3rd GLOBAL LIVER HEALTH FORUM

sanofi

Cardiovascular and metabolic risks of MAFLD: important considerations for clinical practice

Prof. Hartleb

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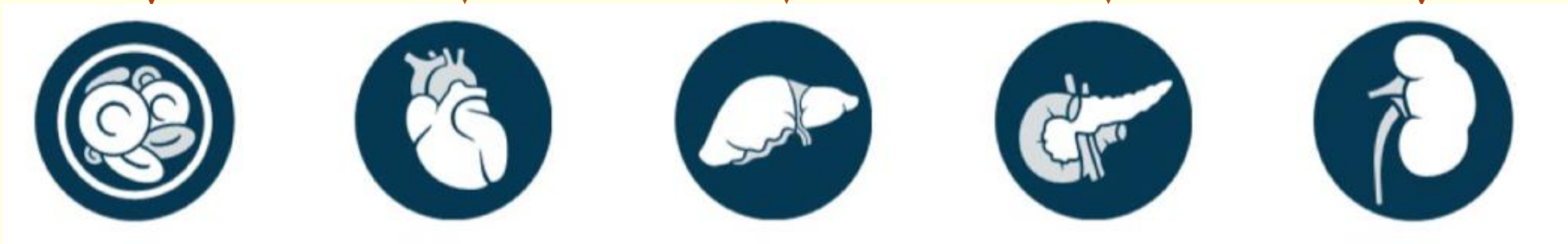
Disclosures

- Lecture honoraria from Sanofi and ProMed

MAFLD is part of a multi-system disorder

Diet-induced obesity

Metabolic stress
Insulin resistance
Systemic inflammation and fibrosis



Arteries	Heart	Liver	Pancreas	Kidney
(HTN, CVD, CAD)	(heart failure)	(MAFLD)	(T2DM)	(CKD)

CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HTN, hypertension; MAFLD, metabolic-associated fatty liver disease; T2DM, type 2 diabetes mellitus

Friedman SL, et al. Nat Med 2018;24:908–22

There is an association between NASH and metabolic dysfunction

NASH is a progressive metabolic disease, which has systemic effects throughout the body

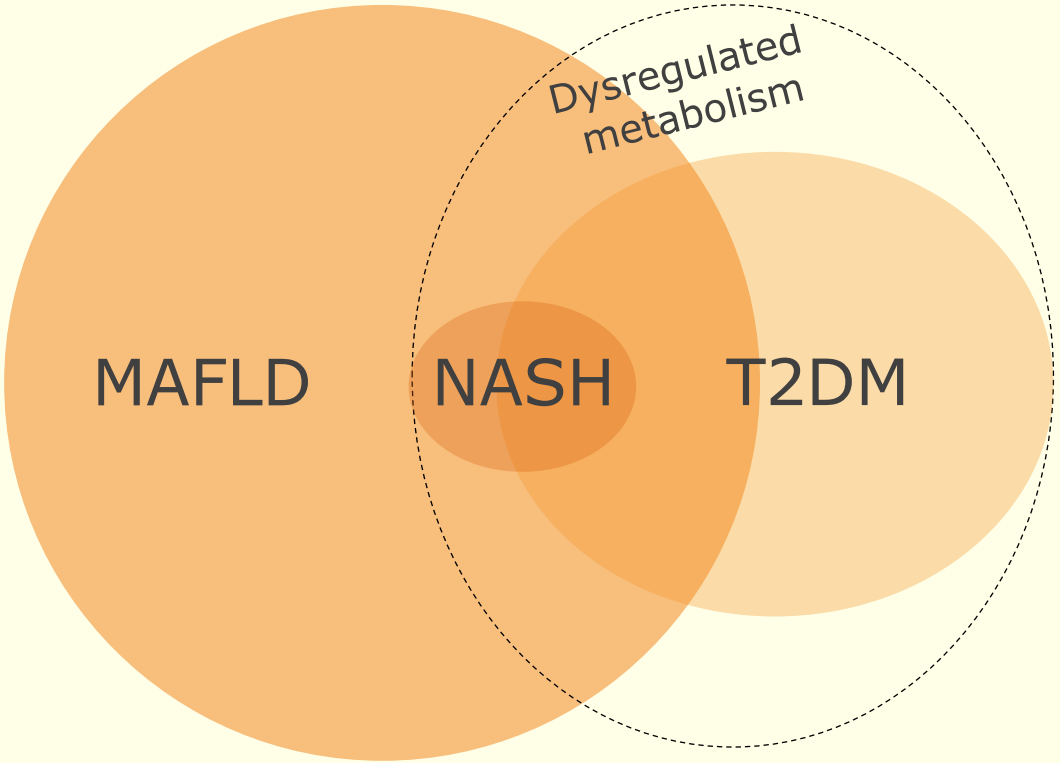


Figure not intended to show prevalence of disorders; for illustration purposes only.
MAFLD, metabolic-associated fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

Classic comorbidities (cardiometabolic risk factors) in MAFLD include features of metabolic syndrome

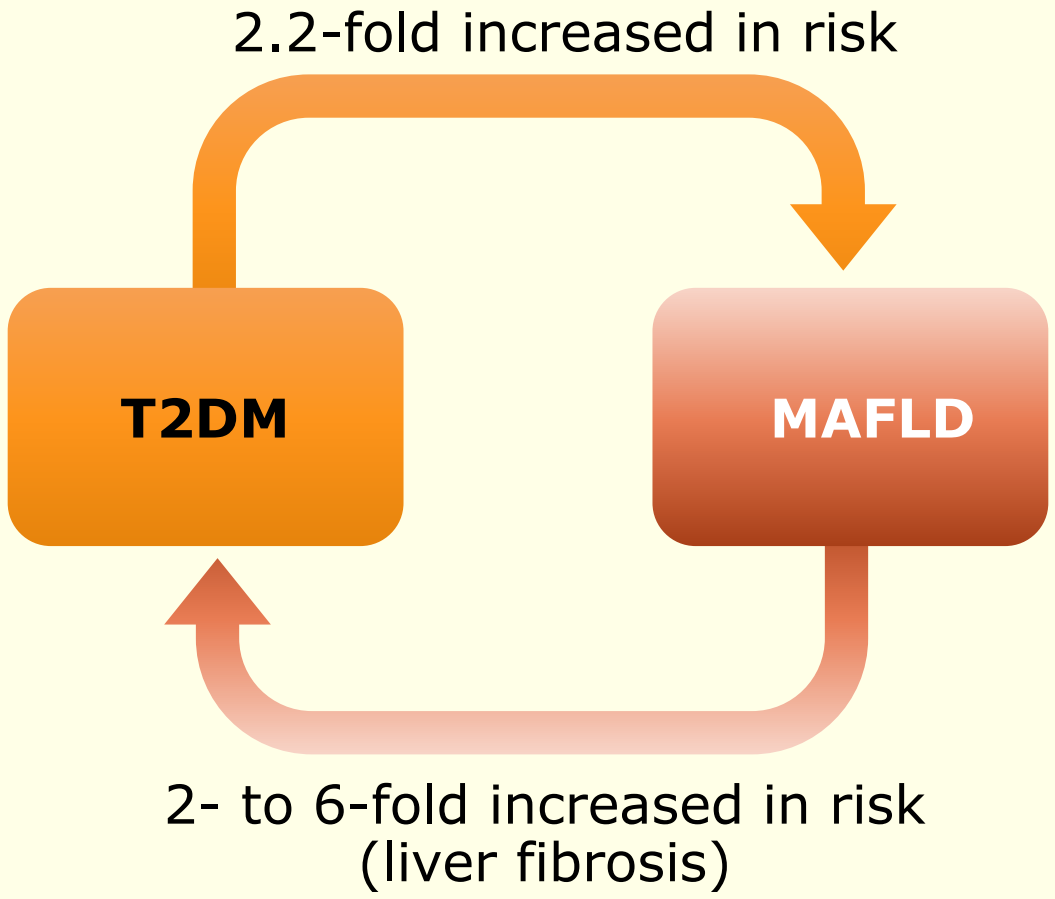
Cardiometabolic disease (%)	General population (USA)	MAFLD (non-NASH)	NASH
Obesity	39.8	51.3	81.8
T2DM	14	22.5	43.6
Hypertension	29	39	68
Hypertriglyceridemia	25	40	83
Metabolic syndrome	34	42.5	71

