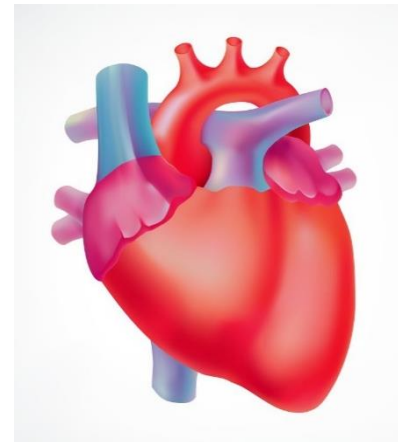
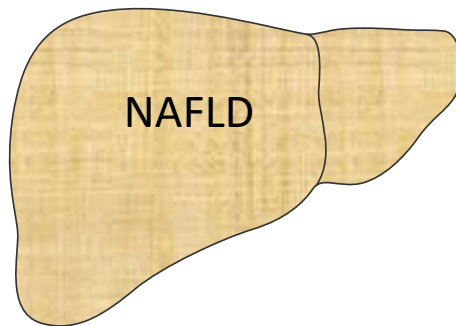


NAFLD and Cardiovascular Complications

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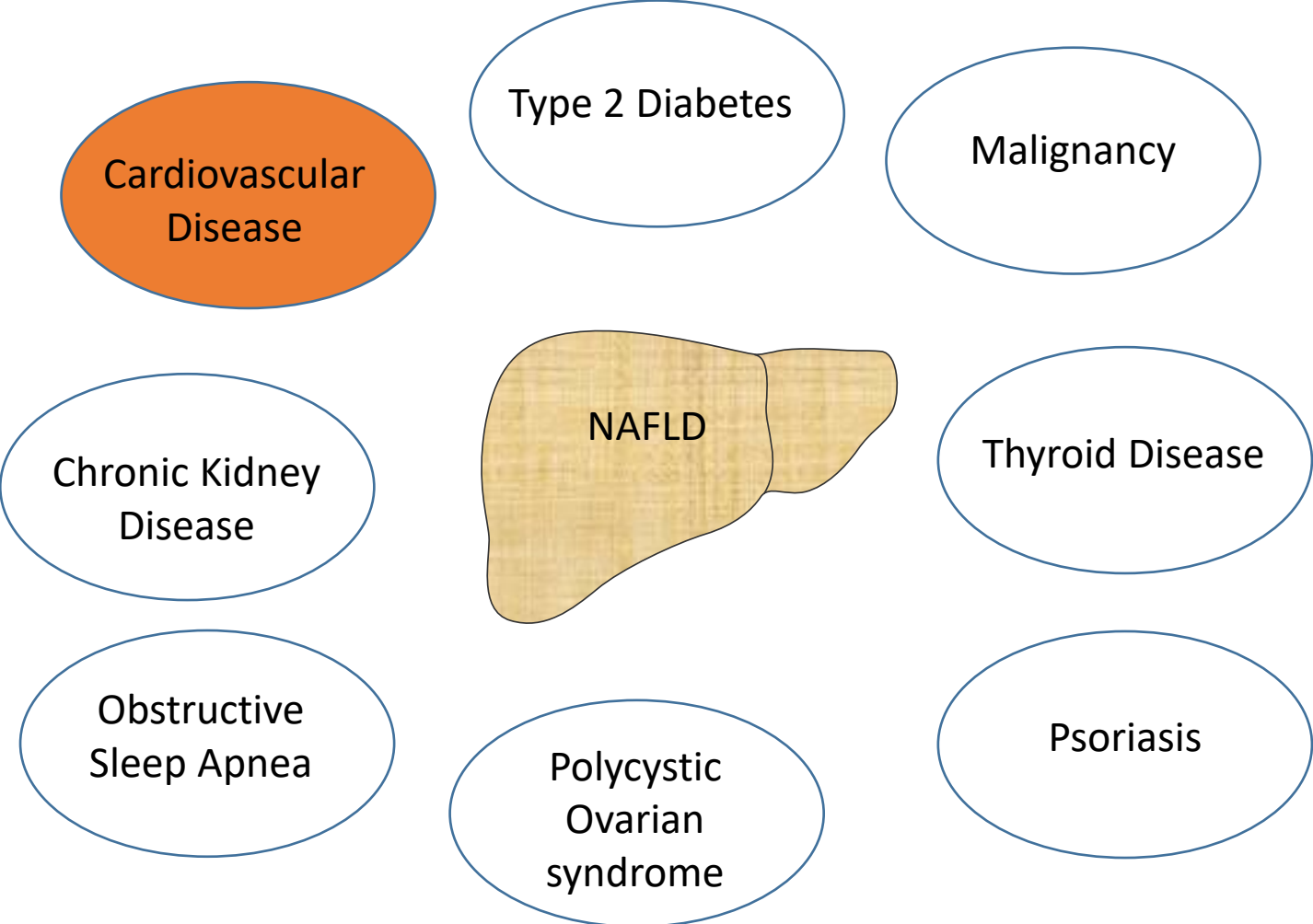
10 July 2020



