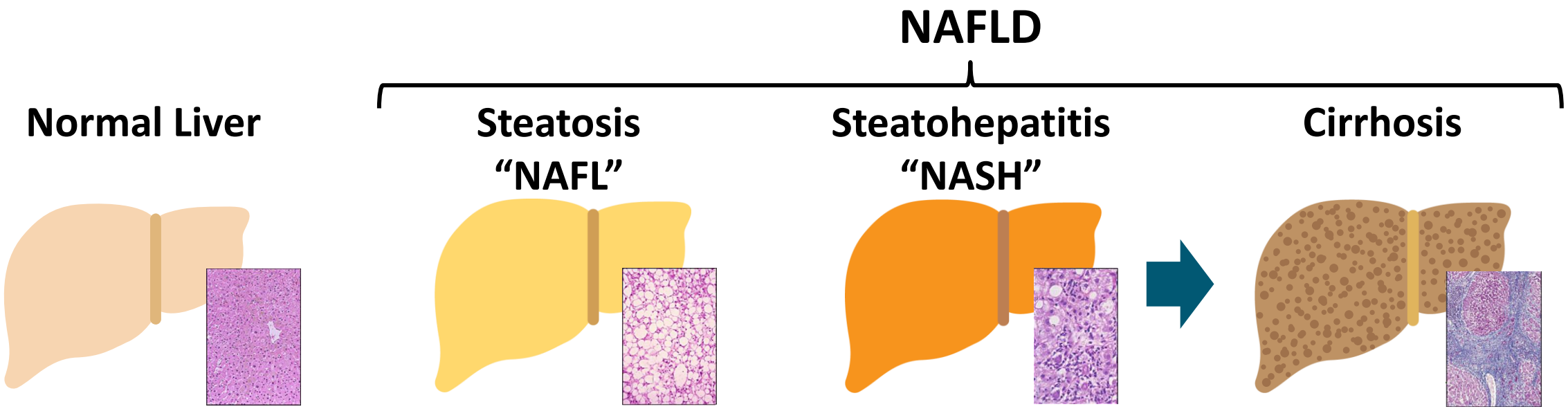
NASH: Management Approaches With Currently Available Treatments

Amir Ali Sohrabpour
Associate Professor of Medicine
Tehran University of Medical Sciences
Director, Iranian Hepatitis Network
Linktr.ee/aasohrabpour

The NAFLD Continuum



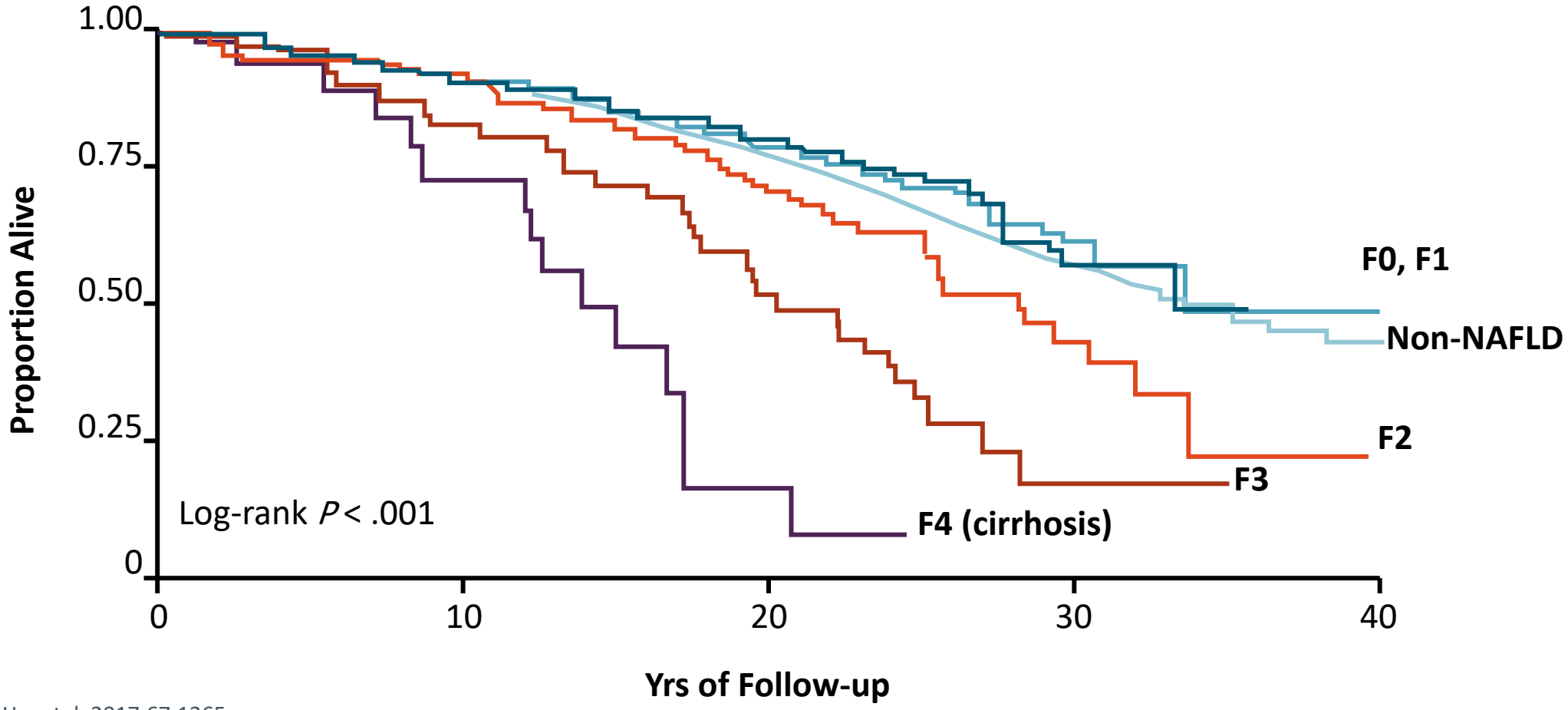
Worldwide prevalence:	25%[1]	3% to 5%[1]	1% to 2% at risk*

*Based on analysis of NHANES data estimating 1.74% prevalence of NASH with advanced fibrosis[2]

1. Younossi. J Hepatol. 2019;70:351. 2. Kabbany. Am J Hepatol. 2017;112:581.

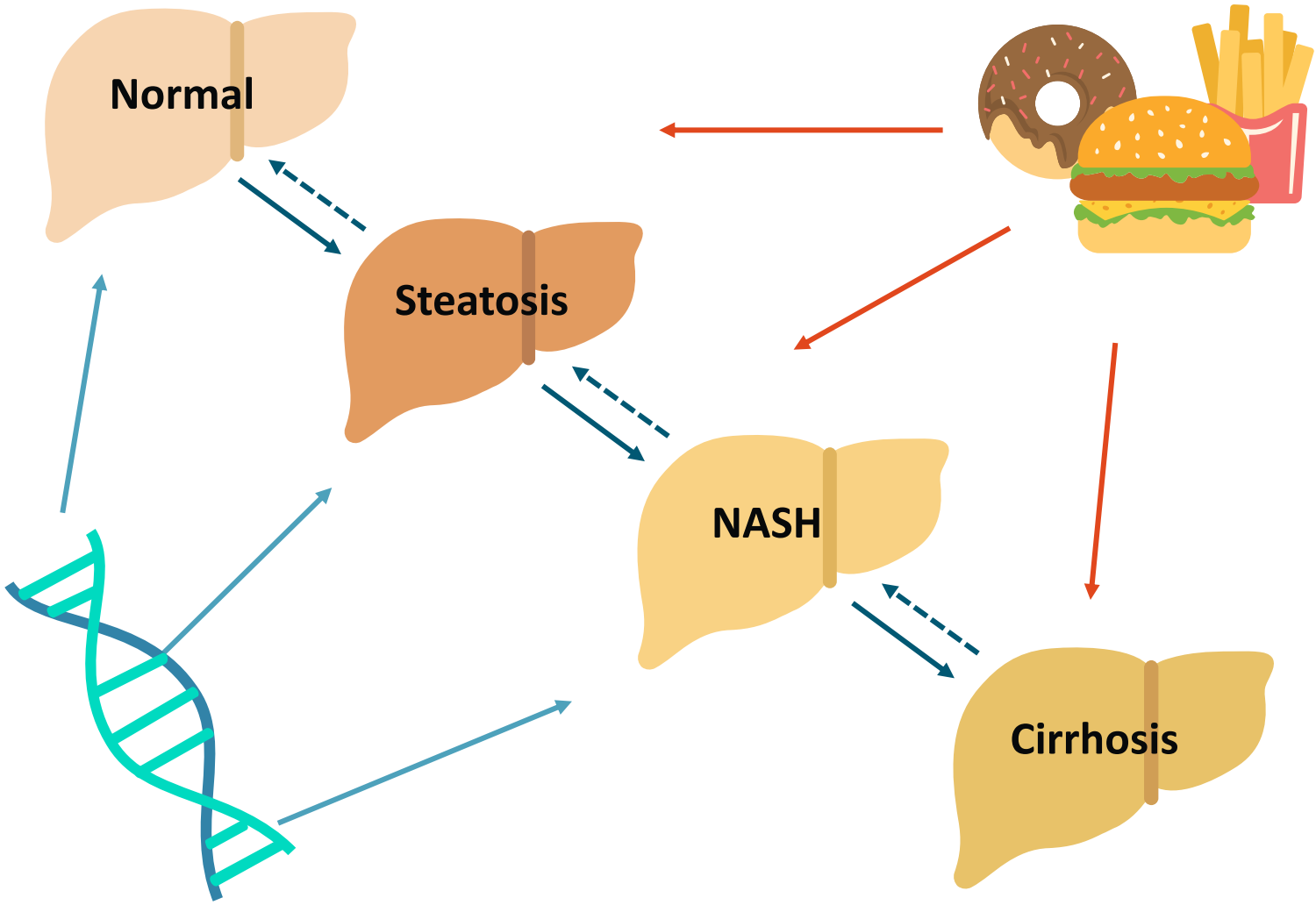
Liver Fibrosis Is a Risk for Adverse Outcomes

- Retrospective survival analysis of 646 NAFLD patients and matched controls



Hagström. J Hepatol. 2017;67:1265.

