Fatty Liver Disease Screening, Diagnosis, & Treatment

August 3, 2022

CHARLES LANDIS, MD

University of Washington
Cardiometabolic
ECHO

Conflict of Interest Disclosure

- Research funding from Pfizer and Lilly

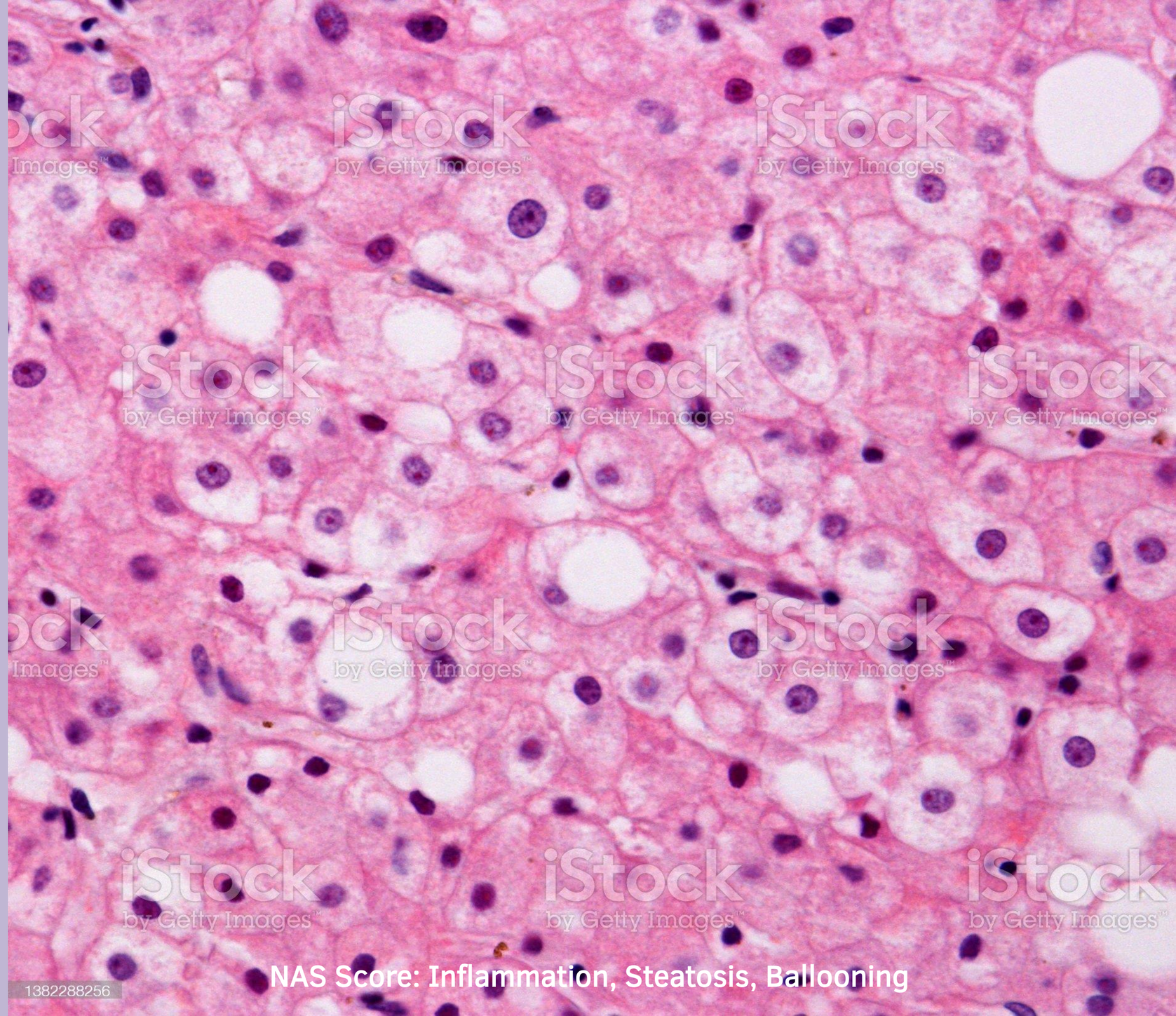
This talk is for educational purposes only and does not constitute specific clinical recommendations

Agenda

- Background
- Identifying patients with MAFLD
  - Who and How to screen
- Treatment for MAFLD
  - Lifestyle modification
  - Medications