Outline

- 1) Review the association between NAFLD and CV disease.
- 2) Highlight NAFLD subgroups deserving of special CV attention.
- 3) CVD risk stratification and reduction strategies among NAFLD patients.

NAFLD is associated with multiple extra-hepatic complications



Cardiovascular disease is the leading cause of death among patients with NAFLD

Summary of longitudinal studies evaluating mortality among people with NAFLD							
Author	NAFLD study population	Control Population	Follow up	Survival among NAFLD vs control	Causes of death		
					CV disease	Malignancy (non-GI)	Liver-related (cirrhosis/HCC)
Adams 2005	420, medical records	General population	8 years	Decreased, Standardized mortality ratio=1.34	25%	28%	2%
Soderberg 2010	118, biopsy	General population	24 years	Decreased, SMR=1.69	33%	28%	19%
Eckstadt 2015	229, biopsy	General Population	26 years	Decreased, Hazard Ratio=1.29, CI 1.04-1.59	43%	19%	9%
Rafiq 2009	173, biopsy	-	13 years	-	13%	8%	7%
Dam Larsen 2009	170, biopsy	-	21 years	-	38%	17%	2%
Angulo 2015	619, biopsy	-	13 years	-	38%	19%	9%

Adams Gastroenterology 2005; Soderberg Hepatology 2010; Eckstadt Hepatology 2015; Rafiq CGH 2009; Dam Larsen Scand J of Gastroenterol 2009; Angulo Gastro 2015.

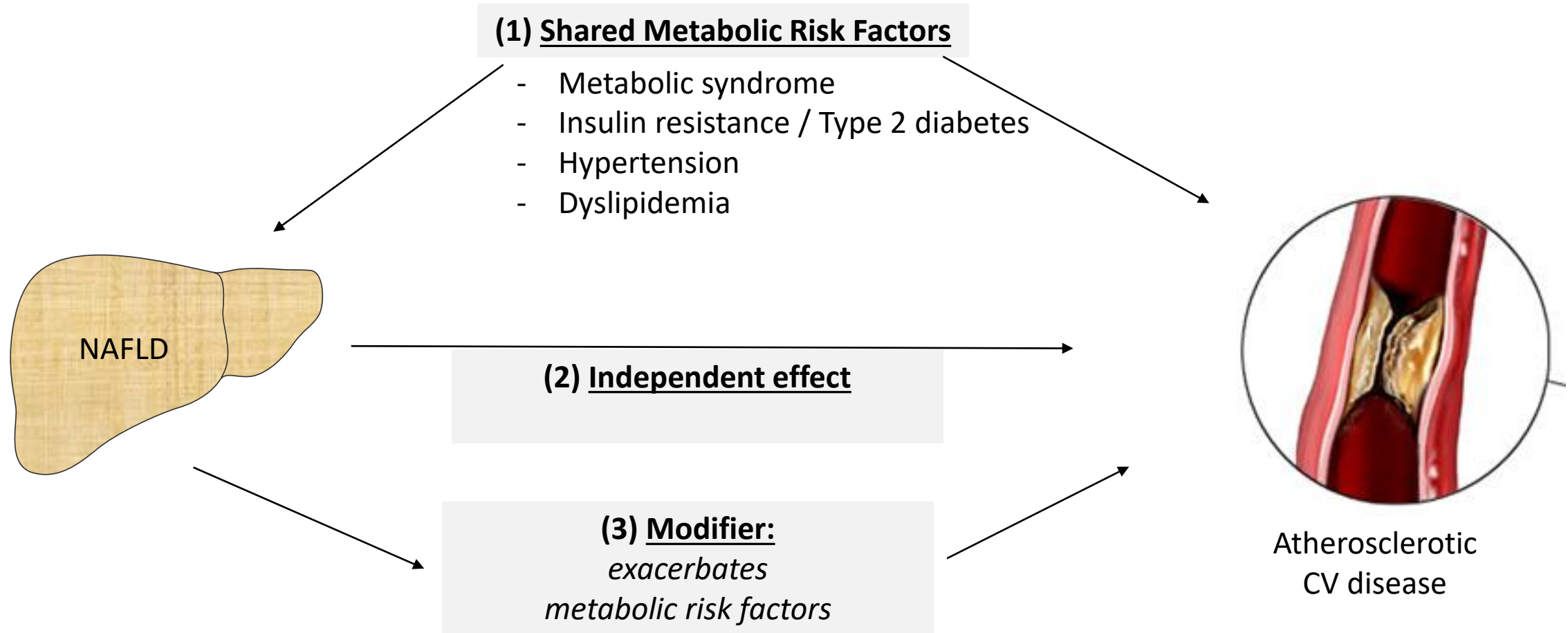
NAFLD is associated with higher incidence of major adverse CV events