NAFLD as a Complex Disease Trait: Genetic and Environmental Modifiers



Genes
PNPLA3
TM6SF2
GCKR
SOD2
MBOAT7

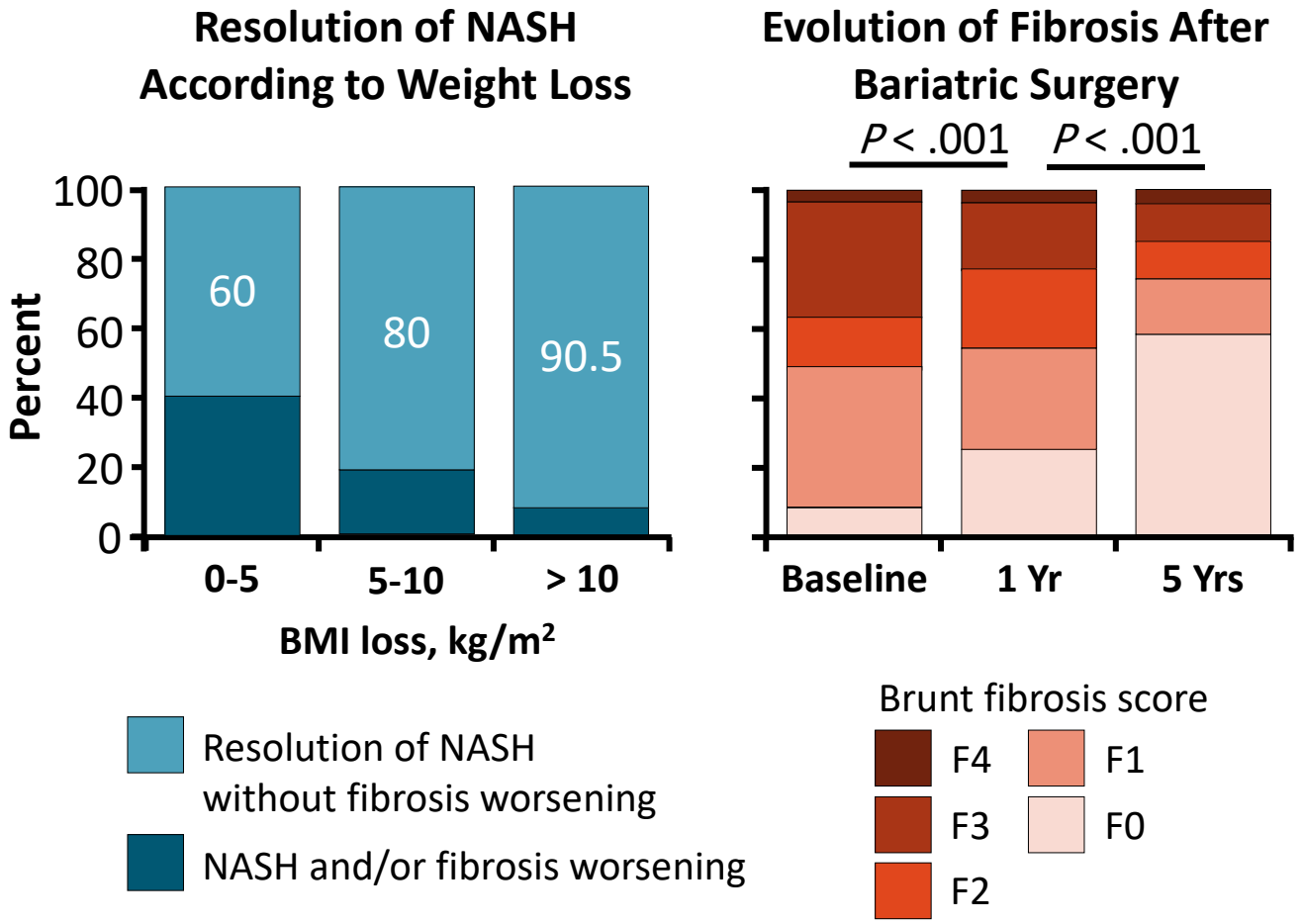
Environment
Sedentary lifestyle
Snacking, fast food
Saturated fats
Trans fats
Processed red meat

Epigenetics
Gut microbiome

Cotter. Gastroenterology. 2020;158:1851. Krawczyk. Gastroenterology. 2020;158:1865.

Is NASH Reversible?

- French single-center study of **bariatric surgery** in severely obese patients with biopsy-confirmed NASH (N = 180)
- At 5 yrs post surgery, 64 of 94 patients (84%) had NASH resolution with no worsening of fibrosis
  - NASH improvement correlated with weight loss



Lassailly. Gastroenterology. 2020;159:1290.

Liver Enzymes: Inadequate in Assessing NAFLD/NASH

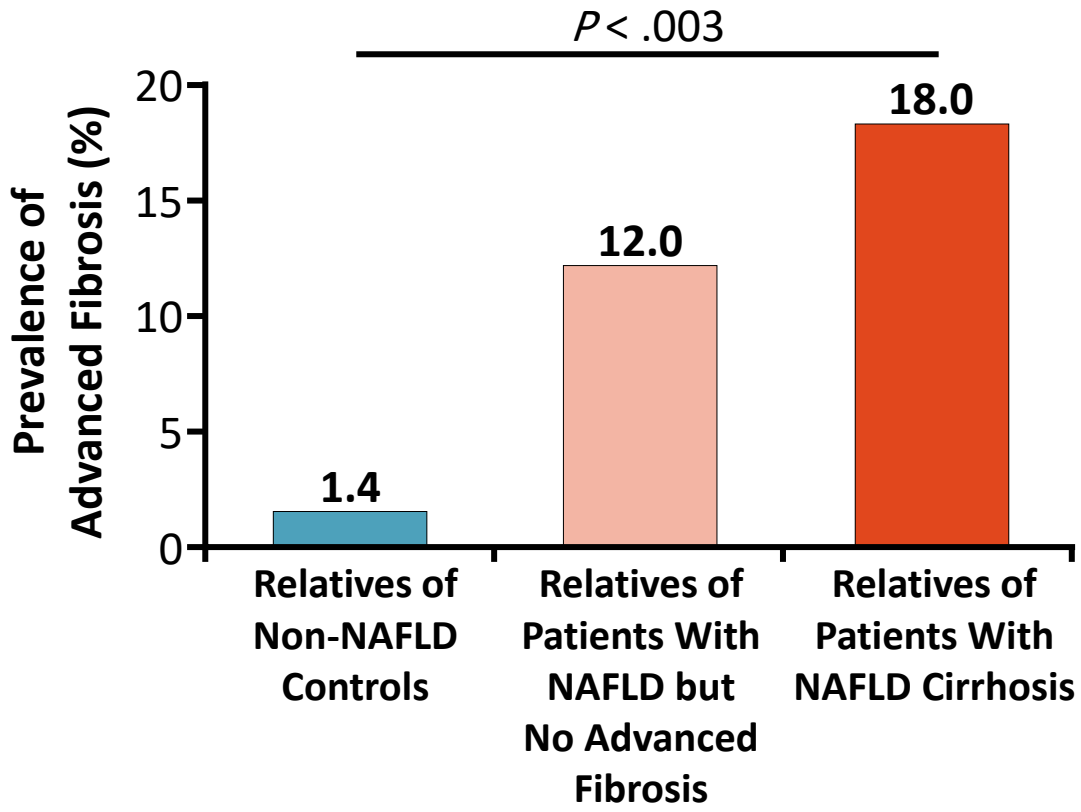
- ALT can be normal in > 50% of individuals with NASH, 80% of individuals with NAFLD[1,2]
- In NAFLD, ALT is neither indicative nor predictive of NASH or fibrosis stage:
  - Normal ALT does not preclude NASH/progressive disease
  - Elevated ALT cannot predict NASH or fibrosis
  - **ALT or AST not sensitive for NAFLD/NASH**

Abnormal ALT may warrant workup for NAFLD,
but is not sensitive to confirm, rule out, or characterize NAFLD

1. Browning. Hepatology. 2004;40:1387. 2. Dyson. Frontline Gastroenterol. 2014;5:211.
3. Mofrad. Hepatology. 2003;37:1286. 4. Younossi. Am J Gastroenterol. 2020;00:1.

Who Is at Risk for NASH and Advanced Hepatic Fibrosis?