Non-Alcoholic Metabolic associated fatty liver disease (NAFLD -> MAGLD)

- NAFLD -
  - Term coined by Ludwig and colleagues in 1980 to describe fatty liver disease arising in the absence of significant alcohol intake
  - May trivialize the problem by including ‘non’, and introducing the word ‘alcoholic’ potentially placing the blame on the patient as having caused their condition
- MAFLD – Updated nomenclature
- Histopathology of N/MAFLD is largely indistinguishable for that of Alcohol related fatty liver disease (AFLD)



NAS Score: Inflammation, Steatosis, Ballooning

Eslam et al, Gastroenterology 2020

MAFLD – Substrate Overload Lipotoxic Liver Injury

ENERGY INTAKE

Glucose + Fructose

Acetyl CoA

Circulating free fatty acids

Adipose Tissue

Chylomicron triglyceride

INJURY AND RESPONSE TO OVERLOAD

Lipotoxic lipids

Steatosis

Oxidative and ER stress
Mitochondrial dysfunction
Hepatocellular injury
Inflammation

NASH

Fibrosis

HCC

Liver free fatty acids

HEPATIC METABOLISM

"Burned"

"Repackaged"

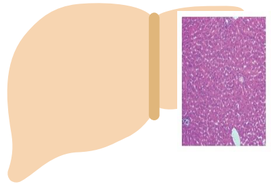
Triglyceride

VLDL + Hypertriglyceridemia

Mitochondrial beta-oxidation

Fatty Liver Continuum

Normal Liver[1,2]



Risk factors (metabolic syndrome, genetic factors)

↓

Reduced Hepatocyte insulin sensitivity

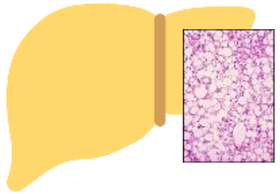
↓

Increased fat storage
Decreased fatty acid oxidation
Fat droplets in cells

→ Substrate Overload Lipotoxic Liver Injury

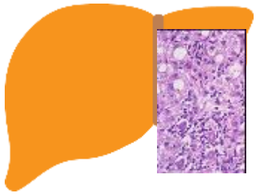
Asymptomatic

Steatosis (NAFL)[1,2]



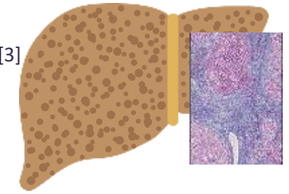
47%[3]
8-13 yrs

Steatohepatitis (NASH)[1,2]



25% to 50%[3]
8-13 yrs

Cirrhosis[1,2]



- Hepatic stellate cells produce extracellular matrix deposits

↓ 10 yrs[3]

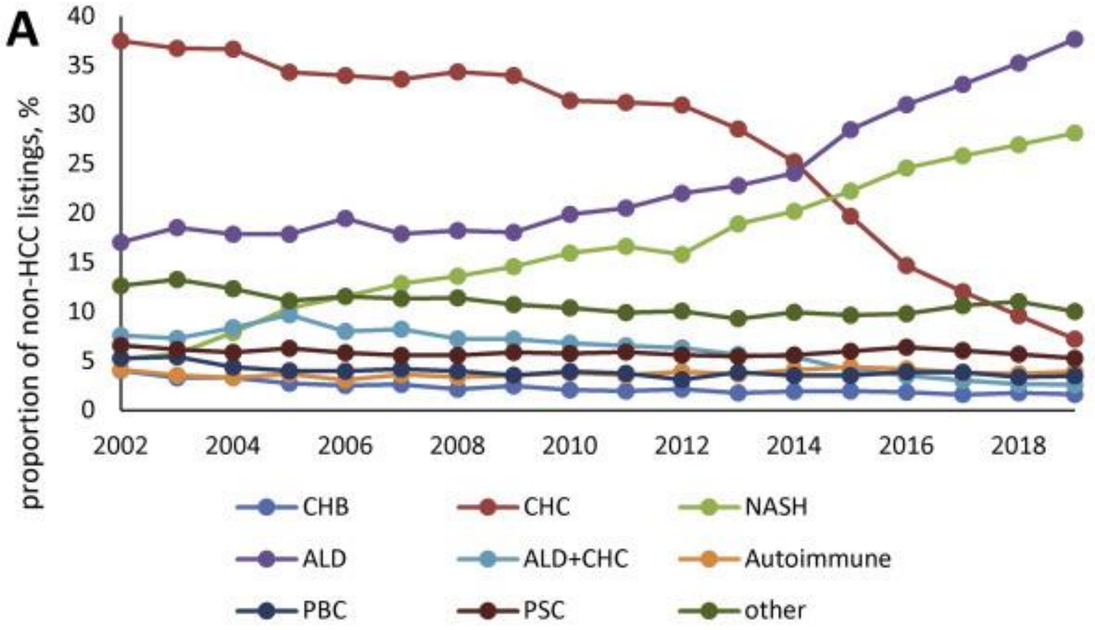
5% HCC
50% OLT
20% liver-related mortality

