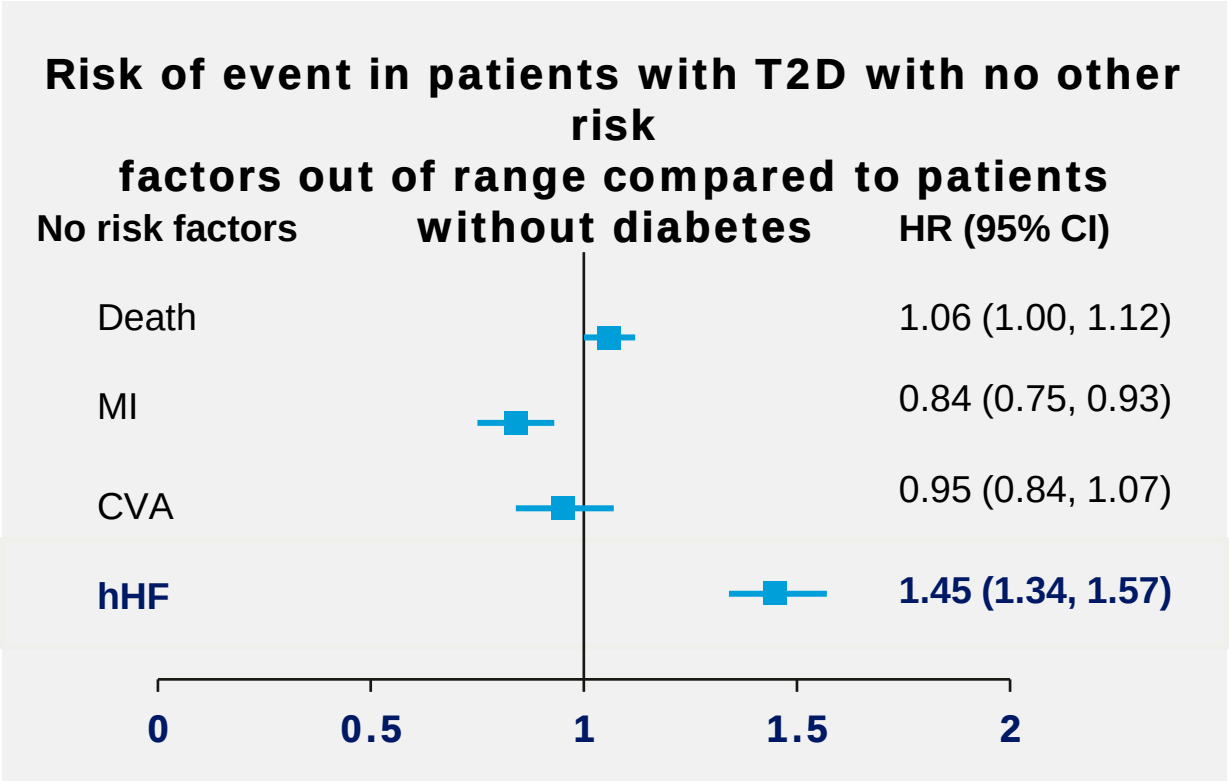
Association between diabetes and HHF observed in participants with and without known atherothrombosis

History of HF at baseline in individuals with diabetes (16.1%) was independently associated with

- 2-fold ↑ in CV death (HR_{adj} 2.45 [2.17-2.77])
- 5-fold ↑ in HHF (OR_{adj} 4.72 [4.22-5.29])

adj, adjusted for baseline confounders; CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; OR, odds ratio.
Cavender MA et al. Circulation. 2015;132:923-31.

Despite control of known CV risk factors, patients with T2D remain at elevated risk of developing HF



- In this analysis the risk of hHF in patients with T2D (n=271,174) was compared to those without T2D (n=1,355,870)
- The following risk factors were either not present or within guideline range: systolic and diastolic BP, LDL-C, albuminuria and tobacco use
- A substantial risk for hHF remained among patients who had all the variables within target range

On average, the patients with T2D had a 45% increase in the risk of hHF, despite other major risk factors in guideline recommended range or absent

BP, blood pressure; CV, cardiovascular; CVA, cerebrovascular accident; HF, heart failure; hHF, hospitalisation for HF; HR, hazard ratio; LDL-C, low density–lipoprotein cholesterol; MI, myocardial infarction; T2D, type 2 diabetes.

Rawshani A, et al. *N Engl J Med.* 2018;379:633-644.

2. Obesity and HFpEF

Obesity: it’s here and it’s real!