Risk Factors for NAFLD[1]
Type 2 diabetes
Obesity
Dyslipidemia
Metabolic syndrome
Polycystic ovary syndrome



- Risk of advanced fibrosis higher in first-degree relatives of patients with NAFLD cirrhosis[2]

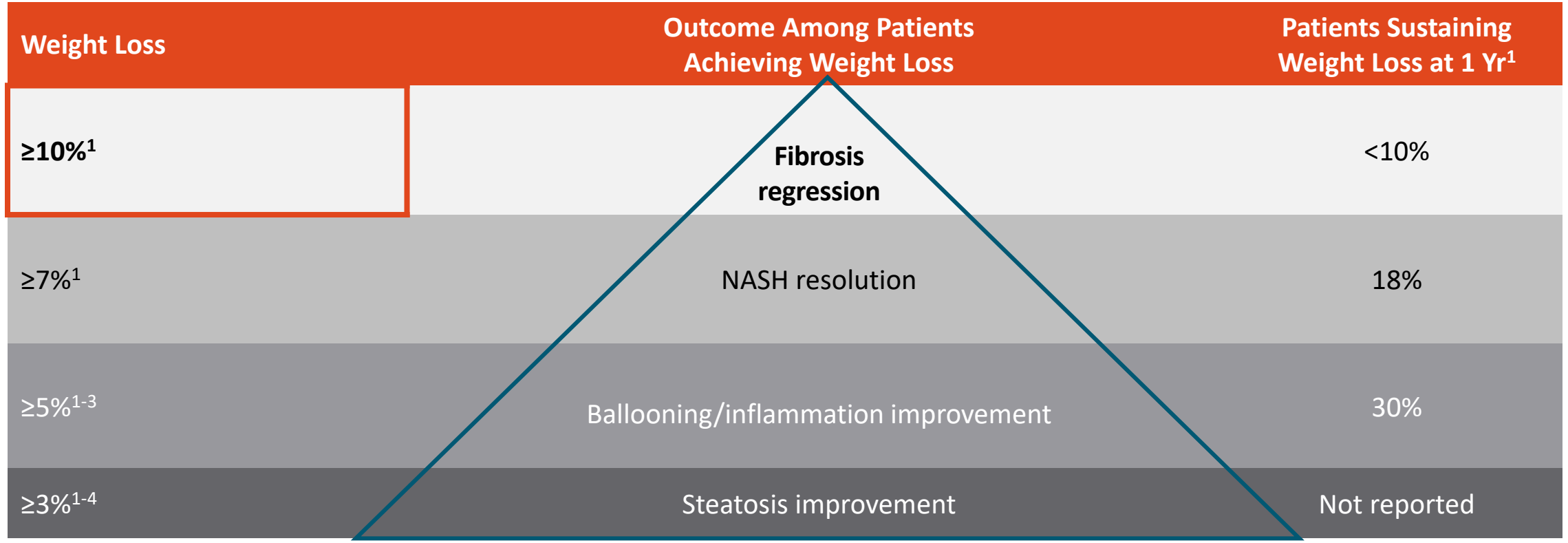
1. Chalasani. Hepatology. 2018;67:328. 2. Caussy. J Clin Invest. 2017;127:2697.

Lifestyle Guidelines in NASH

	AASLD 2018[1]	EASL 2016[2]	APASL 2020[3]
Program	Lifestyle modification including **dietary change**, **weight loss**, and structured **exercise** intervention		
Diet	500-1000 kcal energy deficit to induce a weight loss of 500-1000 g/wk ▪ Prospective trials comparing macronutrient diets in NAFLD are limited	▪ Exclusion of NAFLD-promoting components (processed food, added fructose) ▪ Mediterranean diet suggested	
Weight Loss	7% to %10% weight loss is the target of lifestyle interventions to improve NASH and fibrosis		
Exercise	▪ Exercise alone may prevent/ reduce hepatic steatosis – Effect on other aspects of liver histology unknown	▪ Both aerobic exercise and resistance training reduce liver fat – Tailor to patient preferences	
Bariatric Surgery	▪ Reduces liver fat, improves histologic lesions of NASH, including fibrosis ▪ Individualize decision in cirrhosis		

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388. 3. Eslam. Hepatol Intern. 2020;14:889.

Sustained Weight Loss Through Lifestyle Modification



1. Vilar-Gomez. Gastroenterology. 2015;149:367. 2. Promrat. Hepatology. 2010;51:121.
3. Harrison. Hepatology. 2009;49:80. 4. Wong. J Hepatol. 2013;59:536.

Pharmacotherapy in NAFLD Reserved for Patients With NASH and Fibrosis

AASLD[1]	EASL-EASD-EASO[2]	APASL[3]
▪ Pharmacologic treatments should generally be limited to those with ***biopsy-proven NASH and fibrosis***	▪ Pharmacotherapy should be reserved for *patients* ***with NASH, particularly if significant fibrosis***. ▪ Patients with less severe disease, but at high risk of progression (diabetes, MetS, persistently increased ALT, high necroinflammation) could also be candidates	▪ Patients ***without steatohepatitis or fibrosis*** should receive counseling for a healthy diet and physical activity and ***no pharmacotherapy*** for their liver disease

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388. 3. Eslam. Hepatol Intern. 2020;14:889.

Pharmacotherapy in NAFLD and NASH (Off Label)

	AASLD 2018[1]	EASL-EASD-EASO 2016[2]	APASL 2020[3]
Vitamin E	**Recommended** in nondiabetic patients with biopsy-proven NASH (800 IU/day)	**Recommended** (800 IU/day)	Insufficient evidence, no firm recommendation
Pioglitazone	**Recommended** in patients with and without T2D and biopsy-proven NASH	**Recommended** in patients with T2D and biopsy-proven NASH	
Metformin	Not recommended		
Statin	▪ Can be used to treat dyslipidemia, not NASH ▪ No higher risk for serious liver injury		Reduce cardiovascular mortality, consider in all NAFLD patients with hyperlipidemia
UDCA	Not recommended		Not mentioned
Omega-3 Fatty Acids	▪ Not a specific treatment of NAFLD ▪ Consider to treat hypertriglyceridemia		Not mentioned
Obeticholic Acid	Further data needed		
GLP-1 RAs	Further data needed		Improve fibrosis, weight
SGLT2 Inhibitors	Not mentioned		Further data needed

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388. 3. Eslam. Hepatol Intern. 2020:14:889.

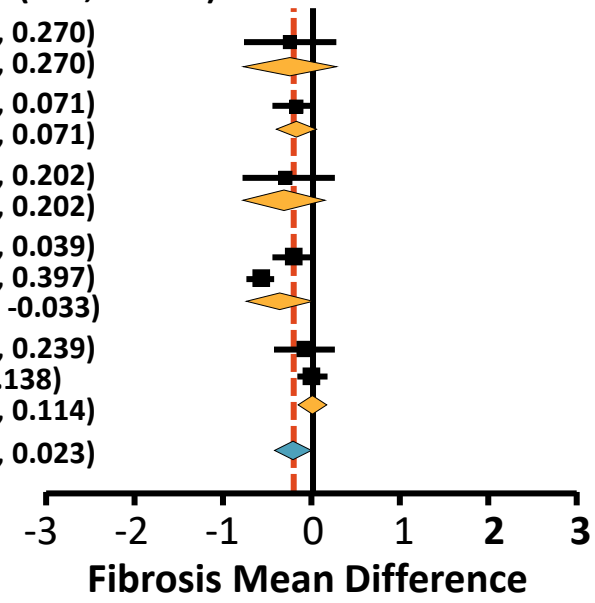
Vitamin E:
Recent Evidence in NAFLD/NASH

Meta-analysis:
Vitamin E Reduces NAS and Fibrosis in NAFLD

- Meta-analysis of N = 1317 patients with NAFLD in 15 RCTs
  - Study limitations: variations in definition of NAFLD; moderately small sample sizes

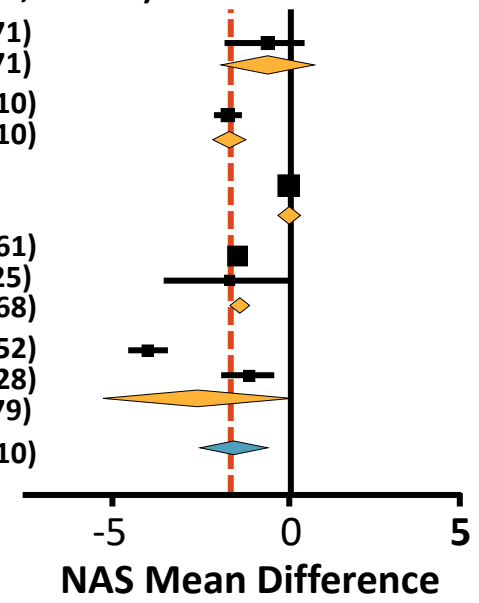
Fibrosis

Studies	Vitamin E vs Placebo (MD, 95% CI)
Harrison 2003	-0.250 (-0.770, 0.270)
--Subgroup 6 mo	-0.250 (-0.770, 0.270)
Zohrer 2017	-0.170 (-0.411, 0.071)
-Subgroup 12 mo	-0.170 (-0.411, 0.071)
Brill 2019	-0.300 (-0.802, 0.202)
--Subgroup 18 mo	-0.300 (-0.802, 0.202)
Sanyal 2010	-0.200 (-0.439, 0.039)
Dufour 2006	-0.570 (-0.743, 0.397)
--Subgroup 24 mo	-0.395 (-0.757, -0.033)
Lavine 2011	-0.100 (-0.439, 0.239)
Nobili 2008	0 (-0.138, 0.138)
--Subgroup 24 mo	-0.014 (-0.142, 0.114)
Overall (I^2 = 77.09%; P = 0)	-0.224 (-0.426, 0.023)