1. Machado. Gastroenterology. 2016;150:1769. 2. Schuppan. J Gastroenterol Hepatol. 2013;28:68.
3. Moore. Proc Nutr Soc. 2010;69:211. 4. Spengler. Mayo Clin Proc. 2015;90:1233.

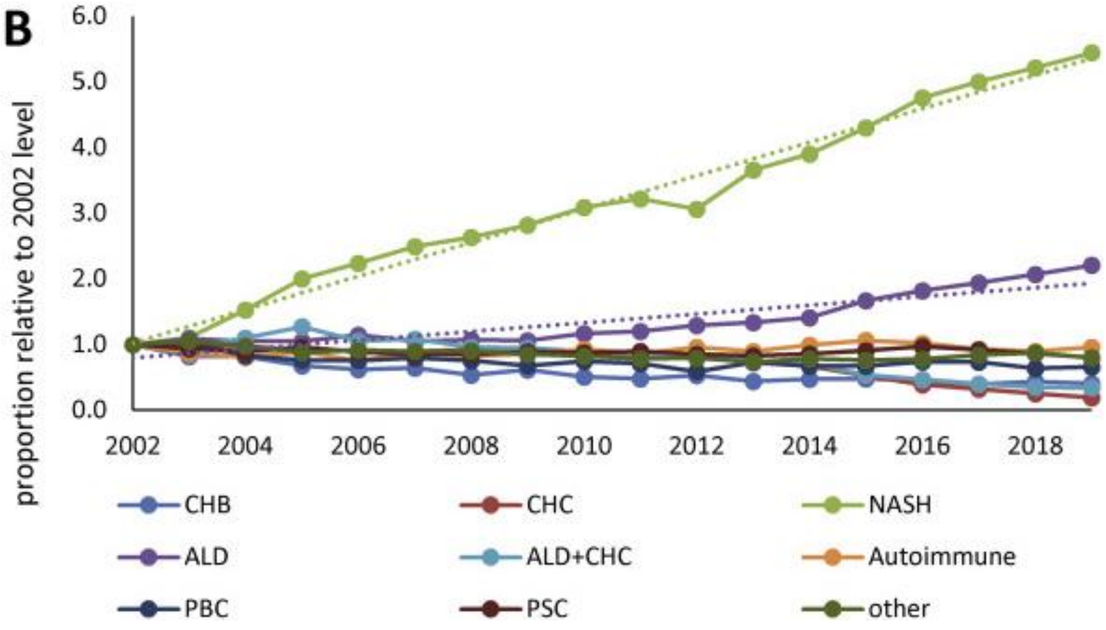
NASH: Most Rapidly Increasing Indication for Liver Transplantation in the United States

Non-HCC listings

Absolute Rise



Relative Rise compared to 2002



STRT data: Yousini et al Clinical Gastro Hep 2021

Case

A 51 year old man presents to the clinic for routine follow up

PMH: DM, Hypertension, Hyperlipidemia

Meds: Lisinopril, metformin, simvastatin, fenofibrate

SH: Rare social alcohol, works in the IT industry

FH: Father has T2 DM and CAD

Exam: BMI 36, Otherwise normal

Lab Test	Patient Results	Normal Range
BMI	36.0	18.5-24.9
Fasting glucose, mg/dL	144	< 100
A1C, %	6.9	≤ 5.6
Platelets, cells/mm^3	190	150-450
Lipids, mg/dL ▪ LDL ▪ HDL ▪ Triglycerides	 93 31 170	 < 100 > 60 < 150

Order liver tests and/or screen for fatty liver disease ?