NAFLD and clinically significant CVD: summary of meta-analyses				
Author	Study population	Study types included	Outcome	Pooled Odds or hazard ratio (95% CI)
Targher 2016	34,043 36% NAFLD	16 retrospective & prospective cohort studies	Incident CVD:	1.64 (1.26-2.13)
Wu 2016	165,000	13 retrospective & prospective cohort studies	Incident CVD:	1.37 (1.10-1.72)
Haddad 2017	25,837 23% NAFLD	6 prospective cohort studies	Incident CVD:	1.77 (1.26-2.48)

NAFLD is associated with 13-60% higher risk of subclinical atherosclerosis

NAFLD and subclinical atherosclerosis: summary of meta-analyses				
Author	Study population	Study types included	Outcome	Pooled Odds or hazard ratio (95% CI)
Sookian 2008	3,497 41% NAFLD	7 case-control studies (2 popl & 5 hospital based studies)	Carotid artery intimal media thickness:	13% increase risk among NAFLD v non-NAFLD
Jaruvonganich 2016	58,150 28% NAFLD	16 cross-sectional studies	Coronary artery calcium score>0 Coronary artery calcium score>100	1.41 (1.26-1.57) 1.24 (1.02-1.52)
Zhou 2018	85,395 35% NAFLD	20 cross-sectional, 4 case-control, & 2 prospective cohort studies.	CIMT, arterial stiffness, CAC or endothelial dysfunction	1.60 (1.45-1.78)