NAS

Studies	Vitamin E vs Placebo (MD, 95% CI)
Aller 2015	-0.600 (-1.771, 0.571)
--Subgroup first 3 mo	-0.600 (-1.771, 0.571)
Zohrer 2017	-1.700 (-2.090, -1.310)
--Subgroup 12 mo	-1.700 (-2.090, -1.310)
Brill 2019	0 (-0.190, 0.190)
--Subgroup 18 mo	0 (-0.190, 0.190)
Sanyal 2010	-1.400 (-1.639, -1.161)
Dufour 2006	-1.700 (-3.525, 0.125)
--Subgroup 24 mo	-1.405 (-1.642, -1.168)
Nobili 2008	-4.000 (-4.548, -3.452)
Lavine 2011	-1.100 (-1.872, -0.328)
--Subgroup 24 mo	-2.563 (-5.405, 0.279)
Overall (I^2 = 97.53%; P = 0)	-1.503 (-2.495, -0.510)

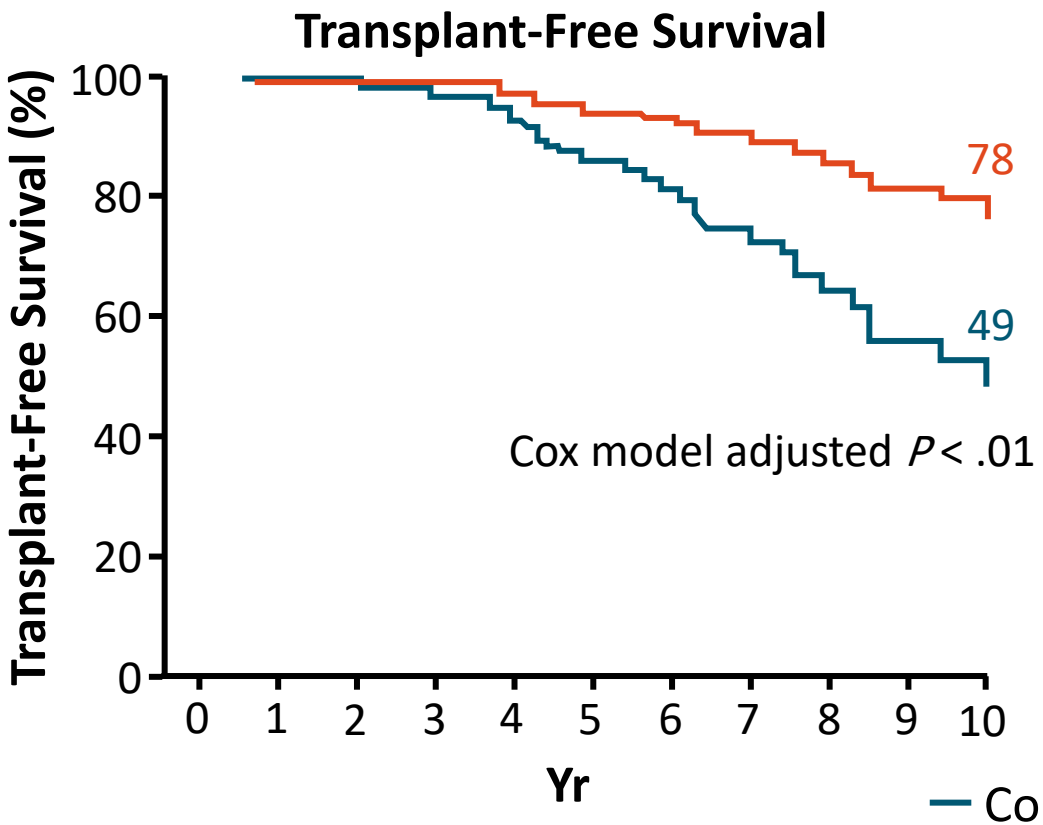


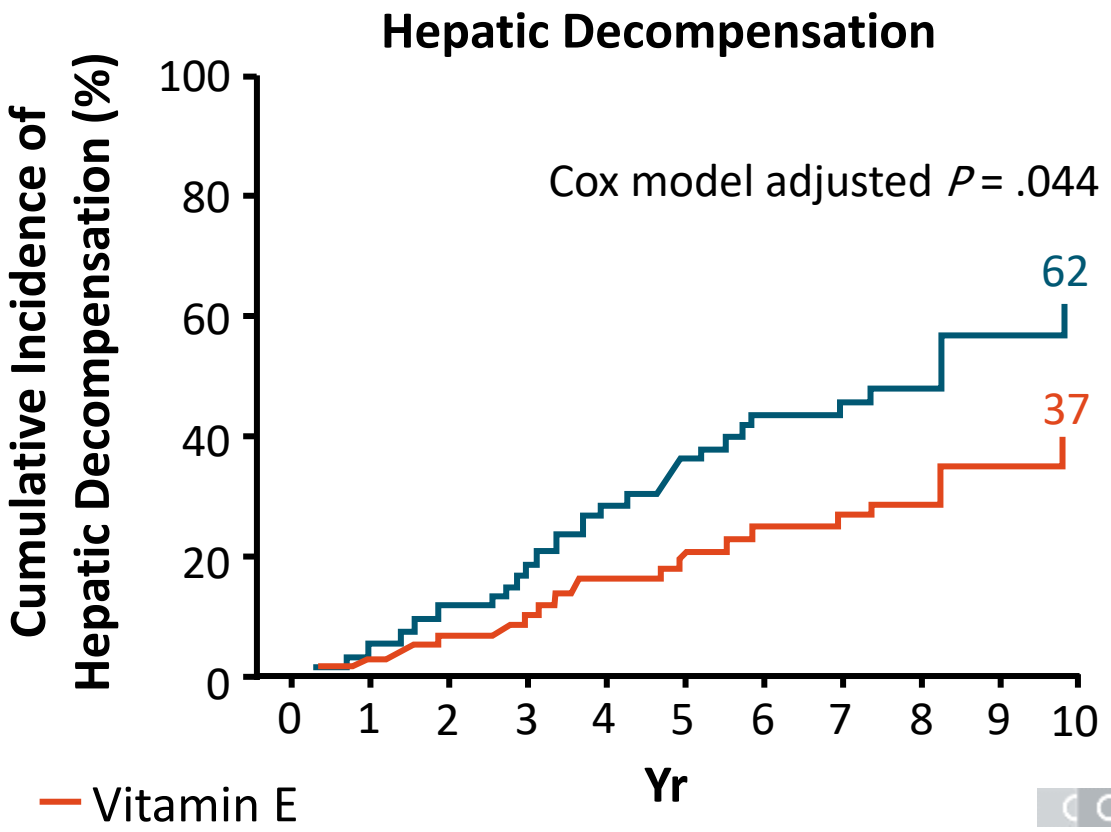
- **Most promising patient for vitamin E treatment: an obese patient aged 15-50 yr, baseline AST >50 IU/L, daily intake of 400-800 IU vitamin E, liability to lose 5-10 kg**

Abdel-Maboud. Therap Adv Gastroenterology. 2020;13:1756284820974917.

Vitamin E Improves Transplant-Free Survival and Hepatic Decompensation in NASH

- Single-center study of patients with biopsy-proven NASH and bridging fibrosis or cirrhosis (N = 236) followed for median 5.62 yr





Vilar-Gomez. Hepatology. 2020;71:495.

Slide credit: clinicaloptions.com

AASLD Guidance: Vitamin E

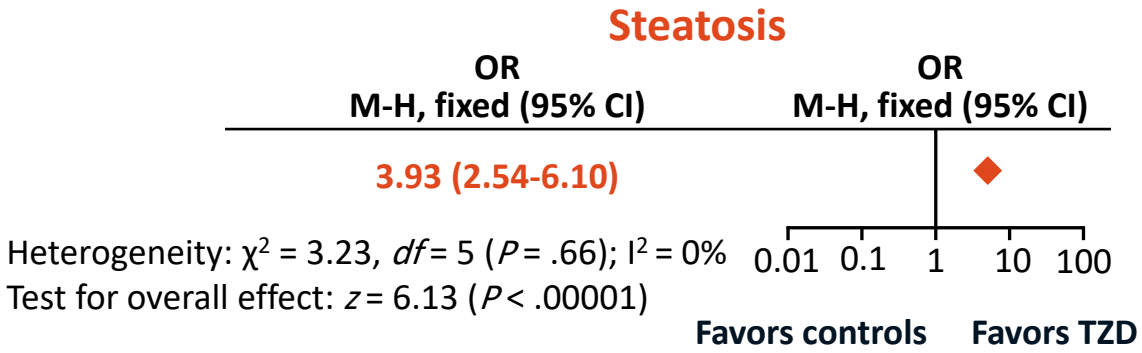
- **May be considered** to treat biopsy-proven NASH in **nondiabetic** adults
- At 800 IU/day improves liver histology but not fibrosis
- Risks and benefits should be discussed with each patient
  - Long-term safety issues concerns linger (eg, impact on long-term mortality, prostate cancer)
- **Not recommended** to treat NASH in **diabetic** patients, NAFLD without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis
  - More data on safety and efficacy needed