MAFLD, metabolic-associated fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus
Data provided by speaker

There is an increased risk of cardiovascular events in patients with MAFLD and T2DM

Diabetes promotes:

- ⇧ **Risk of NASH**
- ⇧ **Risk of cirrhosis**
- ⇧ **Risk of HCC**



MAFLD promotes:

Worsening of IR
- ⇧ **Risk of T2DM** (difficulty to manage)
- ⇧ **Risk of atherogenic dyslipidemia**
- ⇧ **Risk of CVD**

CVD, cardiovascular disease; HCC, hepatocellular carcinoma; IR, insulin resistance; MAFLD, metabolic-associated fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

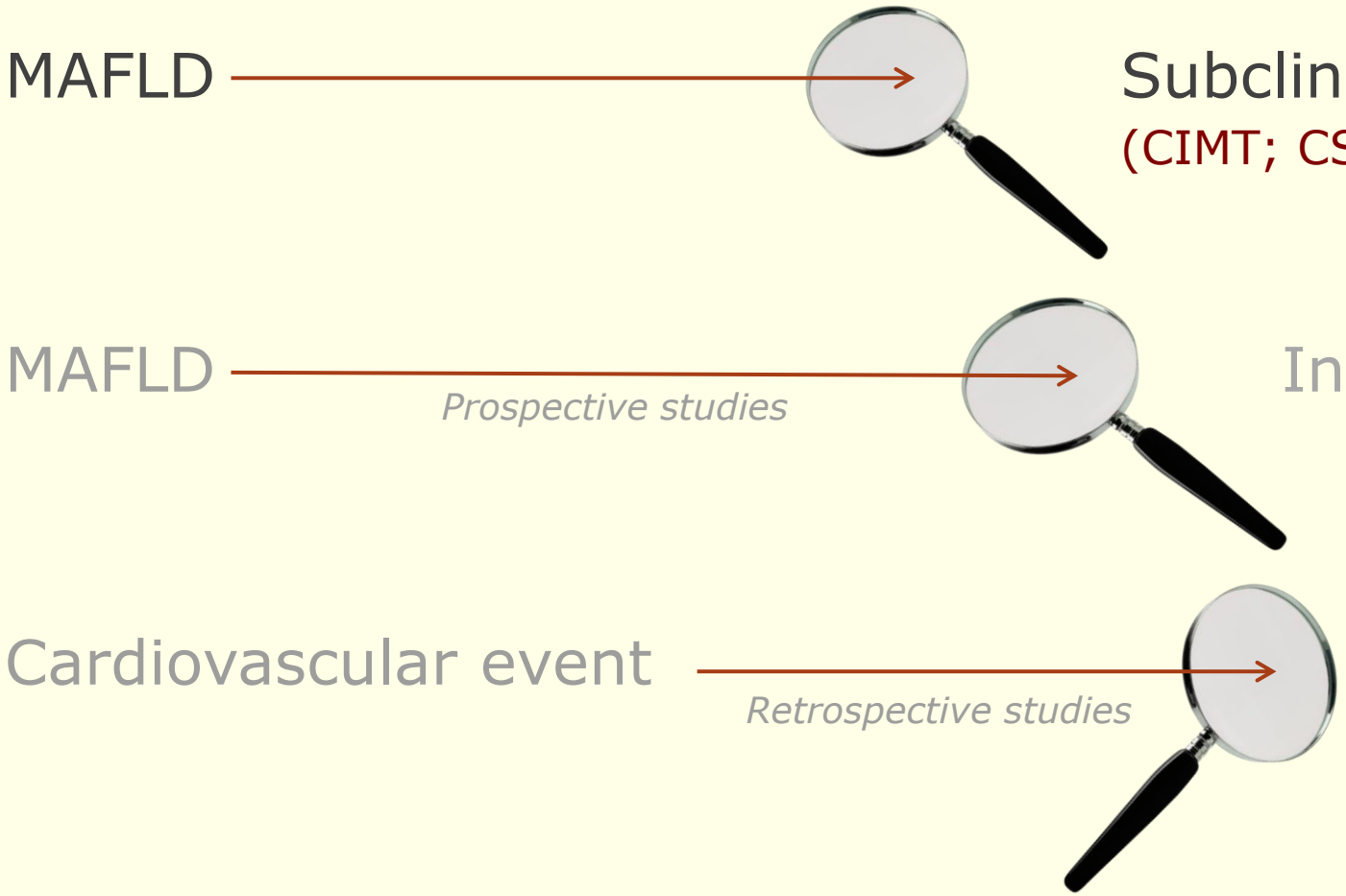
Budd J, Cusi K. Curr Diab Rep 2020;20:59

How familiar are you with the evidence associated with MAFLD and cardiovascular events?

1. I am fully up to date with the latest data on MAFLD and cardiovascular events
2. I am aware of some data on MAFLD and cardiovascular events
3. I am aware of data for other comorbidities associated with MAFLD, but not cardiovascular events
4. I am not aware of data on MAFLD and cardiovascular events

MAFLD, metabolic associated fatty liver disease

Studies on relationships between MAFLD and CVD



CIMT, carotid intima-media thickness; CS, calcium score; CVD, cardiovascular disease; MAFLD, metabolic-associated fatty liver disease

MAFLD increases the risk of subclinical atherosclerosis, CAD and cardiovascular events

Meta-analysis (14 studies; N=2,932)[1]

- **Aim**: To evaluate NAFLD influence on subclinical atherosclerosis and CAD*
- 10 studies evaluated patients with subclinical atherosclerosis
- 4 studies evaluated patients with CAD†

Results:

In patients with MAFLD vs those without MAFLD, there was a higher prevalence of:

- **CIMT:** (35.1% vs 21.8%; p<0.0001), **OR 2.04** (95% CI: 1.65–2.51)
- Carotid plaques: OR 2.82 (95% CI: 1.87–4.27)
- **CAD:** (80.4% vs 60.7%; p<0.0001), **OR 3.31** (95% CI: 2.21–4.95)

Cross-sectional study (N=5,121)[2]

- **Aim**: To evaluate coronary plaques by coronary CT angiography in asymptomatic population with no history of coronary artery disease
- In 38.6% MAFLD diagnosed with US examination

Results:

In patients with MAFLD vs those without MAFLD, after adjustment for cardiovascular risk factors, there was a higher prevalence of:

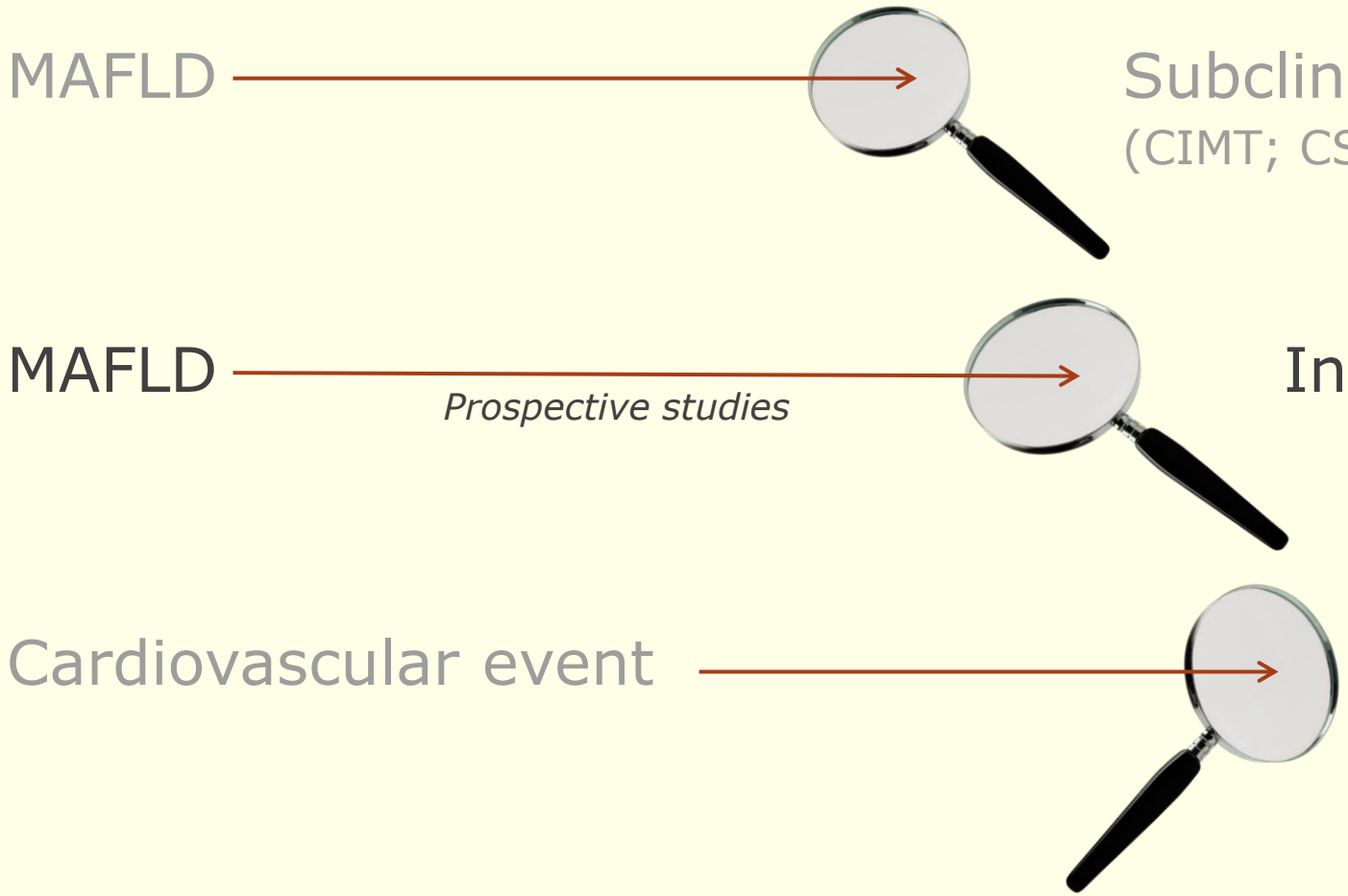
Any atherosclerotic plaque:
OR 1.18 (95% CI: 1,03-1.3%; p=0.016)

Non-calcified plaque:
OR 1.27 (95% CI: 1.08-1.48; p=0.003)

*Diagnosis of MAFLD was defined using US liver biopsy; †Defined as when patients showed at least 50% stenosis at one or more coronary artery; ‡Patients with diagnosis of MAFLD using US or biopsy, CIMT, presence of plaques, and fatty liver
CAD, coronary artery disease; CI, confidence interval; CIMT, carotid intima-media thickness; HR, hazard ratio; MAFLD, metabolic-associated fatty liver disease; OR, odds ratio; US, ultrasound

1. Ampuero J, et al. Rev Esp Enferm Dig 2015;107:10–16; 2. Lee SB, et al. J Hepatol 2018; 68: 1018-1024.

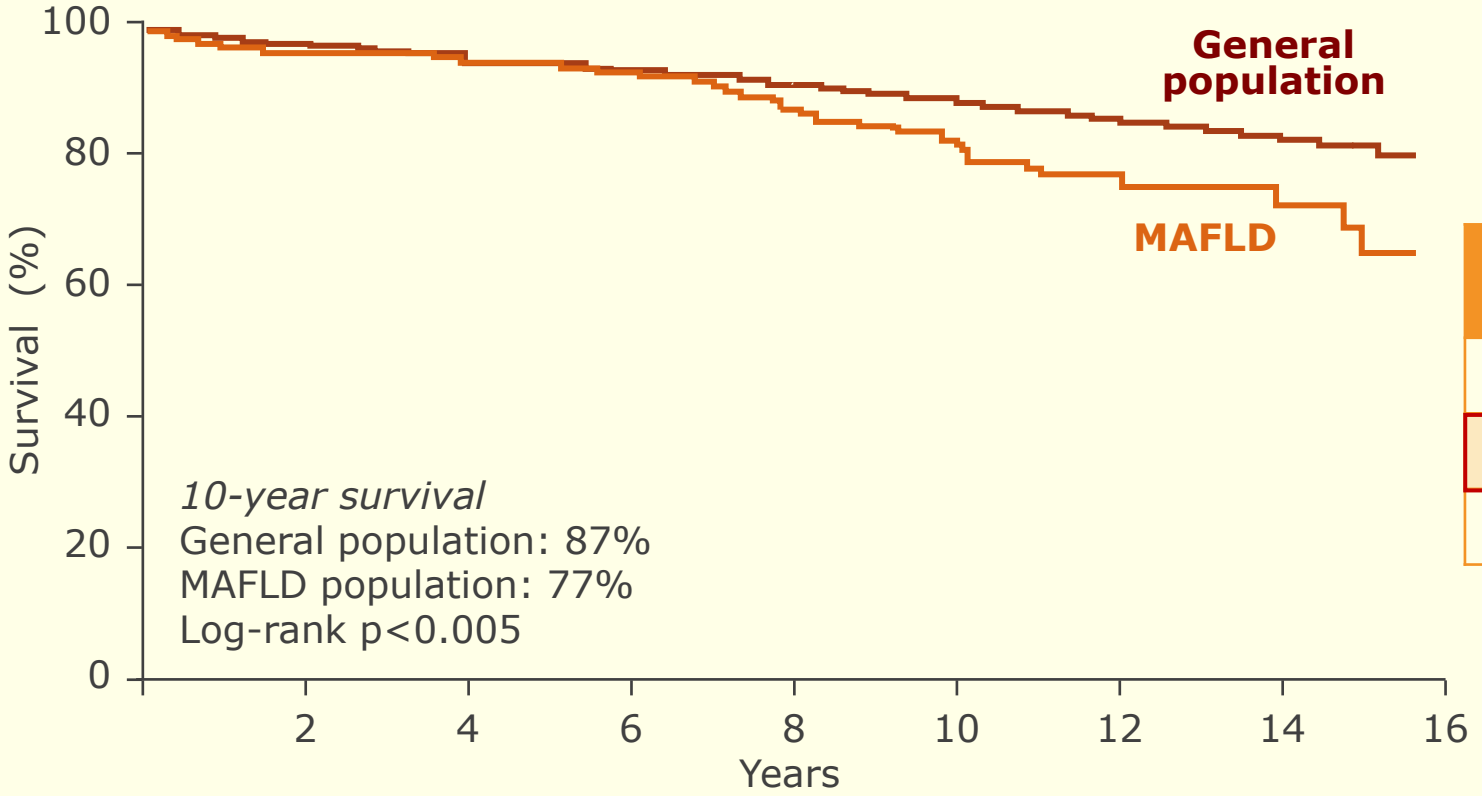
Studies on relationships between MAFLD and CVD