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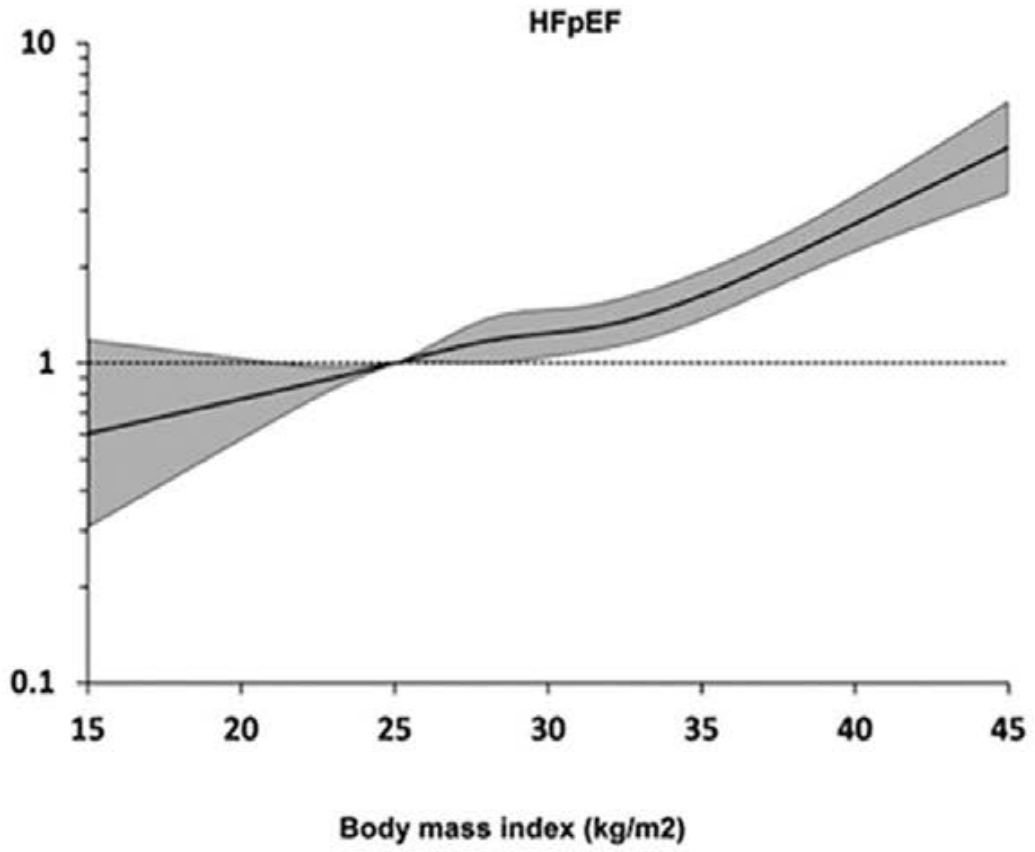
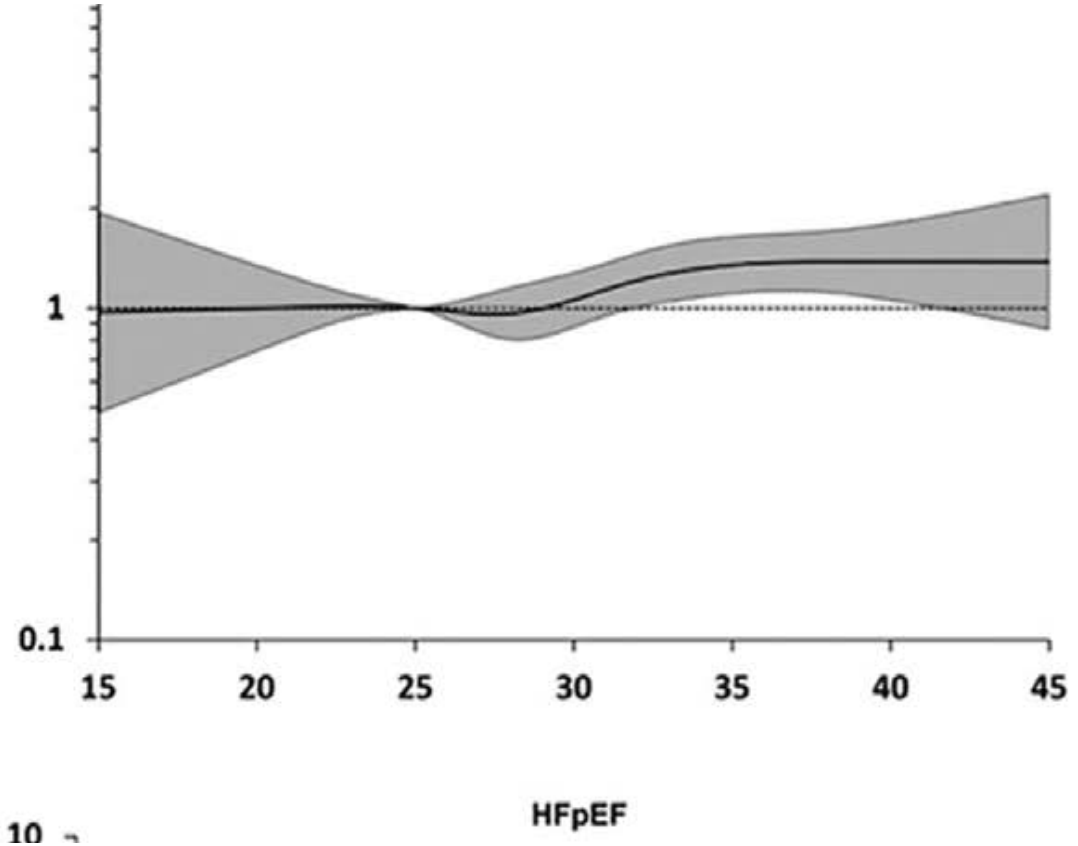
Conditions included in CVD definition may vary.
CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease.
WHO Fact sheet – CVDs. Available at: http://www.who.int/mediacentre/factsheets/fs317/en/; Roth GA et al. J Am Coll Cardiol 2017;70(1):1–25;
WHO, Obesity & Overweight. 2020. Available from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed November 2020;
GBD 2015 Obesity Collaborators. N Engl J Med 2017; 377(1):13–27.