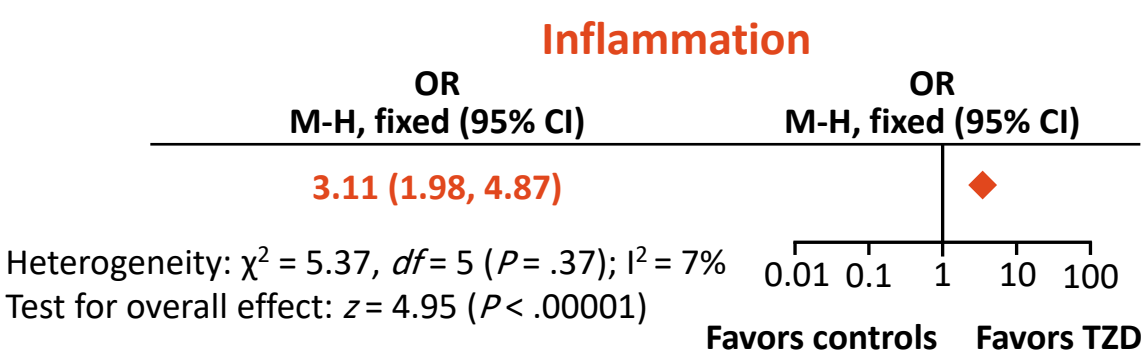
Chalasani. Hepatology. 2018;67:328.

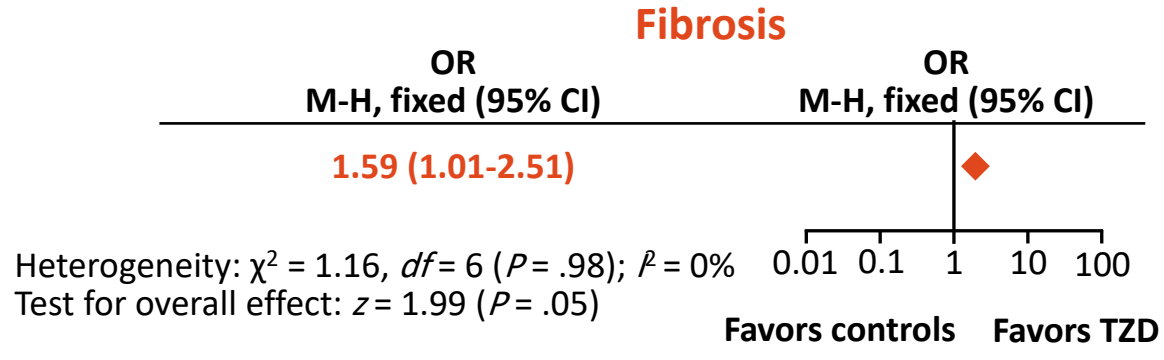
Pioglitazone:
Recent Evidence in NAFLD/NASH

Pioglitazone for NASH Without Diabetes

- Subset of n = 7 TZD studies in systemic review and metanalysis of randomized trials examining outcomes in NAFLD/NASH



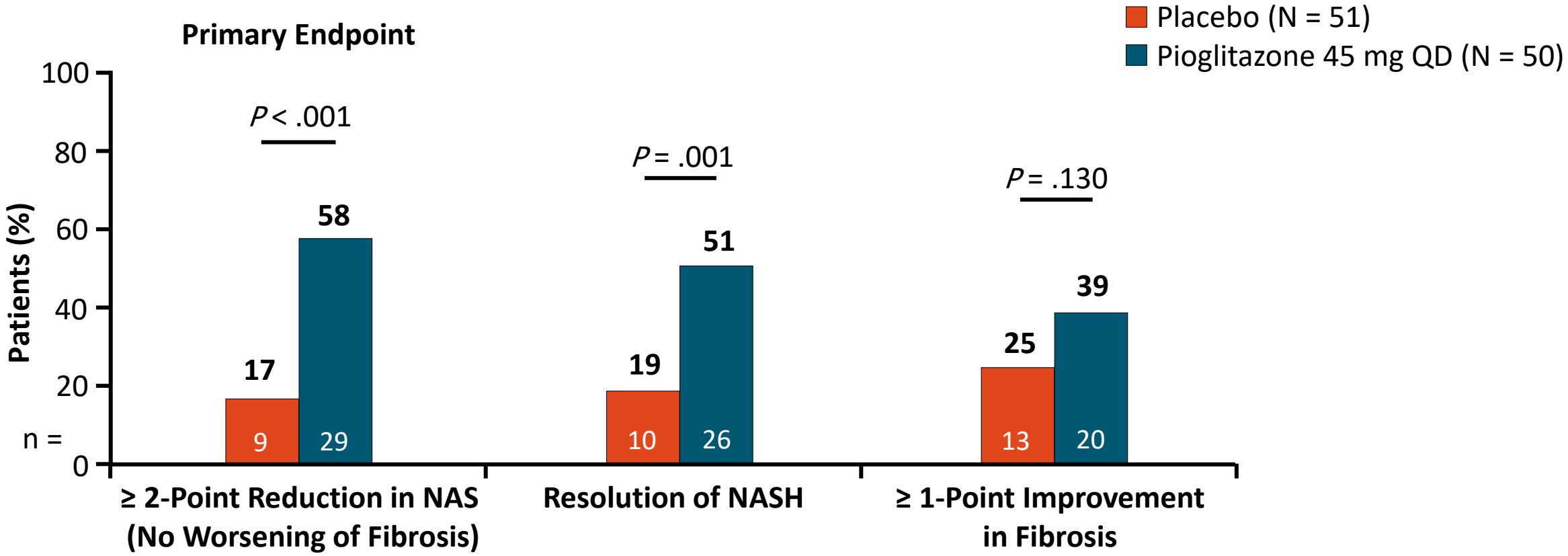




Musso. Diabetologia. 2012;55:855.

TZD Pioglitazone in NASH and Prediabetes or Type 2 Diabetes: 18-Mo Outcomes

- Randomized, placebo-controlled, double-blind phase IV study of patients with NASH and prediabetes or type 2 diabetes (N = 101)[1]



Cusi. Ann Intern Med. 2016;165:305.

Safety and Tolerability

Vitamin E (800 IU/day)

- Possible all-cause mortality risk at > 800 IU/day,[1] not confirmed by a subsequent meta-analysis[2]
- Increased hemorrhagic stroke risk[3]
  - Also shows reduced ischemic stroke risk
- Increased prostate carcinoma risk (HR vs placebo: 1.17; 99% CI: 1.004-1.36; *P* = .008)[4]

Pioglitazone

- Edema, weight gain (~2-3 kg over 2-4 yr)[5]
- Risk of osteoporosis in women[6]
- Equivocal bladder cancer risk
  - Increased in some studies[7]
  - No association in most studies[8]

Use of these agents should be personalized for selected patients with histologically confirmed NASH after careful consideration of risk/benefit ratio

1. Miller. Ann Intern Med. 2005;142:37. 2. Abner. Curr Aging Sci. 2011;4:158. 3. Schurks. BMJ. 2010;341:c5702. 4. Klein. JAMA. 2011;306:1549.
5. Bril. Diabetes Care. 2017;40:419. 6. Yau. Curr Diab Rep. 2013;13:329. 7. Tuccori. BMJ. 2016;352:i1541. 8. Lewis. JAMA. 2015;314:265.

Statins

	Participants on statins				Participants not on statins			
	Baseline (n=227)	End of study (n=227)	Percentage change	p value	Baseline (n=210)	End of study (n=210)	Percentage change	p value
Total cholesterol (mmol/L)	6·36 (0·70)	4·16 (0·21)*	−35%	<0·0001	6·41 (0·75)	6·21 (0·83)	−3%	0·8
LDL cholesterol (mmol/L)	4·37 (0·47)	2·46 (0·16)*	−44%	<0·0001	4·45 (0·72)	4·24 (0·83)	−5%	0·8
HDL cholesterol (mmol/L)	0·96 (0·18)	1·03 (0·18)*	8%	0·02	0·98 (0·26)	0·96 (0·23)	3%	0·9
Triglycerides (mmol/L)	2·20 (0·63)	1·49 (0·26)*	−32%	<0·0001	2·13 (0·58)	1·98 (0·62)	−7%	0·8
Alanine aminotransferase (IU/L)	57 (8)	37 (6)*	−35%	<0·0001	56 (9)	63 (7)	12%	0·003
Aspartate aminotransferase (IU/L)	49 (7)	26 (4)*	−47%	<0·0001	49 (7)	55 (8)	12%	0·01
γ-glutamyl transpeptidase (IU/L)	70 (10)	38 (6)*	−46%	<0·0001	68 (10)	79 (12)	16%	0·001
EGFR (mL/min per 1·73 m²)	59 (17)	70 (10)*	19%	<0·0001	68 (19)	64 (18)	−6%	0·8
Cardiovascular events	..	22 (9·7%)	..	..	..	63 (30·0%)	..	..
Cardiovascular events per 100 patient-years	..	3·2	..	..	..	10·0	..	..

Data are mean (SD) or n (%) unless otherwise stated. EGFR=estimated glomerular filtration rate. ..=not applicable. *p<0·05 versus end of study in participants with abnormal liver function tests who were not on statins.