CIMT, carotid intima-media thickness; CS, calcium score; CVD, cardiovascular disease; MAFLD, metabolic-associated fatty liver disease

Increased mortality is also observed in patients with MAFLD vs those without MAFLD

- Medical records were used to identify patients diagnosed with MAFLD **(N=420)** between **1980–2000**
- Overall survival was compared with the general population of the same sex and age
- Mean follow-up was **7.6 ± 4.0 years** (range, 0.1–23.5); **3,192 person-years** follow-up



3 major causes of death in MAFLD	Patients (%) (n=53)
Cancers	28
Cardiovascular events*	25
Liver disease including HCC†	13

*Specifically ischemic heart disease. †Other diseases included in "liver disease" were liver failure and variceal haemorrhage. HCC, hepatocellular carcinoma; MAFLD, metabolic-associated fatty liver disease

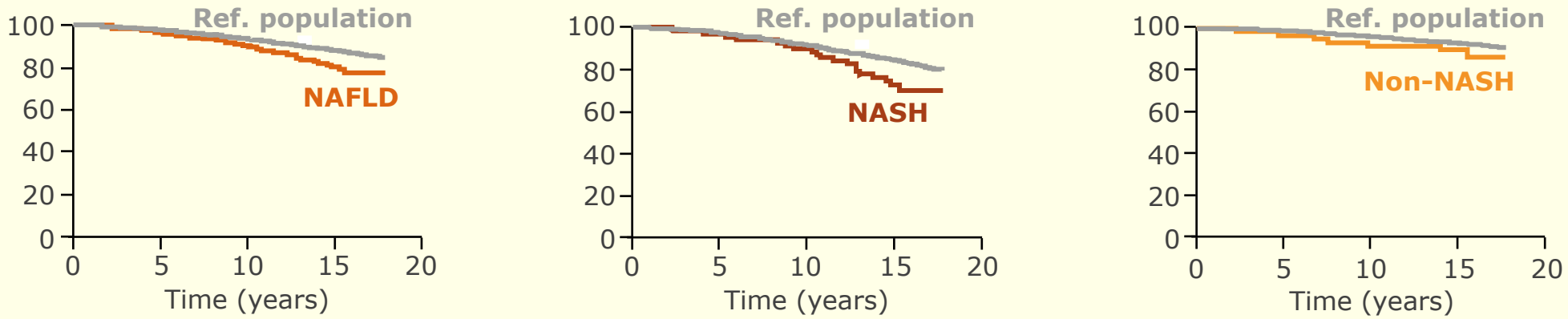
Adams LA, et al. Gastroenterology 2005;129:113–21

Decreased survival has been observed in patients with MAFLD/NASH than those without

- Cohort study re-evaluating **survival** and **cause of death** in patients **diagnosed with NAFLD (n=129)*** compared with a matched reference population (n=44,745) of the same age and sex.
- Median follow-up (SD) 13.7 (1.3) years; **25 deaths** (19.4%) during follow-up

Cause of death (%)	Patients with NASH (n=71)	Reference population (n=44,745)	p value
Liver failure/HCC (n=7)	**2.8**	**0.2**	**p=0.04**
CVD (n=14)	**15.5**	**7.5**	**p=0.04**
Extrahepatic cancers (n=5)	**5.6**	**–**	**–**

Overall survival compared with reference population (%)



*NAFLD was diagnosed by biopsy. ALT, alanine transferase; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; USG, ultrasonography; SD, standard deviation

Ekstedt M, et al. Hepatology 2006;44:865–73

Patients with MAFLD have a higher risk of fatal and/or non-fatal CVD events than those without MAFLD

- **Meta-analysis** of **16** observational, prospective and retrospective studies[1]
- **N=34,043 adults** (36.3% with NAFLD) and approximately **2,600 CVD outcomes** (>70% CVD deaths) over a median period of **6.9 years**[1]

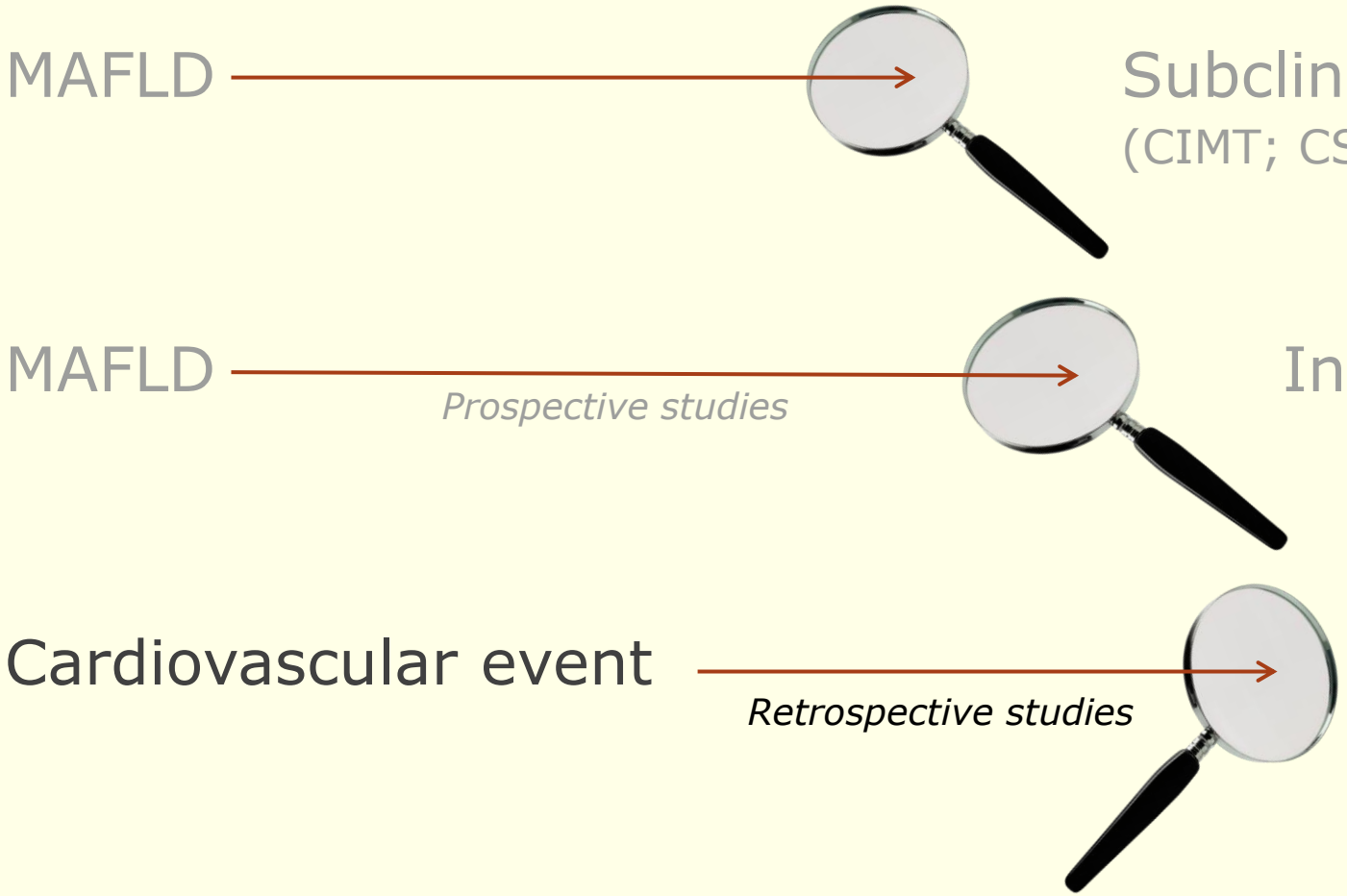
Incidence for progression of MAFLD and NASH (OR 2.58)[2]