NAFLD: correlate, independent risk factor, or modifier

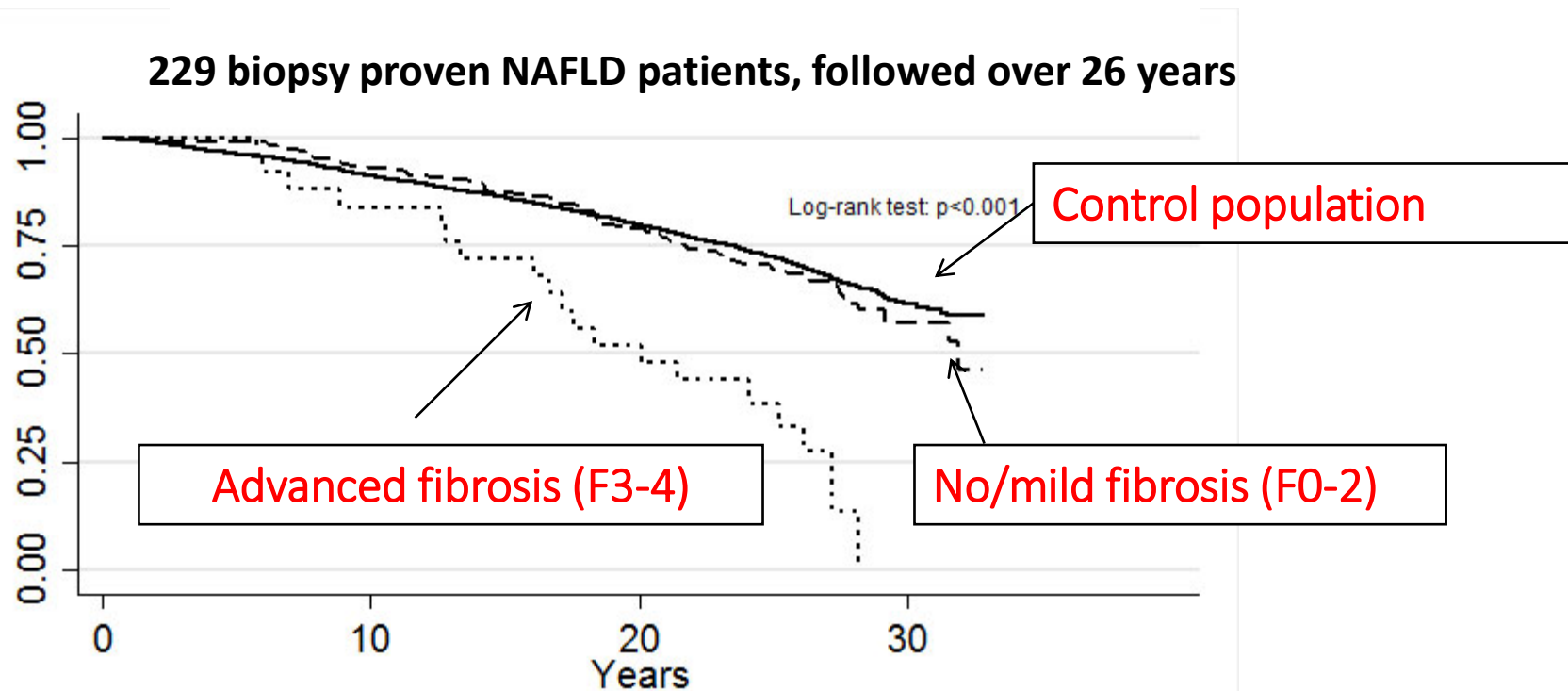


“Though the causal relationship is unclear, NAFLD at minimum, represents a risk marker, and thus attention to and control of CVD risk factors is critical.”

CV risk among specific NAFLD subgroups

1. NAFLD with advanced fibrosis.
2. NAFLD with multiple metabolic syndrome components, especially type 2 diabetes.

Among patients with NAFLD, advanced fibrosis is associated with highest risk of all-cause and CV mortality

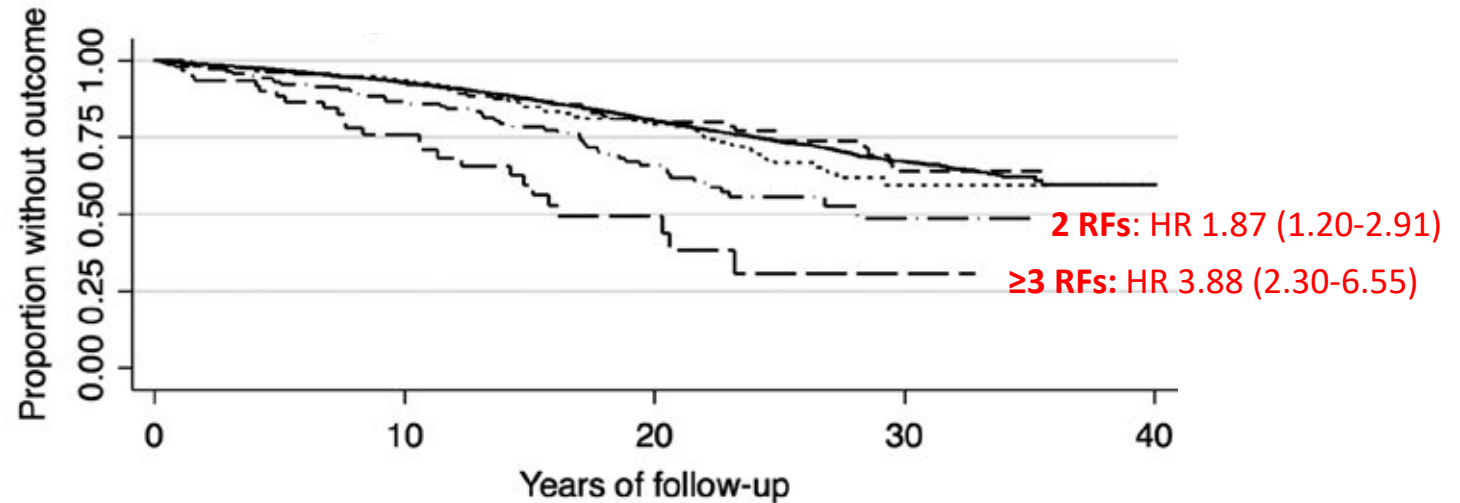


	Hazard ratios : fibrosis subgroup v control	
	No/mild fibrosis	Adv fibrosis
All-cause mortality	1.13 (0.79-1.60)	3.28 (2.27-4.76)
CV mortality	1.19 (0.65-2.20)	4.36 (2.29-8.29)

Metabolic factors may account for the high CV risk observed among patients with advanced fibrosis

Retrospective cohort study, 603 biopsy proven NAFLD patients v. matched population controls, 19 years follow up¹:

- Fibrosis stage did not predict CV events (fatal/nonfatal MI/stroke) after adjusting for age, sex, and traditional CV risk factors.
- Traditional CV risk factors at baseline predicted risk of incident CVD in a dose response manner.