Table 3: **Changes in characteristics of GREACE participants with abnormal liver function tests**

Have a smart phrase that states it is safe and beneficial for your patient with NAFLD/NASH/elevated LFTs to take a statin!

Athyros et al. "Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis" Lancet, 2010.

Statins Lower Risk of Portal Hypertension in Cirrhosis

- Systematic review and meta-analysis of statin use in patients with cirrhosis
  - 8 studies (7 RCTs, 1 cohort study; N = 3195); pooled relative risk and 95% CI calculated by random effects model
- Relative risk for primary outcome (improvement in portal hypertension) with statins vs control: 1.91 (95% CI: 1.04-3.52; I^2 = 63%)
  - Sub-analysis showed 1 mo of statin use may be sufficient vs 3 mo

Analysis	Statin		Control		Risk Ratio (95% CI)	*P* Value
	Events*	n	Events*	n		
Overall	67	148	42	153	1.91 (1.04-3.52)	.04
1 mo statin use	35	82	17	83	2.01 (1.31-3.10)	.002
3 mo statin use	32	66	25	70	3.76 (0.36-39.77)	.27

*Event: Decrease in HVPG >20% or <12 mm Hg.

Wan. BMJ Open. 2019;9:e030038.

AASLD Guidance: Use of Insulin Sensitizers to Treat NAFLD/NASH

- **Metformin**
  - Not recommended for treating NASH in adults
  - Improves serum aminotransferases and IR, but does not significantly improve liver histology
- **GLP-1 RAs**
  - It is premature to consider GLP-1 RAs to specifically treat liver disease in patients with NAFLD or NASH
- **Pioglitazone** ✓
  - With biopsy-proven NASH: improves liver histology in patients **with and without T2D**
  - Risks and benefits should be discussed with each patient
  - Without biopsy-proven NASH: should not be used for NAFLD

Chalasani. Hepatology. 2018;67:328.

Optimal Diabetes Therapies in NAFLD/NASH

An Integrated Approach to Obesity, Diabetes, and NAFLD

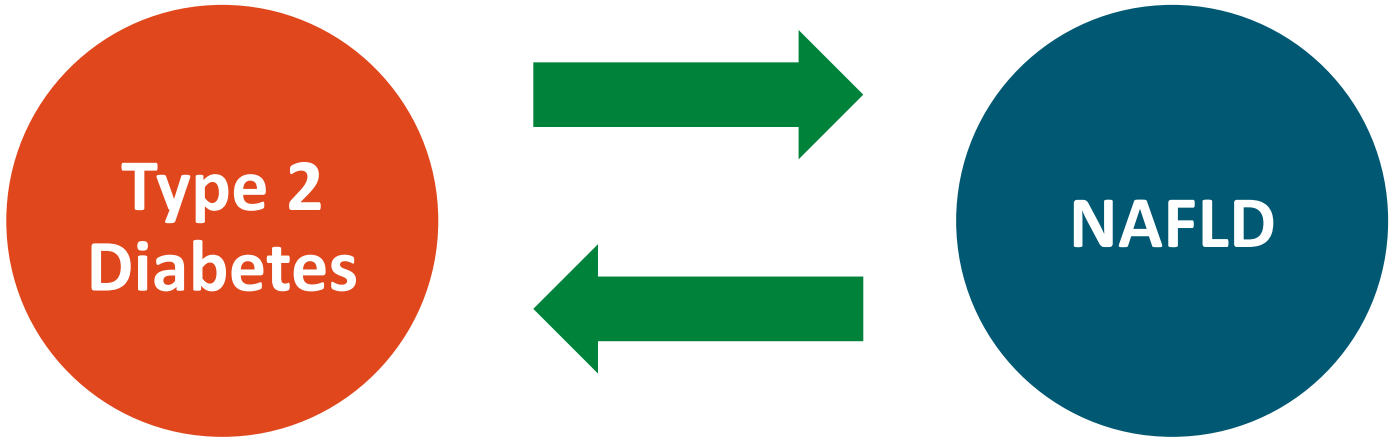
- **Multidisciplinary: hepatologist, endocrinologist, nutritionist**
  - Also psychologist, clinical pharmacist, physical therapist

- **Cardiovascular risk reduction is essential**
  - Manage dyslipidemia, hypertension, smoking cessation, antiplatelet therapy

- **Screen and treat other comorbid conditions**
  - Obstructive sleep apnea, degenerative joint disease

- Lifestyle interventions for all; add obesity pharmacotherapy and bariatric surgery when appropriate
- Individualize antihyperglycemic medications, targeting CV risk and body weight reduction when appropriate
- In patients with advanced liver disease, choose or dose drugs for diabetes or weight management appropriately

Type 2 Diabetes and Fatty Liver Disease: "Bidirectional Association"



"Traditionally a disease of hepatologists, nonalcoholic fatty liver disease (NAFLD) has recently become a major concern of a broad spectrum of healthcare providers"

"Endocrinologists and those caring for patients with type 2 diabetes mellitus (T2DM) are at center stage, as T2DM appears to worsen the course of NAFLD and the liver disease makes diabetes management more challenging"

Bril. Diabetes Care. 2017:40;419.

Pharmacotherapy for T2D Patients With Comorbidities Associated With NAFLD/NASH

- In adults with diabetes and preexisting ASVCD or HF or CKD, ADA guidelines recommend[1]:
  - GLP-1 RA with proven CV benefit
  - SGLT2 inhibitors with proven HF and CKD benefit
- Some GLP-1 RAs and SGLT2 inhibitors may have benefits in NAFLD

American Diabetes Association. Diabetes Care 2019;42(suppl 1):S90.

Approaches for Currently Available Treatments

Weight loss[1-3]

- Lifestyle (diet, physical activity)
- Weight loss medications
- Bariatric surgery

In patients with advanced liver disease, choose or dose drugs appropriately.

Treat T2D and CV risk factors[4,5]

- Hyperglycemia (GLP-1 RA and/or SGLT-2i)
- Hypertension
- Dyslipidemia*

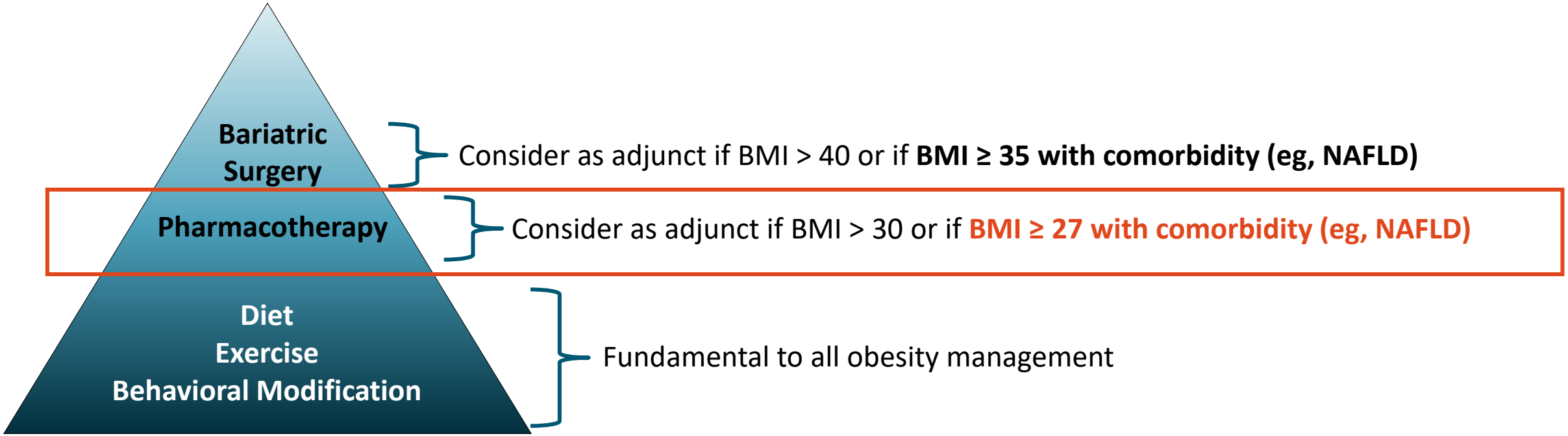
*NAFLD does not increase statin risk of drug-induced liver injury.[8]

Liver-directed treatment

- Vitamin E (except in diabetes)[6]
- Pioglitazone[6,7]

1. Promrat. Hepatology. 2010;51:121. 2. Vilar-Gomez. Gastroenterology. 2015;149:367. 3. Lassailly. Gastroenterology. 2015;149:379. 4. Musso. Hepatology. 2010;52:79. 5. Ratziu. J Hepatol. 2010;53:372. 6. Sanyal. NEJM. 2010;362:1675. 7. Cusi. Ann Intern Med. 2016;165:305. 8. Bril. J Clin Endocrinol Metab. 2017;102:2950.

Weight Loss: Endocrine Society 2015 Obesity Guidelines



"... we suggest the use of approved weight loss medication (over no pharmacologic therapy)"

Apovian. J Clin Endocrinol Metab. 2015;100:342.