Society Screening Guidelines

AASLD (2018)	EASL (2016)	ADA (2022)
“Vigilance” for high risk groups (Obesity, DM, MetS) No algorithm	Recommend screening in patients with obesity, DM2, MetS NFS and FIB-4 to stratify into low vs. medium vs. high risk Hepatology referral for medium/high risk	Screen: “High risk” patients: obesity +/- MetS +/- elevated liver tests. **All DM**, even with normal liver enzymes FIB-4, if indeterminate or high risk, perform liver stiffness measurement (LSM) Hepatology referral for indeterminate /high risk based on Fib-4 and LSM

Screening and Diagnosis of Fatty Liver Disease

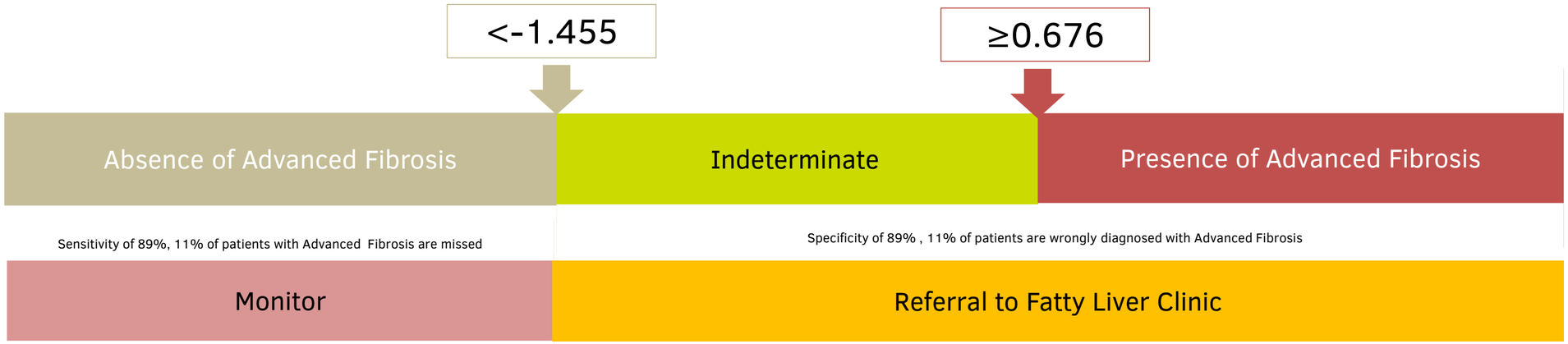
- An ideal screening / diagnostic tests is not available
- ALT and Ultrasound are currently recommended for screening
- Lab based scoring systems
  - NFS score
  - FIB-4
  - Fibrosure
- Liver elastography with controlled attenuation parameter
- FAST score – combines liver tests with elastography
- Liver biopsy

Bril. Diabetes Care. 2017;40:419

NFS Score to screen for Advanced Fibrosis

- Includes: AST, ALT, Albumin, Platelets, Age, presence of DM
- Recognized by AASLD as clinically useful in identifying patients with a higher likelihood of F3 or F4[2]

NFS cut-off scores and accuracy for measurement of Advanced Fibrosis[1]
AUROC: 0.74 (95% CI:0.74–0.74)