Association of obesity with HFpEF, but not HFrEF





Multiple mechanisms connect obesity to HFpEF

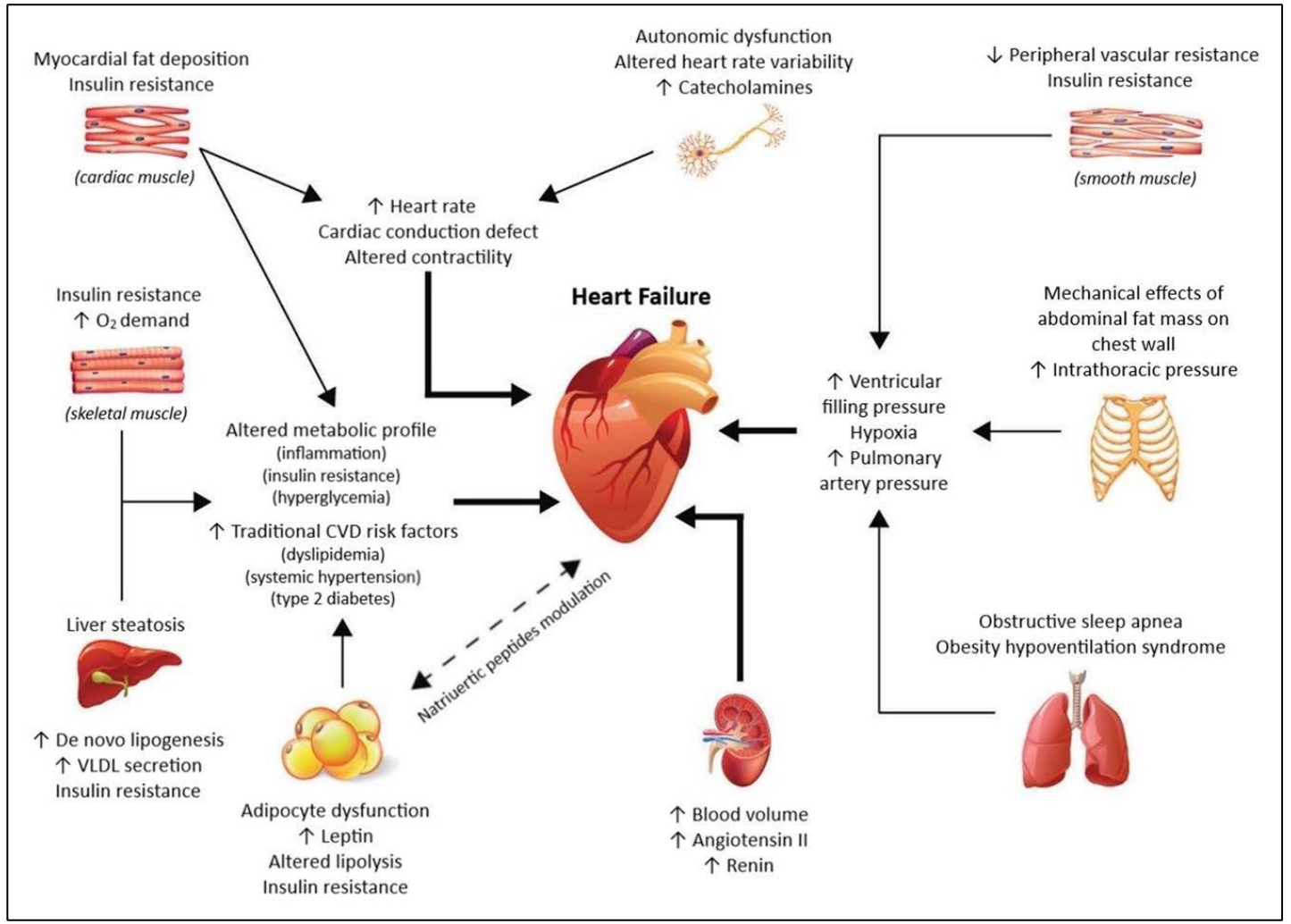


Figure 1. Pathophysiology of heart failure in obesity.
CVD indicates cardiovascular disease; and VLDL, very-low-density lipoprotein. Adapted from Rodriguez Flores et al[240] with permission from Taylor & Francis Ltd (https://www.tandfonline.com). Copyright © 2017, Taylor & Francis Ltd.

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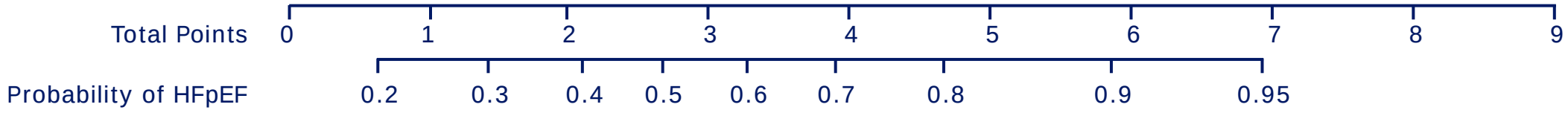
H_2FPEF Score

	Clinical Variable	Values	Points
H_2	Heavy	Body mass index >30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or persistent	3
P	Pulmonary Hypertension	Doppler echocardiographic estimated pulmonary artery systolic pressure >35 mmHg	1
E	Elder	Age >60 years	1
F	Filling Pressure	Doppler echocardiographic E/e' >9	1
H_2FPEF score			Sum (0-9)



Reddy YNV et al, Circulation 2018 Aug 28;138(9):861-870. doi: 10.1161/Circulation AHA.118.034646