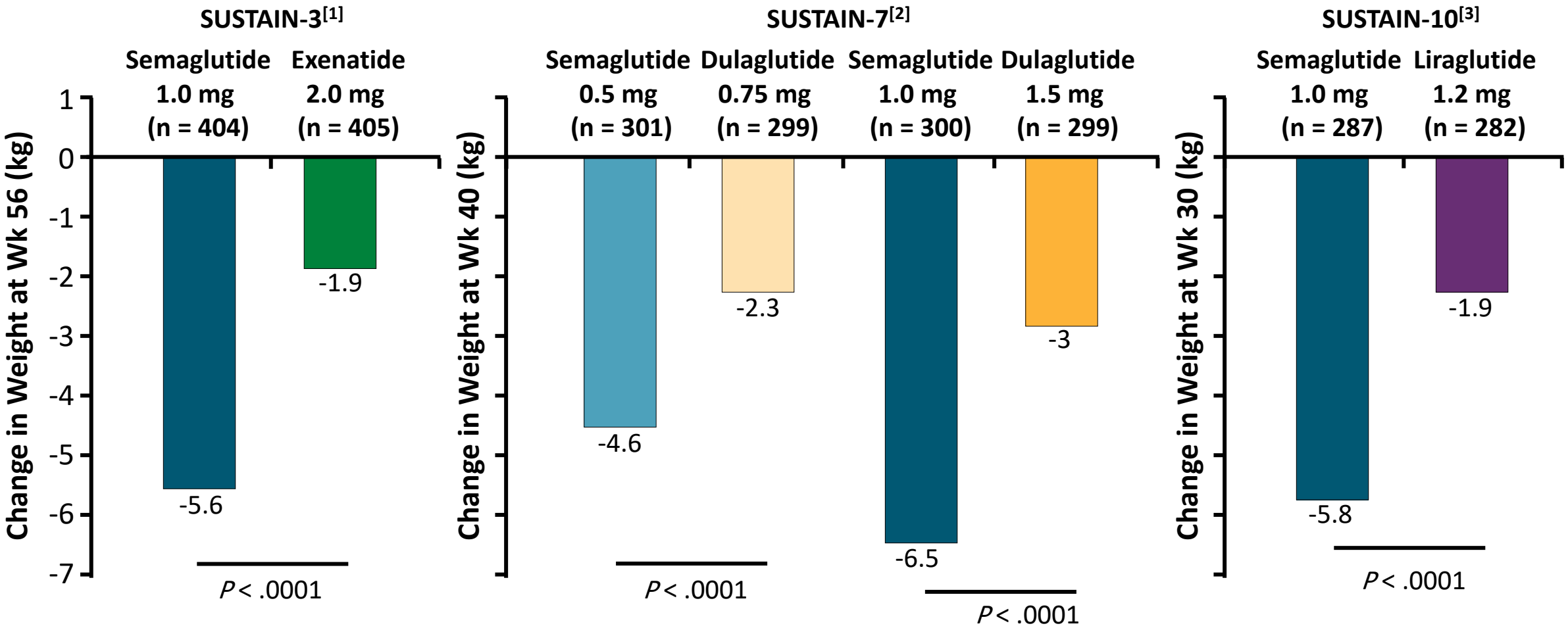
Weight Loss Through Lifestyle Modification in NAFLD

Weight Loss	Outcome Among Patients Achieving Weight Loss	Patients Sustaining Weight Loss at 1 Yr[1]
≥ 10%[1]	Fibrosis regression (45% of patients)[1]	< 10%
≥ 7%[1]	NASH resolution (64% to 90% of patients)*	18%
≥ 5%[1-3]	Ballooning/inflammation improvement (41% to 100% of patients)*	30%
≥ 3%[1-4]	Steatosis improvement (35% to 100% of patients)*	Not reported

*Depending on degree of weight loss.

1. Vilar-Gomez. Gastroenterology. 2015;149:367. 2. Promrat. Hepatology. 2010;51:121.
3. Harrison. Hepatology. 2009;49:80. 4. Wong. J Hepatol. 2013;59:536.

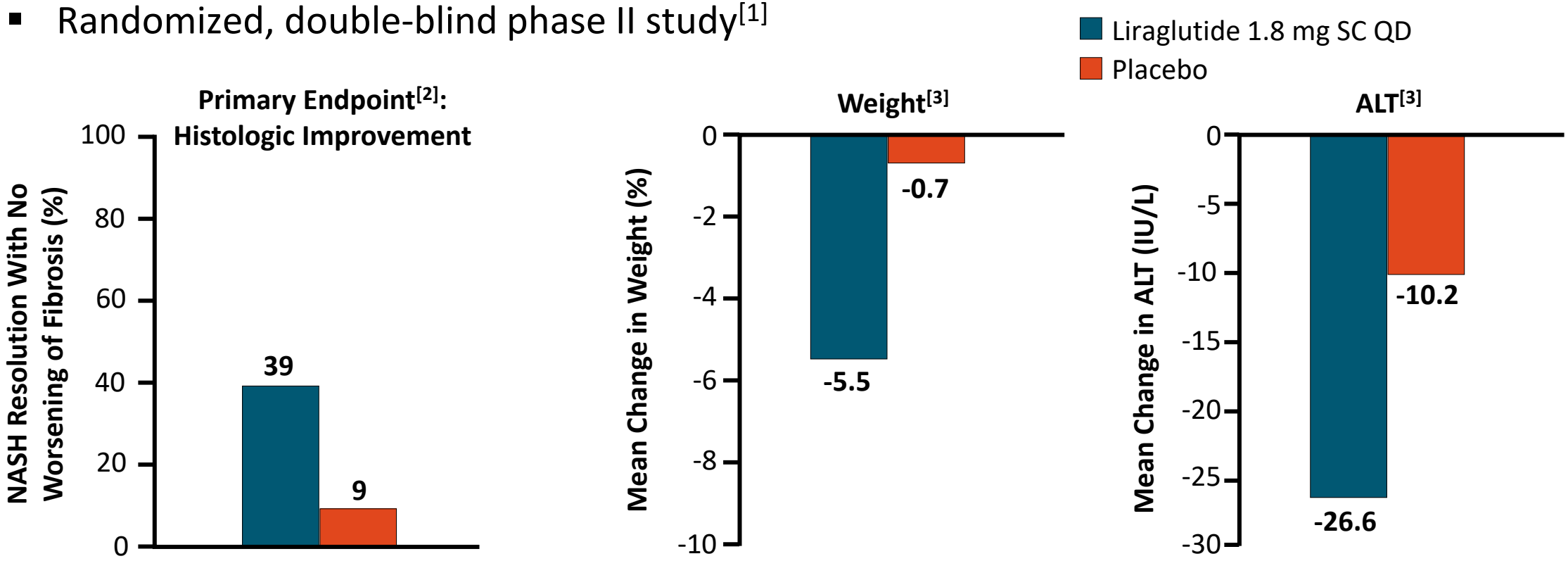
GLP-1 RA Comparative Studies in T2D: Change in Body Weight



1. Ahmann. Diabetes Care. 2018;41:258. 2. Pratley. Lancet Diabetes Endocrinol. 2017;6:275. 3. Capehorn. Diabetes Metab. 2019;[Epub].

LEAN: 48-Wk Results of Liraglutide vs Placebo in Overweight Patients With NASH

- Randomized, double-blind phase II study[1]

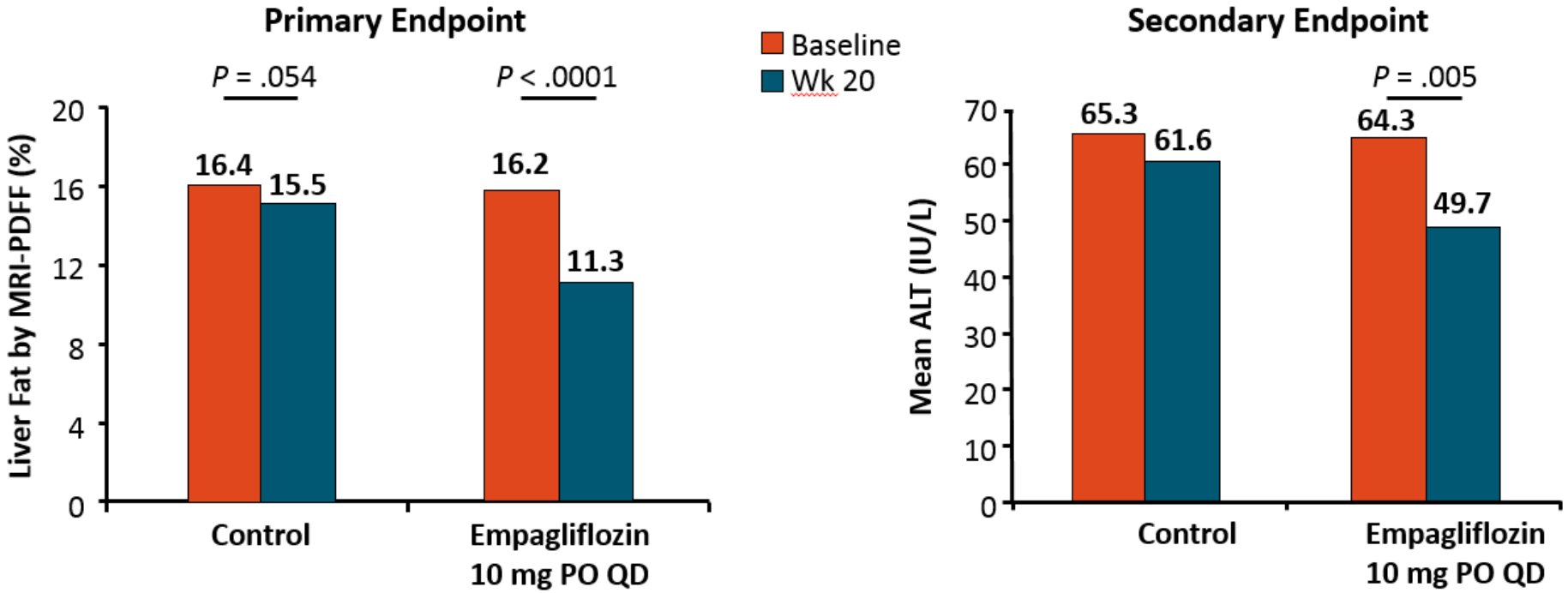


- Semaglutide also associated with ALT reduction and weight loss in nondiabetic adults with NASH and obesity[3]