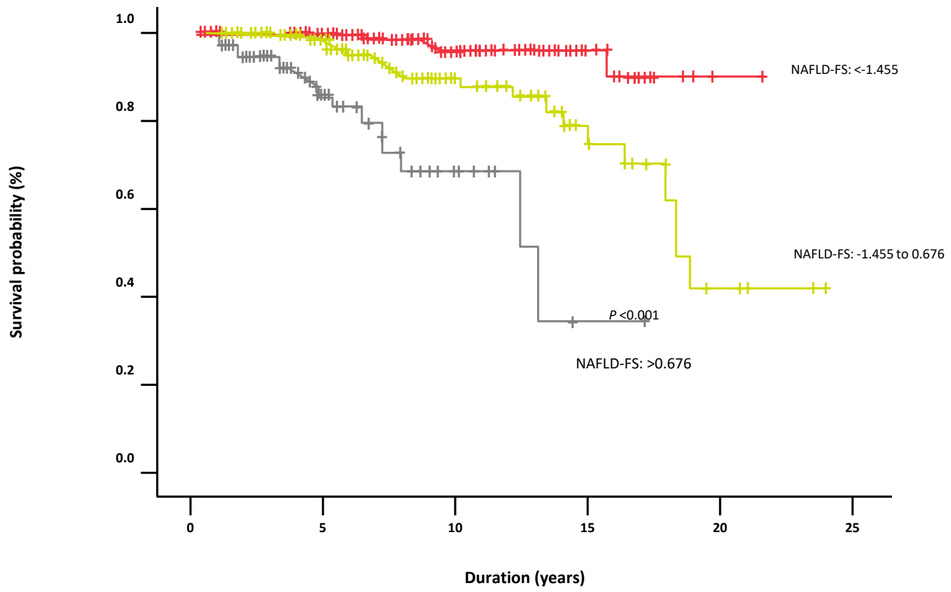


*NFS test results are based on age, hence the accuracy of the test may vary according to age
AASLD, American Association for the Study of Liver Diseases; AUROC, area under the receiver operating curve; CI, confidence interval; F3, stage 3 fibrosis; F4, stage 4 fibrosis; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score
1. Anstee QM et al. *Hepatology* 2019; doi: 10.1002/hep.30842; 2. Chalasani N et al. *Hepatology* 2018;67(1):328–357.

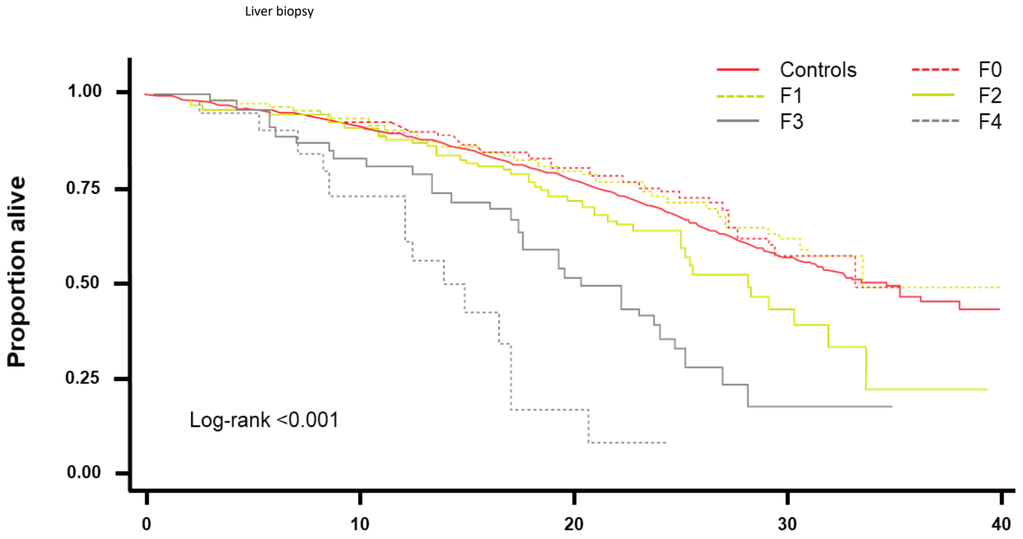
NFS may also predict long-term outcomes

Cumulative probability of death/liver transplantation is related to NFS[1]

NFS



Liver biopsy



Adapted from Angulo P et al. *Gastroenterology* 2013;145:782–789

- NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score
- 1. Angulo P et al. *Gastroenterology* 2013;145:782–789.

Adapted from Hagström H et al. *J Hepatol* 2017;67:1265 –1273

Charts are illustrative and not comparative due to differing patient populations described in the studies

Transient Elastography (e.g. FibroScan®) measures liver stiffness, which correlates with fibrosis[1]

- Liver stiffness is measured via a mechanically induced, controlled 50 Hz frequency shear wave[1]
- The propagation speed of the shear wave is measured with pulse echo ultrasound, with the results presented as kilopascals (kPa)[1]

Measures liver stiffness over an area estimated to be 100x greater than that of liver biopsy[1]

Failure to obtain readings is more likely in patients with a high BMI (>30 kg/m^2), however, use of XL probe may help overcome this limitation[1]

Over-estimation of fibrosis can occur in cases of hepatitis, cholestasis, liver congestion and if mass lesions are present in the liver[2]