Incidence rate per 1,000 person-years	CVD mortality	Liver-specific mortality	All-cause mortality	Incidence HCC
MAFLD	**4.79**	0.77	15.44	0.44
NASH	–	11.77	25.56	5.29

CVD, cardiovascular disease; HCC, hepatocellular carcinoma; MAFLD, metabolic-associated fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio

1. Targher G, et al. J Hepatol 2016;65:589–600; 2. Younossi Z, et al. Hepatology 2016;64:73–84

Studies on relationships between MAFLD and CVD

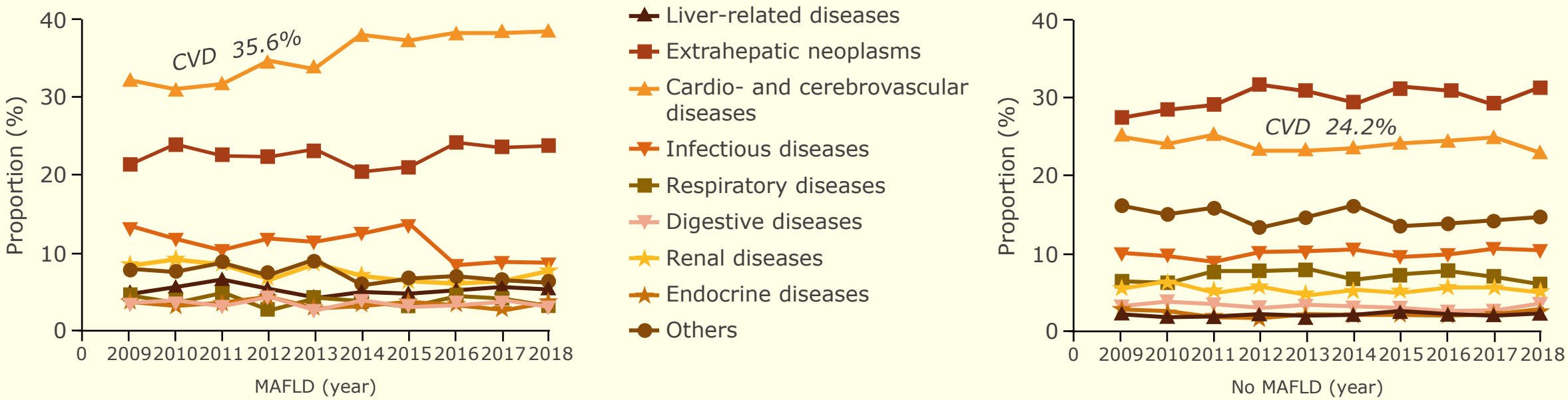


CIMT, carotid intima-media thickness; CS, calcium score; CVD, cardiovascular disease; MAFLD, metabolic-associated fatty liver disease

Patients with MAFLD show higher rates of death due to CVD and liver-related disease than those without MAFLD

- **Multicentre retrospective study** covering **10,071 deaths (2009–2018)** of patients with and without MAFLD, using US graphic assessments

Changing trends in the proportion of cause of death over 10 consecutive years



CVD, cardiovascular disease; MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; US, ultrasound

Lin Y, et al. Front Med 2020;7:584396

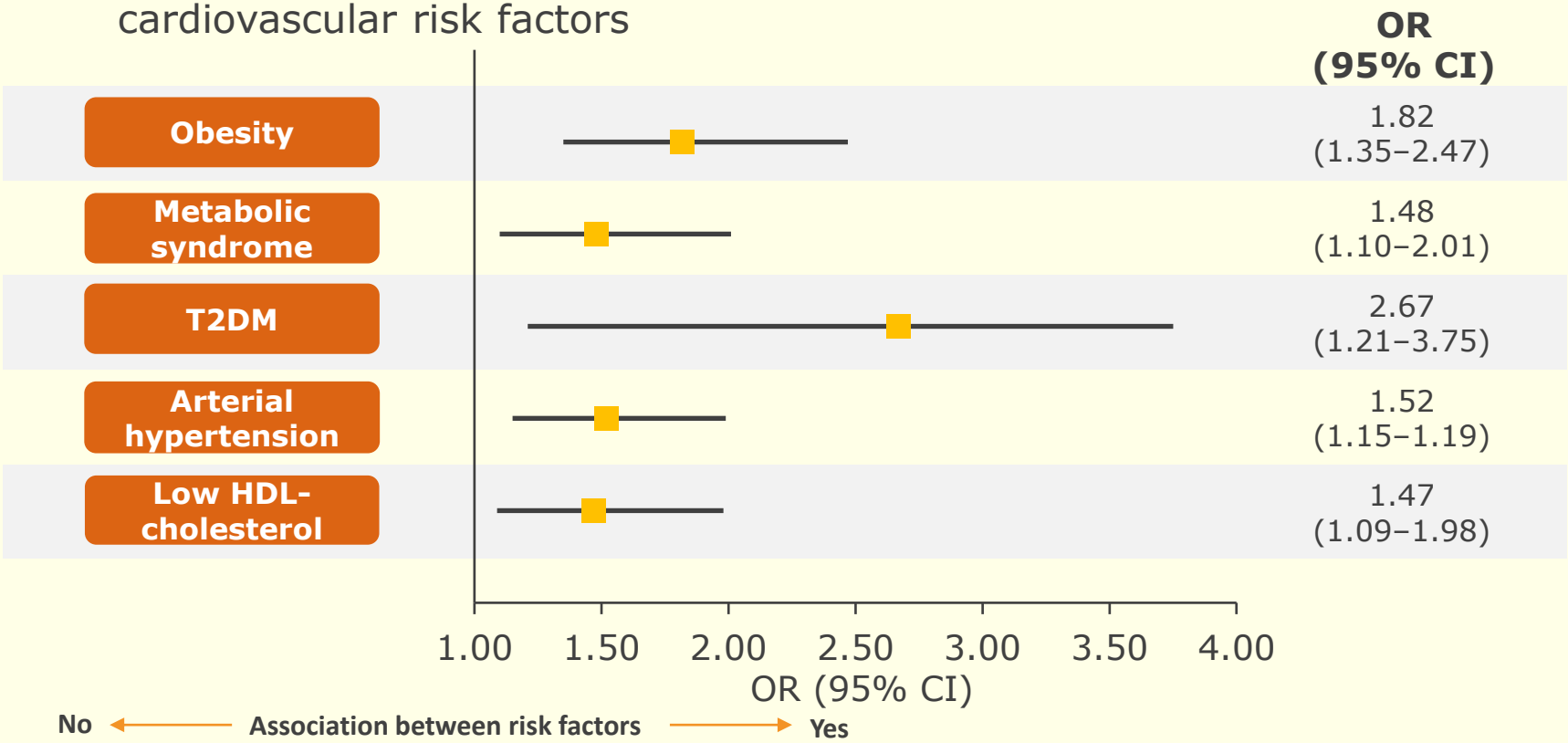
MAFLD has been associated with a variety of CVDs