1. Armstrong. BMJ Open. 2013;3:e003995. 2.Armstrong. Lancet. 2016;387:679. 3. Armstrong. EASL 2015. Abstr G01.

SGLT2 Inhibitors in NAFLD

- E-LIFT: randomized, open-label study of **empagliflozin** vs standard diabetes treatment in N = 42 patients with diabetes and NAFLD[1]



- In a separate double-blind, placebo-controlled study (n = 37 patients with diabetes and NAFLD), **canagliflozin 300 mg PO QD** associated with lower hepatic triglycerides, which correlated with weight loss[2]

1. Kuchay. Diabetes Care. 2018;41:1801. 2. Cusi. Diabetes Obes Metab. 2018;1-10.

Coffee and NAFLD

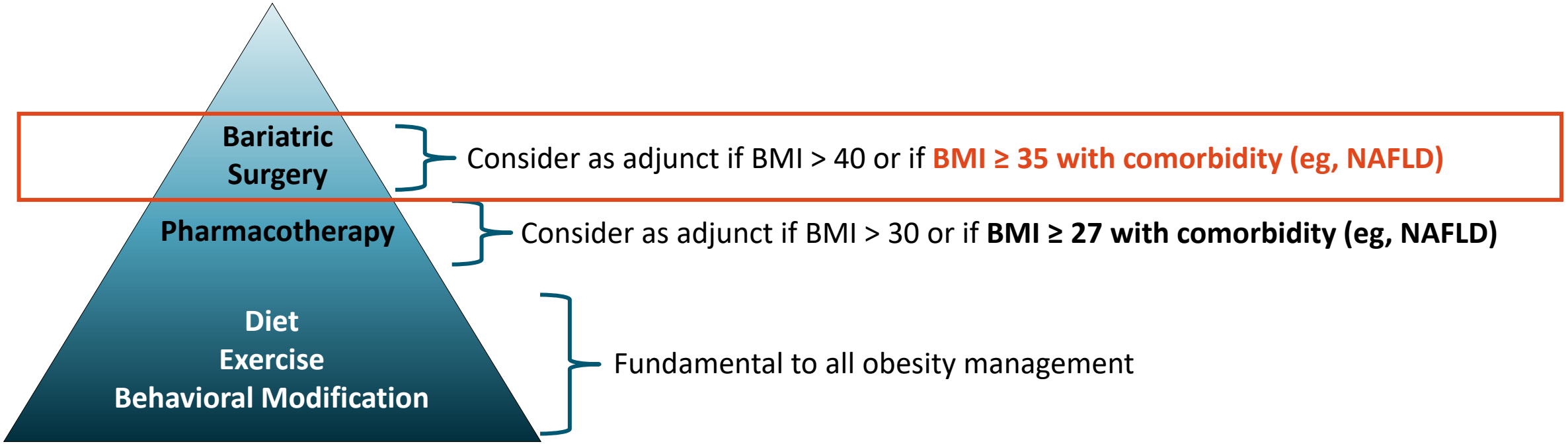
The **risk of NAFLD** among those who drank coffee compared to those who did not was significantly lower with a pooled RR value of 0.77 (95% CI 0.60-0.98)

Liver fibrosis in those who drink coffee compared with those who did not drink in the NAFLD patients showed a lower risk: RR of 0.68 (95% CI 0.68-0.79)

Hayat U, et al. The effect of coffee consumption on the non-alcoholic fatty liver disease and liv
fibrosis: A meta-analysis of 11 epidemiological studies. Ann Hepatol. 2021 Jan-Feb;20:100254

Surgical Approaches to Weight Loss and Effect on Liver

Weight Loss: Endocrine Society 2015 Obesity Guidelines

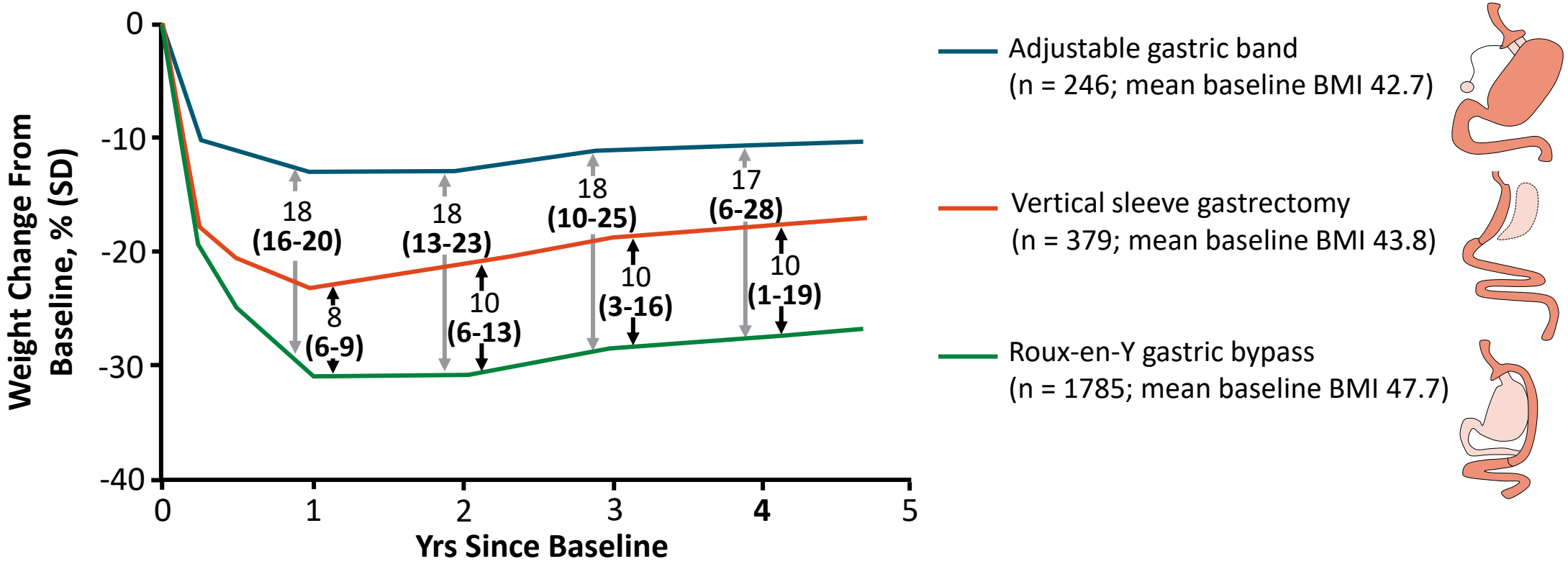


"... we suggest the use of approved weight loss medication (over no pharmacologic therapy)"

Apovian. J Clin Endocrinol Metab. 2015;100:342.

Weight Loss: Long-term Results With Bariatric Surgery Procedures

- Multicenter, retrospective cohort study of N = 2410 veterans with obesity



Would we expect similar results in NAFLD?

Maciejewski. JAMA Surg. 2016;151:1046.

Bariatric Surgery Improves Liver Histology in Obese Patients

- Prospective study in morbidly obese patients with **biopsy-validated NASH,** ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)[1]

Outcome	Baseline	After 1 Yr
Mean BMI ± SD	49.3 ± 8.2	37.4 ± 7.0
Patients with NASH resolution, %	NA	85.0
Patients with fibrosis reduction, %	NA	33.8

- Meta-analysis of 32 cohort studies of bariatric surgery in obese patients (n = 3093 biopsies)[2]

Characteristic	Outcome
Mean reduction in NAS, points	2.39
Patients with resolution of NAFLD components, %	
▪ Steatosis	66
▪ Inflammation	50
▪ Ballooning	76
▪ Fibrosis	40
Patients with new or worsening histologic NAFLD components, %	12

1. Lassailly. Gastroenterology. 2015;149:379. 2. Lee. Clin Gastroenterol Hepatol. 2018;[Epub].

AASLD Guidance: Bariatric Surgery

- Can be considered in otherwise eligible obese individuals with NAFLD or NASH
  - Premature to consider bariatric surgery as an established option to treat NASH
- The type, safety, and efficacy of bariatric surgery are not established in obese individuals with cirrhosis from NAFLD
- In patients with compensated NASH or cryptogenic cirrhosis, bariatric surgery may be considered on a case-by-case basis by an experienced bariatric surgery program

Chalasani. Hepatology. 2018;67:328.

Thank You

Amir Ali Sohrabpour
Associate Professor of Medicine
Tehran University of Medical Sciences
Director, Iranian Hepatitis Network
Linktr.ee/aasohrabpour