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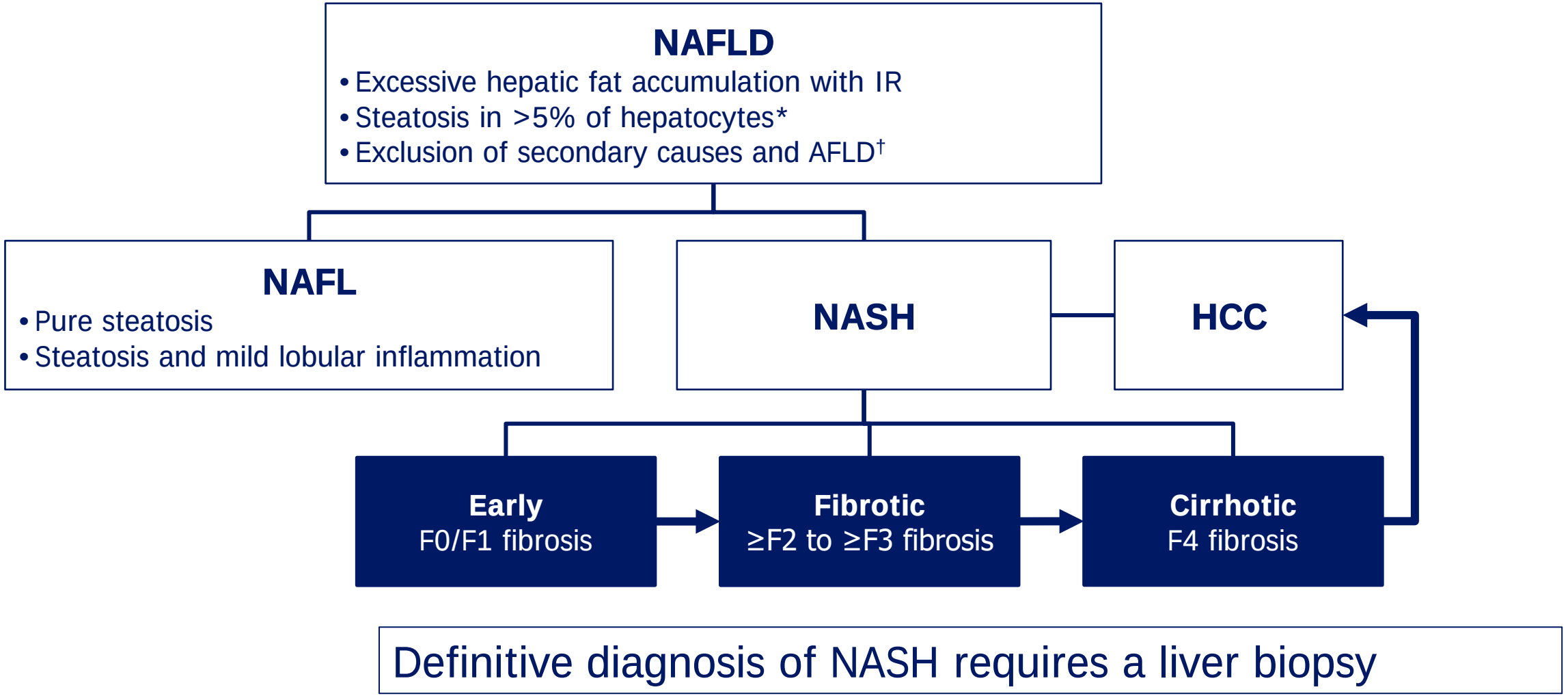
3. Liver disease and HFpEF

Definitions of NAFLD, NAFL and NASH



Definitive diagnosis of NASH requires a liver biopsy

*According to histological analysis or proton density fat fraction or >5.6% by proton MRS or quantitative fat/water-selective MRI;
†Daily alcohol consumption of ≥30 g for men and ≥20 g for women

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

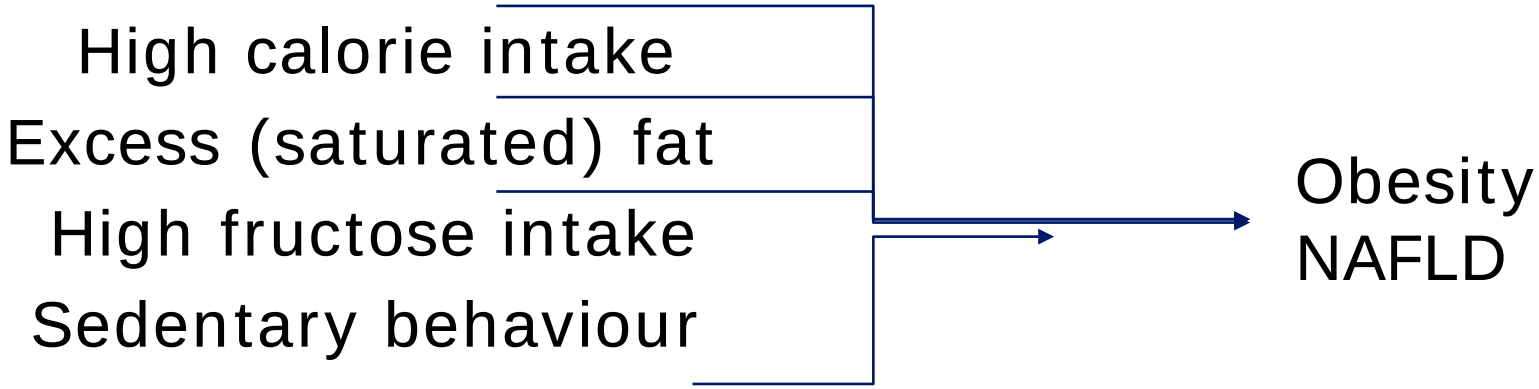
Screening, prevalence and incidence

- NAFLD is the most common liver disorder in Western countries, affecting 17–46% of adults[1]
  - Parallels the prevalence of metabolic syndrome (MetS) and its components, which also increase the risk of more advanced disease
  - NAFLD is also present in 7% of normal-weight (lean) individuals[2]

1. Vernon G, et al. Aliment Pharmacol Ther 2011;34:274–85; 2. Younossi ZM, et al. Medicine 2012;91:319–27; EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Pathogenesis: lifestyle and genes