Tissue/system	Complications
Arterial vessels	Atherosclerosis CAD
Heart muscle	Hypertrophy of left ventricular muscle Diastolic failure of left chamber Heart failure
Conductive system	Atrial fibrillation Other tachyarrhythmias Prolongation of QT segment
Valvular	Calcification of aortic valve Calcification of mitral valve ring

CAD, coronary artery disease; CVD, cardiovascular disease; MAFLD, metabolic-associated fatty liver disease
Data provided by speaker

Liver fibrosis is associated with many CVD risk factors

- Investigated population (using VCTE): **3,276 participants** of Framingham Heart Study (**53.9% women**, mean age **54.3 ± 9.1 years**)
- Multivariable-adjusted logistic regression models were used to determine association between LSM and obesity-related, vascular-related, glucose-related, arterial hypertension and cholesterol-related cardiovascular risk factors



- Prevalence of liver fibrosis (LSM >8.2 kPa) = **9%**
- Prevalence of liver steatosis (CAP >290 dB/m) = **29%**

CAP, controlled attenuation parameter; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; LSM, liver stiffness measure; MAFLD, metabolic-associated fatty liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio; T2DM, type 2 diabetes mellitus; VCTE, Vibration Controlled Transient Elastography

Long MT, et al. Hepatology 2021;73:548–59

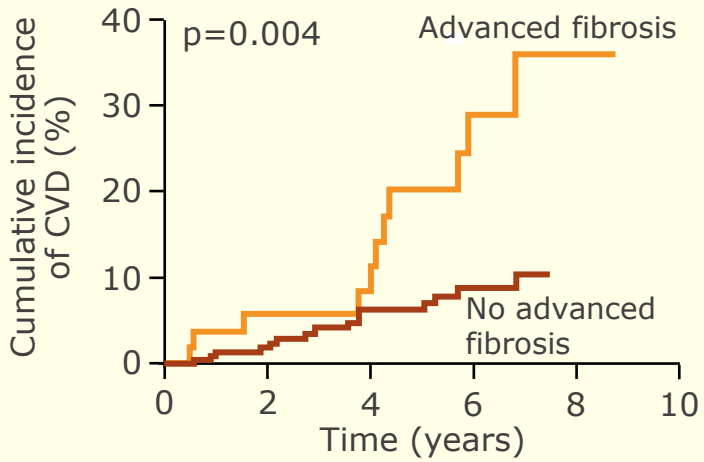
Advanced fibrosis is associated with incident CVD in patients with MAFLD

- **285** patients with histological diagnosis of **MAFLD**
- Prospective follow-up (median 5.2 years)
- At baseline, **26 patients** (9.1%) had experienced a cardiovascular event

Results

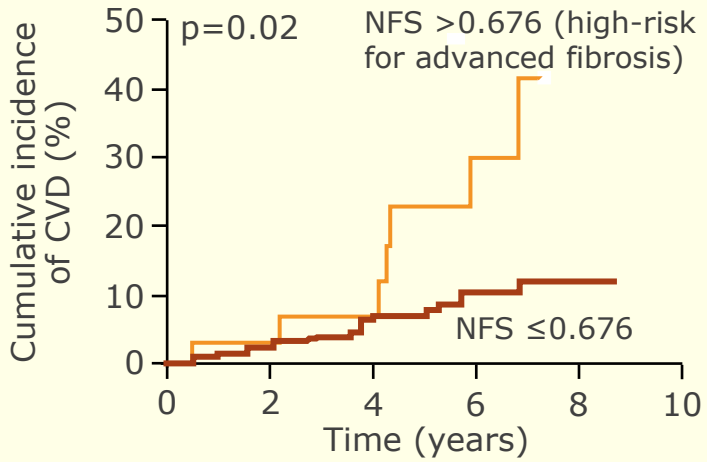
- Advanced fibrosis (stage 3–4) was predictor of incident CVD*
- HR=2.86 (95% CI: 1.36–6.04)

Cumulative incidence curves for incident CVD by advanced fibrosis status



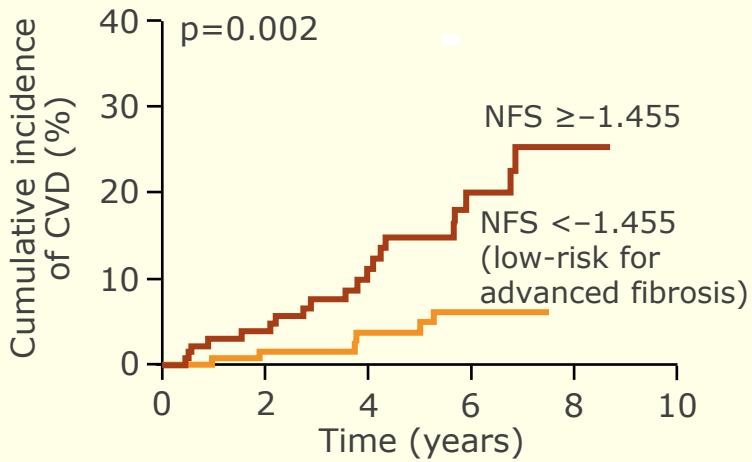
No. at risk:

Advanced fibrosis	43	32	15	1
No adv. fibrosis	185	131	88	0



No. at risk:

NFS >0.676	26	18	9	1
NFS ≤0.676	202	145	94	0



No. at risk:

NFS ≥–1.455	108	75	46	1
NFS <–1.455	120	88	57	0

*Incident CVD was defined as a new diagnosis of CAD, congestive heart failure, peripheral vascular disease, stroke, transient ischaemic attack, or a major adverse cardiac event, which included myocardial infarction, coronary revascularisation, or cardiac-related death

CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MAFLD, metabolic-associated fatty liver disease; NFS, NAFLD fibrosis score

Henson JB, et al. Aliment Pharmacol Ther 2020;51:728–36

Can CVD or T2DM be predicted in MAFLD patients?