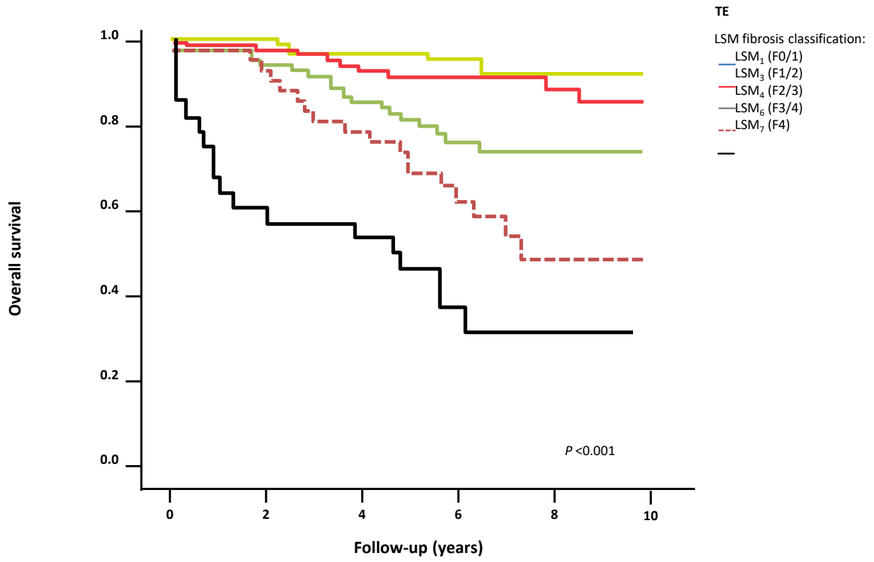
- BMI, body mass index
- 1. Grandison GA and Angulo P. *Clin Liver Dis* 2012;16(3):567–585; 2. Kemp W and Roberts S. *Aust Fam Physician* 2013;42(7):468–471.

FibroScan® is a registered trademark of EchoSens™, Paris

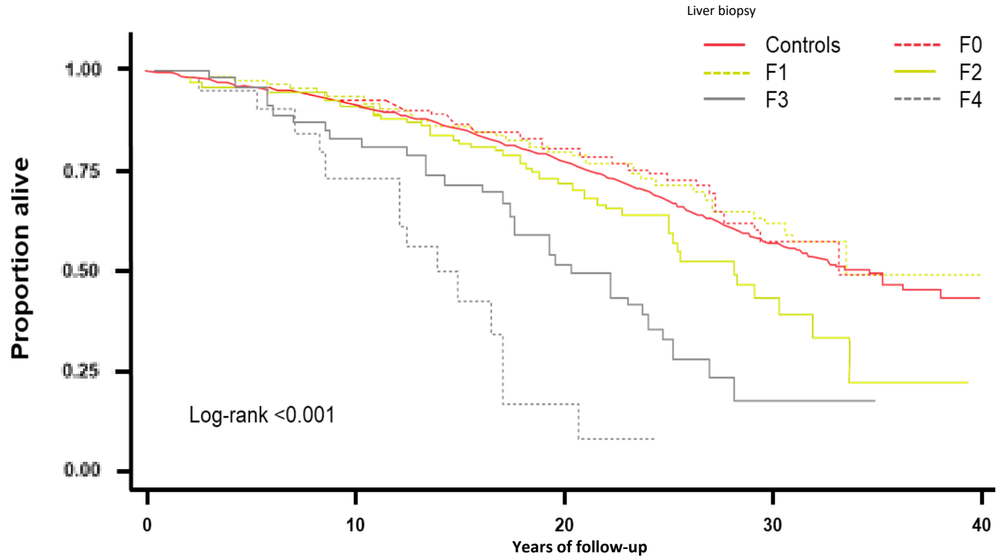
Fibrosis stage measured by Transient Elastography is predictive of mortality

Cumulative probability of death is related to Transient Elastography score[1]

TE



Liver biopsy



Adapted from Boursier J et al. *J Hepatol* 2016;65(3):570–578

- LSM, liver stiffness measurement; TE, transient elastography
- 1. Boursier J et al. *J Hepatol* 2016;65(3):570–578.