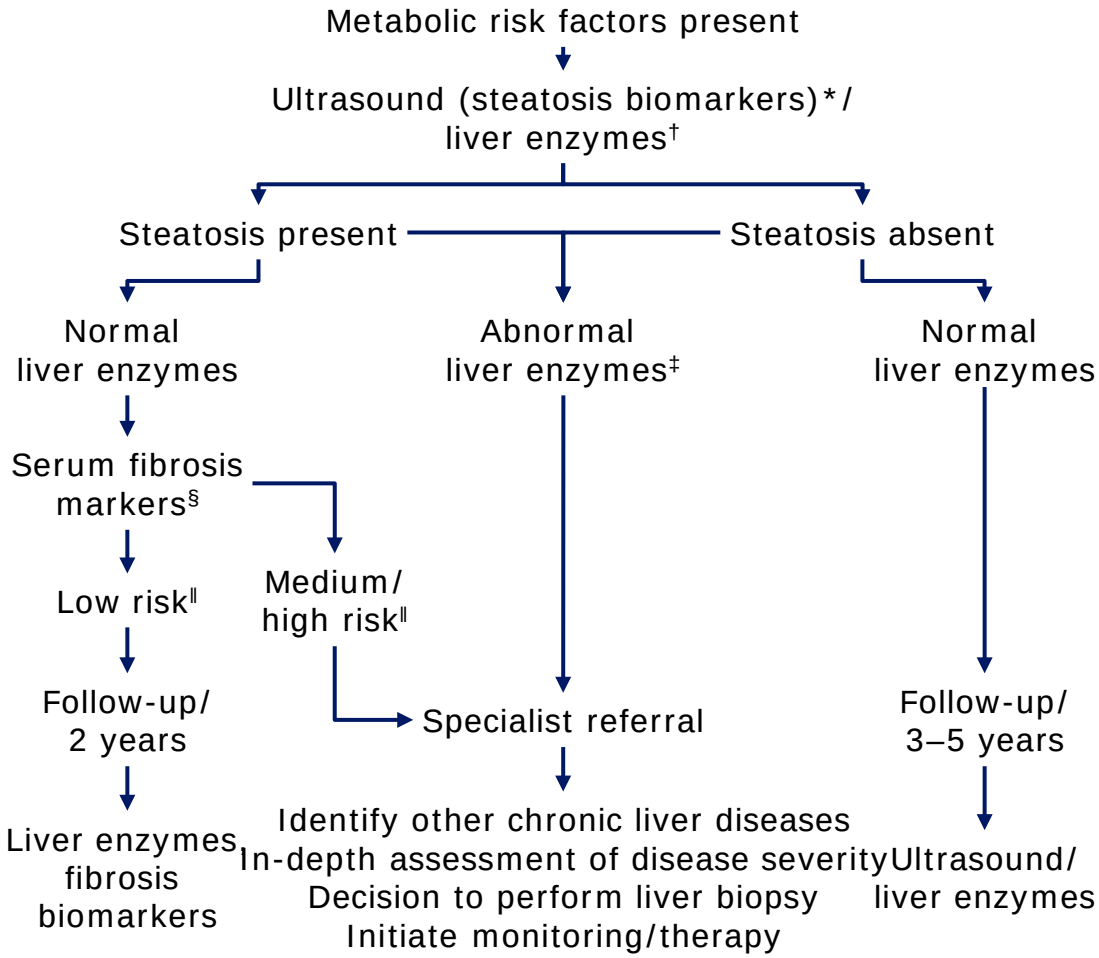
- A Western diet/lifestyle has been associated with weight gain and obesity, and NAFLD[1]