Kaplan-Meier survival curve stratified by number of CVD risk factors present at baseline

Special considerations among patients with advanced NASH fibrosis

1. NAFLD patients with advanced fibrosis (pre-cirrhosis and cirrhosis) face competing risks of CV and liver disease related morbidity and death.
2. Among patients with cirrhosis, those with NASH (v other etiologies) have a higher prevalence of CVD.¹
3. Therefore, AASLD guidelines recommend that patients with NASH cirrhosis undergoing transplant evaluation undergo careful CVD assessment starting with noninvasive functional cardiac testing with progression to coronary angiography when indicated.²
4. Patients with stage 3 fibrosis (pre-cirrhosis) predominantly experience a CV complications, while patients with stage 4 fibrosis (cirrhosis) predominantly experience liver disease complications.³

CVD risk assessment

- CVD risk assessment is warranted among all patients with NAFLD.¹
- Screen for metabolic risk factors: hypertension, prediabetes/T2DM, dyslipidemia.
- Apply standard-of-care risk stratification tools to determine 10 year risk of CV event and to guide CV risk factor management, including dyslipidemia.

Method	Age	Sex	Tot chol	HDL	HTN	Smoking	Race	T2DM	Validated in NAFLD?
Framingham risk score	x	x	x	x	x	x			Yes ²
ASCVD risk score	x	x	x	x	x	x	x	x	No

¹ Chalasani N, Diagnosis & Management of NAFLD, Hepatology 2018;

² Treeprasertsuk S, The FRS and heart disease in NAFLD, Liver Int 2012.

Reducing CVD Risk

- Lifestyle modifications
 - Recommendations are similar and beneficial for improving NAFLD histology and CV risk.¹
 - 5-10% weight loss, aerobic physical activity (150 min moderate exercise or 75 min vigorous exercise per week), Mediterranean/plant based dietary pattern
- Statins
 - Lowering LDL cholesterol is effective for CV disease prevention among primary care as well as NAFLD study populations^{2,3}
 - Standard guidelines for statin use should be applied to NAFLD patients^{2,4}:
 - LDL \geq 190, T2DM patients 40-75 years old, \geq 7.5% risk of CV event in 10 years
 - Statins are under-prescribed among appropriate NAFLD candidates (~10% of high CV risk patients), mainly because of persistent though unsubstantiated fears of hepatotoxicity.³

1 Stahl, NAFLD & CVD JACC 2019.; 2 Grundy SM, AHA/ACC Guidelines on Management of Blood Cholesterol, JACC 2019; 3 Athyros, The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and related cardiovascular risk, Metabolism 2017; 4 Speliotes, Treatment of Dyslipidemia in Common Liver Diseases, CGH 2019

CV considerations when choosing diabetes or NASH directed treatment

	Indication	Effect on NAFLD histology	Effect on CVD mediators	Effect on CVD risk	Other considerations
Metformin	DM2	None	Improves insulin sensitivity	unclear	May↓ HCC risk
Liraglutide	DM2	NASH resolution	Weight loss Improves insulin sensitivity Improves HTN	↓(DM2 popl)	
SGL2-inhibitors	DM2	?	Improve glycemic control	↓(DM2 popl)	↓ CHF risk (DM2) ↓death(CHF popl)
Pioglitazone	-DM2 -NASH+preDM/DM2 (off-label)	NASH resolution Improves fibrosis	Improves insulin sensitivity Prevents DM2 among preDM Improves HTN	↓ (preDM/ DM2 popl)	Exacerbates CHF
Vitamin E	-NASH without DM2 (off-label)	NASH improvement	Worsens insulin sensitivity	None	
Obeticholic acid	Phase 3 RCT, NASH	Improves fibrosis*	Worsens dyslipidemia: ↑ LDL, ↓ HDL	?	
Elafibranor	Phase 3 RCT, NASH	Improves NASH**	Improves dyslipidemia: ↓ LDL	?	

*Findings from Phase 2 RCT & Interim phase 3 RCT analysis

**Findings from Phase 2 RCT

Musso, impact of current treatments on liver disease, glucose, and CV risk in NAFLD: systematic review and meta-analysis of RCTs, Diabetologia 2012;
Targher, NAFLD and increased risk of CV disease, BMJ 2020.

Key Points

1. CV disease is the leading cause of death among patients with NAFLD.
2. However, NAFLD has not been established as traditional or independent risk factor for CV disease.
3. CV risk assessment is warranted – use standard of care approaches to risk stratify, screen for/manage traditional CV risk factors.
4. Consider CV side effect profiles when choosing diabetes and NASH directed therapies among NAFLD patient populations.