- **Score2** is a prediction model to estimate 10-year fatal and non-fatal CVD risk in individuals without previous CVD or diabetes (aged 40–69) in Europe: https://u-prevent.com/calculators

Patient risk factors used in adjusted risk models

- Geographical region
- Gender
- Age
- Smoking
- Systolic arterial pressure
- Total cholesterol
- HDL-cholesterol
- LDL-cholesterol

There is a need for scores including MAFLD and NASH in prediction of cardiovascular events

CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAFLD, metabolic-associated fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

SCORE2 working group and ESC Cardiovascular risk collaboration. Eur Heart J 2021;42(25):2439–54

There exist several therapeutic approaches for managing MAFLD and associated comorbidities

Weight loss
- Lifestyle (diet, physical activity)
- GLP-1RA and/or SGLT2i
- Bariatric surgery

Control obesity

Reduce CVD risk

Treat T2DM and cardiovascular risk factors
- Hyperglycemia (GLP-1RA and/or SGLT2i)
- Dyslipidaemia (statin)
- Hypertension (ACEi/sartans)
- Smoking cessation
- Antiplatelet drugs

Other approaches
- Statin (reducing portal hypertension)
- Metformin (decrease of HCC risk)

Reduce end-stage complications

Target NASH

Liver-directed treatment
- Vitamin E
- Pioglitazone
- Semaglutide

ACEi, angiotensin-converting enzyme inhibitors; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HCC, hepatocellular carcinoma; MAFLD, metabolic-associated fatty liver disease; NASH, non-alcoholic steatohepatitis; SGLT2i, sodium/glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus
Data provided by speaker

A variety of antidiabetic drugs are used in MAFLD

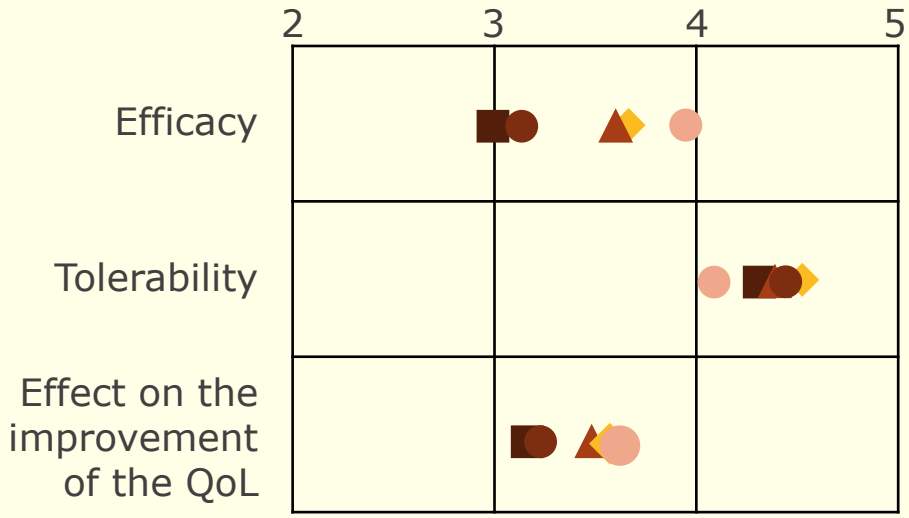
Drug	Action mechanism	Biological effects
Metformin	Insulin resistance ↓	**No significant influence on MAFLD histology** **BMI** ↓, improvement of metabolic profile
Pioglitazon	PPAR-ϒ agonist Insulin resistance ↓↓	**Steatosis regression, improvement of NASH, fibrosis?** Increased capacity to store fat in physiological locations, supression of inflammation in adipose tissue BMI ↑, osteoporosis
Incretin mimetics *(liraglutide, semaglutide)*	GLP-1RA	**NASH regression** **BMI** ↓ (gastric emptying inhibition) Subcutaneous injection
Flozins *(empagliflozin, canagliflozin)*	SGLT2i	**ALT ↓, steatosis ↓, NASH improvement** **BMI** ↓ (energy balance reduced by 250–350 kcal/day) Cardioprotective and nephroprotective properties Impaired absorption of carbohydrates (diarrhoea)

ALT, alanine transferase; BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; MAFLD, metabolic-associated fatty liver disease; NASH, non-alcoholic steatohepatitis; SGLT2i, sodium/glucose cotransporter-2 inhibitor
Data provided by speaker

RESTORE study results: ranking of the five most commonly recommended treatments by the top three criteria

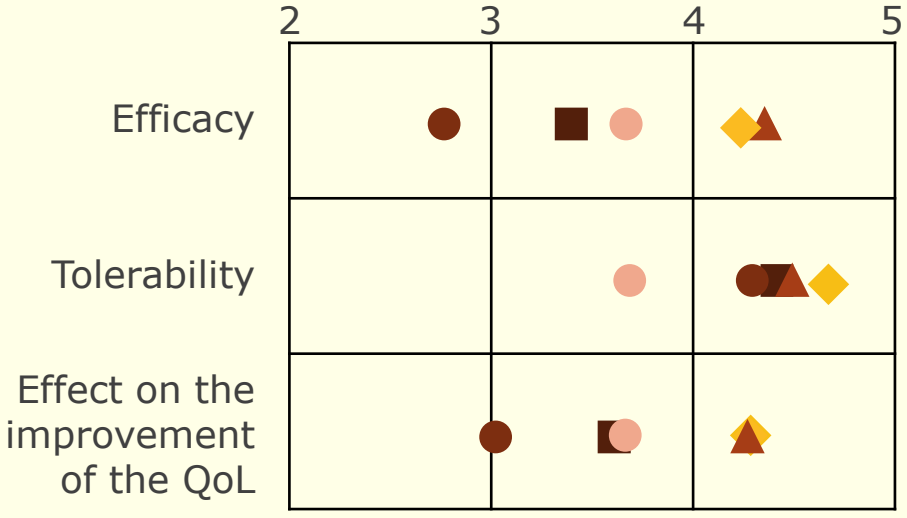
GEs

Average score, n=95 GEs, scale 1–5



GPs

Average score, n=115 GPs, scale 1–5



Essentiale® (EPL) Hepatil Heparegen Proursan Sylimarol

EPL was regarded as having a good efficacy and tolerability in comparison with other interventions

Physicians ranked each drug against each criterion using a scale of 1 (not relevant at all) to 5 (extremely relevant).
Essentiale® (EPL); Hepatil® (ornithine + choline); Heparegen® (timonacic); Proursan® (ursodeoxycholic acid); Sylimarol® (silybinin/silymarin)
EPL, essential phospholipids; GE, gastroenterologist; GP, general practitioner; QoL, quality of life
Hartleb M, et al. Eur J Gastroenterol Hepatol 2021;34(4):426–34