1. Barrera F, George J. Clin Liver Dis 2014;18:91–112;
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

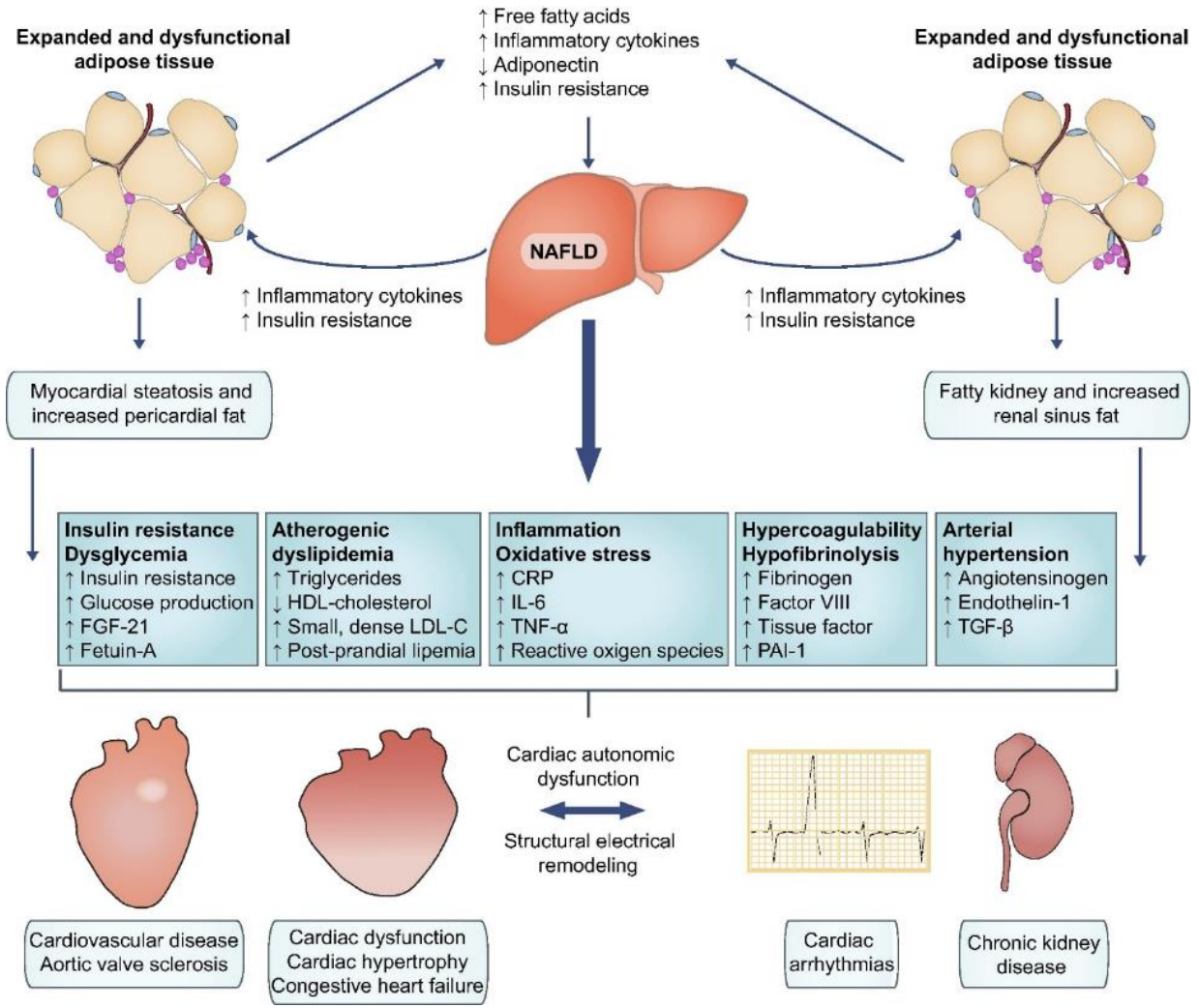
Diagnosis: diagnostic flow-chart

- Metabolic work-up must carefully assess all components of MetS
- Obesity/T2DM or raised liver enzymes in patients with metabolic risk factors should prompt non-invasive screening to predict steatosis, NASH and fibrosis



*Steatosis biomarkers: Fatty Liver Index, SteatoTest, NAFLD Fat score;
†Liver tests: ALT AST, GGT; ‡Any increase in ALT, AST or GGT;
§Serum fibrosis markers: NAFLD Fibrosis Score, FIB-4, Commercial tests (FibroTest, FibroMeter, ELF);
‖Low risk: indicative of no/mild fibrosis; medium/high risk: indicative of significant fibrosis or cirrhosis
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Putative connection between NAFLD, CVD and HF



Byrne CD, Targher G. J Hepatol 2015;62:S47–64

Is there any data to support weight loss and improved HF outcomes?

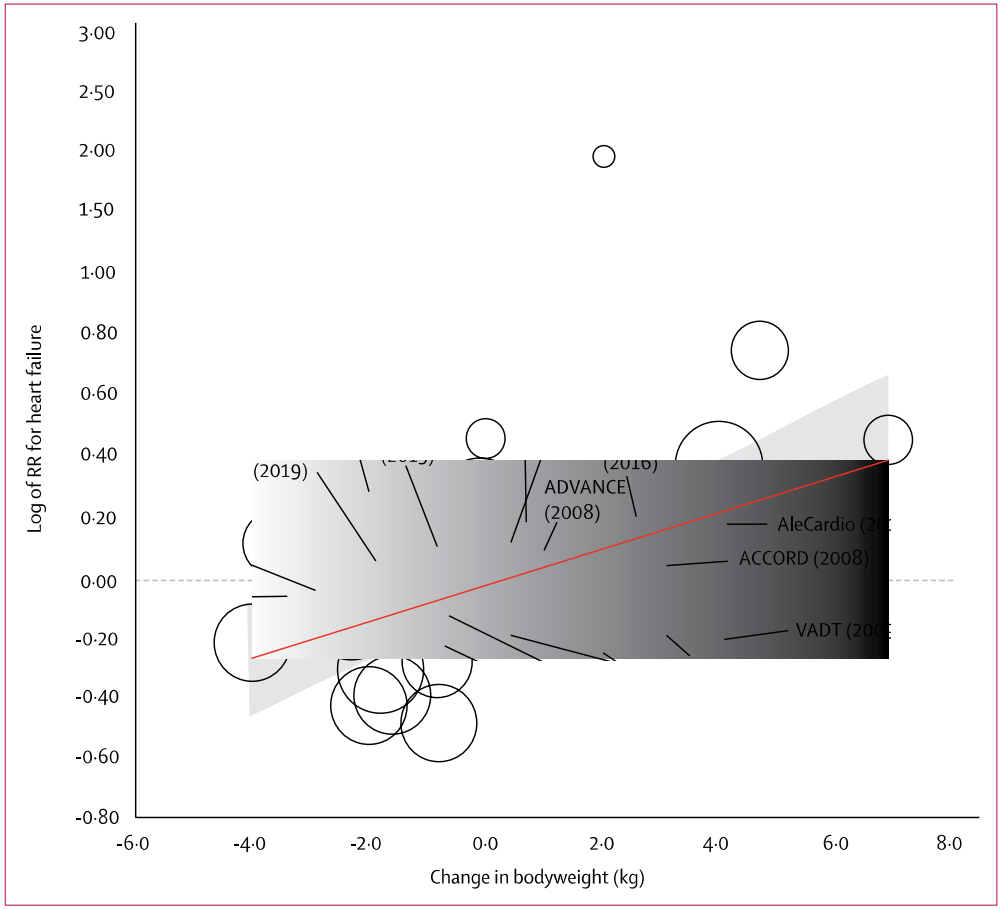


Figure 5: **Relation between change in bodyweight and risk of heart failure**
Red line shows meta-regression with 95% CI shown as shading. The size of the circles reflects the number of outcome events contributed. RR=risk ratio.

Glucose-lowering drugs or strategies, atherosclerotic cardiovascular events, and heart failure in people with or at risk of type 2 diabetes: an updated systematic review and meta-analysis of randomised cardiovascular outcome trials

Olivia R Ghosh-Swaby, Shaun G Goodman, Lawrence A Leiter, Alice Cheng, Kim A Connelly, David Fitchett, Peter Jüni, Michael E Farkouh, Jacob A Udell

Components of a lifestyle approach to NA

Energy restriction
- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Coffee consumption
- No liver-related limitations

Comprehensive lifestyle approach

Macronutrient composition
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

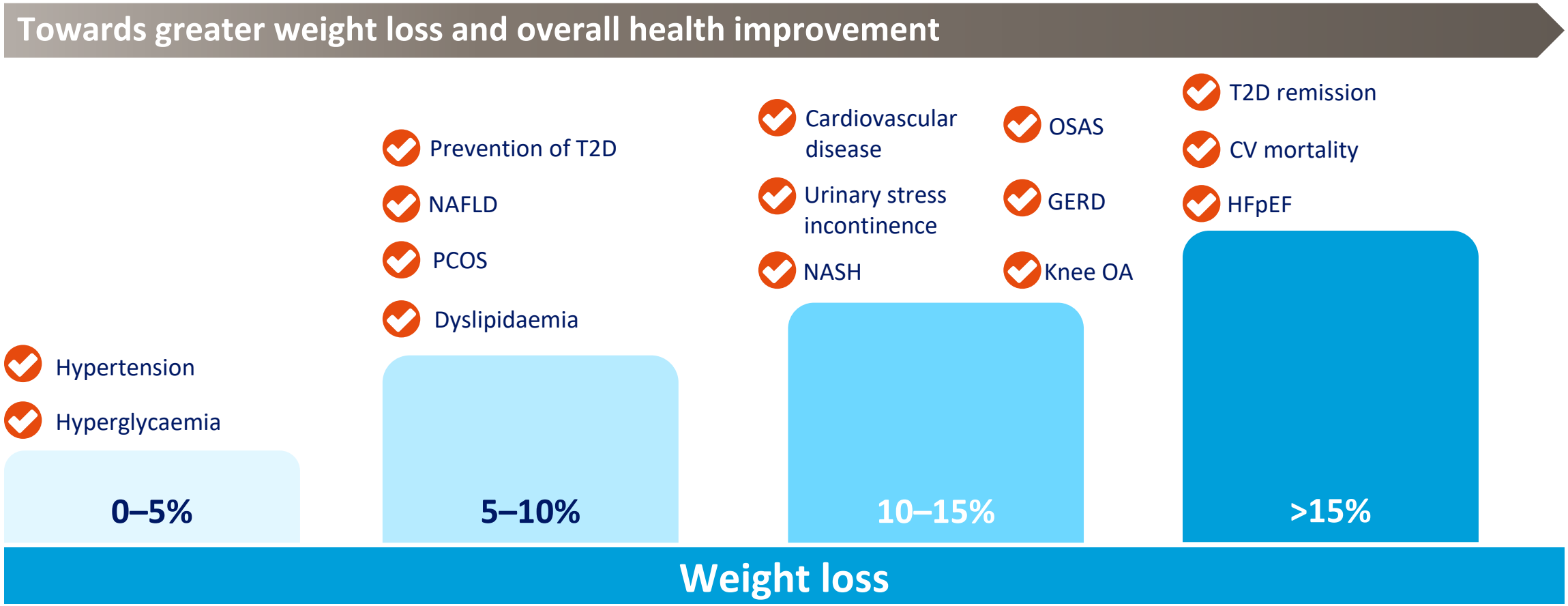
Fructose intake
- Avoid fructose-containing food and drink

Daily alcohol intake
- Strictly below 30 g men and 20 g women

Physical activity
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Greater weight loss leads to improved health outcomes



CV, cardiovascular; GERD, gastro-oesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA: osteoarthritis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes; TG, triglycerides.

Garvey WT et al. Endocr Pract 2016; 22(Suppl. 3):1–203; Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016; 4(11):913–921; Lean ME et al. Lancet 2018; 391(10120):541–551; Benraoune F and Litwin SE. Curr Opin Cardiol 2011; 26(6):555–561; Sundström J et al. Circulation 2017;135(17):1577–1585.

Comparison of available pharmacotherapy options

	Orlistat	Liraglutide 3.0 mg	Naltrexone/bupropion	Semaglutide 2.4 mg**
MoA	• Semisynthetic derivative of lipstatin • Potent and selective inhibitor of pancreatic lipase • Inhibiting the breakdown of dietary triglycerides into absorbable free fatty acids	• Human GLP-1 analog	• Combination of opioid receptor antagonist (naltrexone) and antidepressant (bupropion) • Induces satiety by enhancing production & release of α-MSH and β-endorphin from POMC cells in hypothalamus	• Human GLP-1 analogue that acts on POMC/CART neurons to improve satiation and satiety reduce hunger and cravings
Efficacy	• Systematic review and meta-analysis of orlistat RCTs have reported a mean placebo subtracted weight loss of 2.9% at one year • 54% and 26% of patients on orlistat achieved ≥ 5% and ≥ 10% weight loss, respectively, compared to 33% and 14% for placebo	• Liraglutide 3.0 mg with health behaviour-modifications resulted in 8.0% weight loss at one year, compared to 2.6% with placebo with normoglycemia or prediabetes	• Naltrexone/bupropion with hypocaloric diet and exercise was associated with 6.1% weight loss compared to 1.3% in placebo in patients without diabetes • Weight loss of ≥ 5% and ≥10% was seen in 48% and 25% of patients with naltrexone/bupropion respectively, compared with 16% and 7% in the placebo group respectively	• Semaglutide 2.4 mg with health behaviour-modifications resulted in 14.9% weight loss at 68 weeks, compared to 2.4% with health behaviour modifications alone
Safety	• GI adverse events were observed • May interfere with absorption of fat-soluble vitamins and anticonvulsants • Rare cases of liver injury or acute liver failure	• Most common adverse effect is **nausea** • GI adverse events were common, but gradual titration can help mitigate them • Small increased risk of pancreatitis	• Common adverse events include **nausea, constipation, headache, vomiting, insomnia, dry mouth, dizziness and diarrhea.** • Potential for multiple drug interactions due to naltrexone/bupropion inhibiting CYP2D6	• GI adverse events were observed at similar proportions to patients taking liraglutide • Small increased risk of pancreatitis

****Semaglutide 2.4 mg weekly is not yet commercially available in Canada.**

CART, cocaine- and amphetamine-regulated transcript; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; MoA, mechanism of action; MSH, melanocyte stimulating hormone; PM, Product Monograph; POMC, pro-opiomelanocortin. Pedersen SD, et al. Canadian Adult Obesity Clinical Practice Guidelines: Pharmacotherapy in Obesity Management. Available from: https://obesitycanada.ca/guidelines/pharmacotherapy. Accessed October 21, 2022.