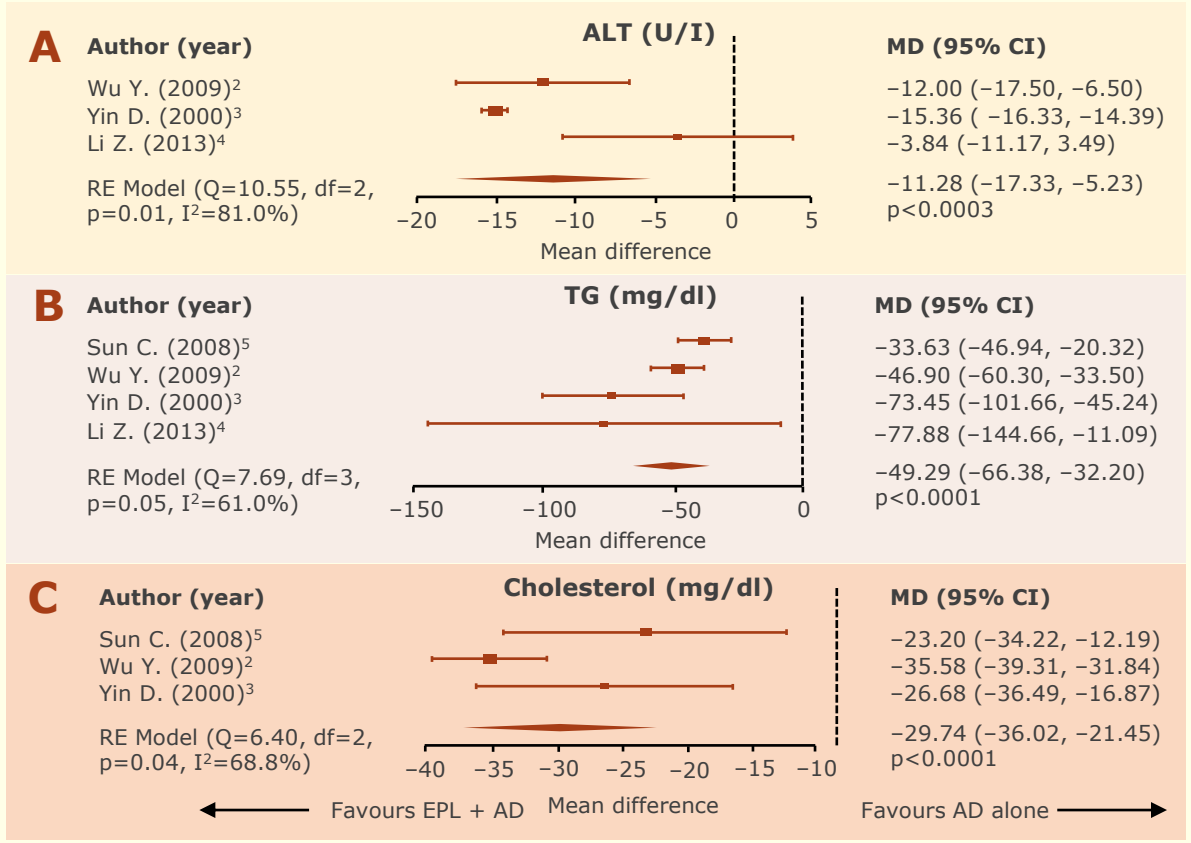
EPL for NAFLD associated with metabolic syndrome: a systematic review and network meta-analysis

Results of a direct meta-analysis of RCTs comparing the effect of treatment with EPL + AD vs AD therapy alone1:

A: Change in ALT: three studies[2–4] (N=371); mean treatment duration, 1.97 months

B: Change in TG levels: four studies[2–5] (N=445); mean treatment duration, 2.1 months

C: Change in total cholesterol levels: three studies[2,3,5] (N=359); mean treatment duration, 2.27 months



AD, anti-diabetic; ALT, alanine aminotransferase; CI, confidence interval; EPL, essential phospholipids; MD, mean difference; NAFLD, non-alcoholic fatty liver disease; RCT, randomised controlled trial; RE, random effects; TG, triglycerides

1. Dajani A, et al World J Clin Cases 2020;8:5235-5249; 2. Wu Y. J TCM Univ Hunan 2009;29:41–42; 3. Yin D, Kong L. Med JQ Illu 2000;15:277–8; 4. Li Z. J Tradit Chinese Med 2013;31:10–1; 5. Sun C, et al. Clin Focus 2008;23:1272–3

Additional data of interest from studies of EPL in patients with NAFLD and cardiometabolic diseases[1]

In an RCT trial of EPL + sibutramine (n=50) vs sibutramine alone (n=30) in patients with **NAFLD and obesity**, **treatment with EPL + sibutramine** resulted in a numerical **reduction of blood glucose from baseline***
Treatment with EPL + sibutramine also resulted in **reductions of HOMA-IR** compared with baseline[2]

In an RTC of EPL + metformin (n=43) vs metformin alone (n=43) in patients with **NAFLD and diabetes**, treatment with both regimens resulted in satisfactory glucose control; however, treatment with **EPL + metformin** resulted in greater **improvements in ALT, triglycerides and ultrasonography** findings compared with metformin alone ($p<0.05$)[3]

In an RCT of patients with **NAFLD due to diabetes** randomised to receive EPL + SOC† (n=125) vs SOC alone (n=60), patients who received EPL had **reduced triglycerides, total cholesterol, LDL-C ($p<0.05$ for all), and ALT ($p<0.01$)** along with **increased HDL-C ($p<0.05$)** compared with baseline[4]

In an observational study of patients with **NAFLD and ≥1 cardiometabolic comorbidity‡** who received **EPL in combination with SOC*** (n=2843), treatment with EPL resulted in **reduced ALT, AST, GGT ($p<0.001$ for all), LDL-C, triglycerides and total cholesterol, increased HDL-C and improved ultrasonography** findings ($p<0.05$ for all) from baseline[5–7]

*Data not reported for sibutramine alone. †SOC is defined as basic diet and exercise. ‡Defined as overweight/obesity, hypertension, type 2 diabetes or hypercholesterolemia. ALT, alanine transaminase; AST, alanine aspartate; EPL, essential phospholipids; GGT, gamma glutamyl transferase; HDL-C, high-density lipoproteins; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; RCT, randomised controlled trial; SOC, standard of care

1. Dajani et al. Drugs Ther Perspect 2021;37:249–64; 2. Sas E et al. Gut 2012;61:A216–7; 3. Li et al. Inner Mongol J Tradition Chin Med 2013;31:10–1; 4. Yin D et al. Med J Q 2000;15:227–8; 5. Maev IV et al. BMJ Open Gastroenterol 2019;6:e000307; 6. Maev IV et al. BMJ Open Gastroenterol 2020;7:e000368; 7. Maev IV et al. BMJ Open Gastroenterol. 2020;7:e000341.

Summary

1. MAFLD* is multi-systemic disease that increases risk of T2DM and CVD due to insulin resistance and atherogenic lipoprotein phenotype
2. The risk of incident cardiovascular events is positively correlated with severity of liver fibrosis
3. In patients with MAFLD, the risk of cardiovascular events should be assessed, and subclinical stages of atherosclerosis actively searched
4. Statins, management of hypertension, and pioglitazone or GLP-1RA in prediabetes/T2DM may be effective in decreasing both the steatosis and inflammation in the liver and CVD risk
5. EPL has demonstrated many potential benefits in treatments of liver diseases, i.e., including good efficacy and tolerability when compared with other similar interventions

*MAFLD and NAFLD have been used interchangeably throughout this presentation. CVD, cardiovascular disease; EPL, essential phospholipids; GLP-1RA, glucagon-like peptide-1 receptor agonist; MAFLD, metabolic-associated fatty liver disease; T2DM, type 2 diabetes mellitus