SELECT

Semaglutide

31-59m

Sept 2023

Assess the efficacy of semaglutide in people living with
Obesity

- ≥45 years **no diabetes**
- **CVD | Stroke | PAD | Peripheral arterial revascularization | Amputation due to ASCVD**
- **BMI ≥27kg/m²**
- **A1C<6.5% (NO diabetes)**

Primary Endpoints
- CV death | Nonfatal MI | Nonfatal stroke

ClinicalTrials.gov Identifier: NCT03574597. Accessed Feb 8, 2023.

STEP-HFpEF

Semaglutide

52w

Apr 2023

- ≥18 years
- **LVEF≥45%**
- **BMI ≥30kg/m²**
- **A1C<6.5% (NO diabetes)**

Assess the efficacy of semaglutide in people living with **HFpEF and Obesity**

Primary Endpoints
- Change in KCCQ CSS (52w)
- Change in body weight (52w)

ClinicalTrials.gov Identifier: NCT04788511. Accessed Feb 8, 2023.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

CONCLUSIONS

This phase 2 trial involving patients with NASH showed that treatment with semaglutide resulted in a significantly higher percentage of patients with NASH resolution than placebo. However, the trial did not show a significant between-group difference in the percentage of patients with an improvement in fibrosis stage. (Funded by Novo Nordisk; ClinicalTrials.gov number, NCT02970942.)

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=82)	Placebo Group (N=80)
Age — yr	55.2±10.9	58.1±9.9	54.3±10.2	52.4±10.8
Female sex — no. (%)	51 (64)	52 (67)	47 (57)	44 (55)
Body weight — kg	98.4±21.1	97.1±22.0	96.6±20.1	101.3±23.3
Body-mass index	36.1±6.4	35.6±6.1	35.2±6.6	36.1±6.6
Type 2 diabetes — no. (%)	49 (61)	51 (65)	49 (60)	50 (62)
Glycated hemoglobin level among patients with type 2 diabetes — %†	7.4±1.3	7.2±1.0	7.2±1.2	7.3±1.2
Liver-enzyme levels — U/liter				
Alanine aminotransferase	55±90	53±78	54±84	55±92
Aspartate aminotransferase	44±82	43±73	44±78	42±83
Liver fibrosis stage — no. (%)‡				
F1	23 (29)	19 (24)	26 (32)	22 (28)
F2	18 (22)	18 (23)	14 (17)	22 (28)
F3	39 (49)	41 (53)	42 (51)	36 (45)
Total activity score for nonalcoholic fatty liver disease§	4.9±0.8	4.9±0.9	4.8±0.9	4.9±0.9
Noninvasive measures of liver steatosis and fibrosis				
Liver steatosis, as assessed by FibroScan — dB/m¶	332.0±46.2	347.4±55.0	335.7±55.8	348.6±35.2
Liver stiffness, as assessed by FibroScan — kPa¶	10.4±78.5	12.3±74.0	11.5±87.1	8.7±90.0
Enhanced liver fibrosis test score‖	9.8±1.0	9.8±0.9	9.9±1.0	9.6±0.9

* Plus–minus values are means ±SD, except for body-mass index, liver-enzyme levels, and liver stiffness as assessed by FibroScan, which are geometric means ±coefficient of variation. Percentages may not total 100 because of rounding.

† These values were based on the number of patients with type 2 diabetes in each group (49, 51, 49, and 50 patients in the 0.1-mg, 0.2-mg, 0.4-mg, and placebo groups, respectively).

‡ Stages are defined as follows: F0, no fibrosis; F1, mild-to-moderate zone 3 perisinusoidal fibrosis or portal or periportal fibrosis only; F2, zone 3 perisinusoidal fibrosis and portal or periportal fibrosis; F3, bridging fibrosis; and F4, cirrhosis.

§ Scores range from 0 to 8 (unweighted sum of the scores for steatosis [assessed on a scale of 0 to 3], lobular inflammation [assessed on a scale of 0 to 3], and hepatocyte ballooning [assessed on a scale of 0 to 2]), with higher scores indicating an increased likelihood of nonalcoholic steatohepatitis.[19]

¶ This assessment was performed only at sites at which FibroScan equipment was available. Liver steatosis was assessed in 161 patients and liver stiffness in 212 patients.

‖ The enhanced liver fibrosis test provides an algorithmic liver fibrosis score that is based on the serum levels of hyaluronic acid, procollagen type III N-terminal peptide, and tissue inhibitor of metalloproteinase 1. A score of greater than 9.8 indicates a moderate risk of advanced fibrosis, and a score of greater than 11.3 denotes a high risk of advanced fibrosis.

Conclusions

- T2DM, obesity and NAFLD are associated with HFpEF
- Neurohormonal activation, inflammation and other signaling cascade activation appear common mechanisms to support this association
- Treatments associated with weight gain appear to increase HF risk
- Persons with RF for metabolic abnormalities i.e. elevated BMI, sedentary behavior etc. should be screened for liver abnormalities as part of routine workup and referred to a specialist if abnormal
- No specific therapies as of yet for this condition, but GLP1-RA agonists under investigation for treatment of obesity and HF