Adapted from Hagström H et al. *J Hepatol* 2017;67:1265 –1273

Charts are illustrative and not comparative due to differing patient populations described in the studies

Case

A 51 year old man presents to the clinic for routine follow up

PMH: Hypertension, Hyperlipidemia

Meds: Lisinopril, metformin, simvastatin, fenofibrate

SH: Rare social alcohol, works in the IT industry

FH: Father has T2 DM and CAD

Exam: BMI 36, Otherwise normal

NFS= 0.42 (Indeterminate) FIB-4 = 1.56 (Indeterminate)

Referred to a liver clinic:

Fibroscan: CAP 312 dB/M, 9.6 Kpa F2-F3; FAST Score = 0.54

Liver biopsy: NAS score 5, Stage 2 fibrosis (Brunt)

Lab Test	Patient Results	Normal Range
BMI	36.0	18.5-24.9
Fasting glucose, mg/dL	144	< 100
A1C, %	6.9	≤ 5.6
ALT, IU/mL	**60**	**7-40**
AST, IU/mL	**45**	**7-40**
Albumin, g/dL	**3.9**	**3.4-5.4**
Platelets, cells/mm^3	**190**	**150-450**
Lipids, mg/dL ▪ LDL ▪ HDL ▪ Triglycerides	 93 31 170	 < 100 > 60 < 150

Order liver tests and/or screen for fatty liver disease ?

MAFLD Management

- General measures
  - Abstain or limit alcohol intake
  - Address risk factors for cardiovascular disease
    - Hypertension
    - Lipid lowering Therapy
- Weight loss
- Pharmacologic therapies
  - DM – Optimized DM control, Pioglitazone, GLP-1
  - No DM – Vitamin E
- Possible future therapies

Weight Loss through diet for NASH

Lifestyle Intervention

Low-fat, average-protein diet (22% fat, 14% protein, and **64% carbohydrate**, saturated fat <8%, dietary fiber >20 g/d, and cholesterol <150 mg/1000 kcal)

Goal calorie intake 750 kcal below daily energy needs

Walk 200 minutes per week

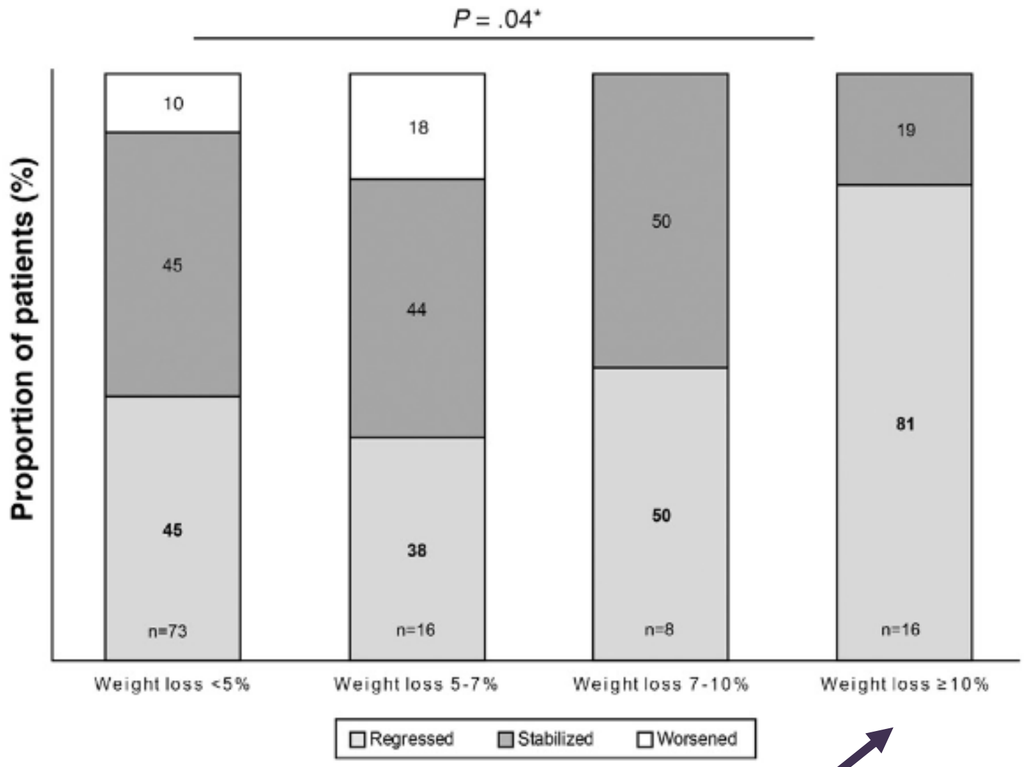
Measurement

Paired liver biopsies with 1 year of follow-up

Caveats

-60% NAS >5, 30% F2 or F3, 70% F0 or F1. F4 excluded.

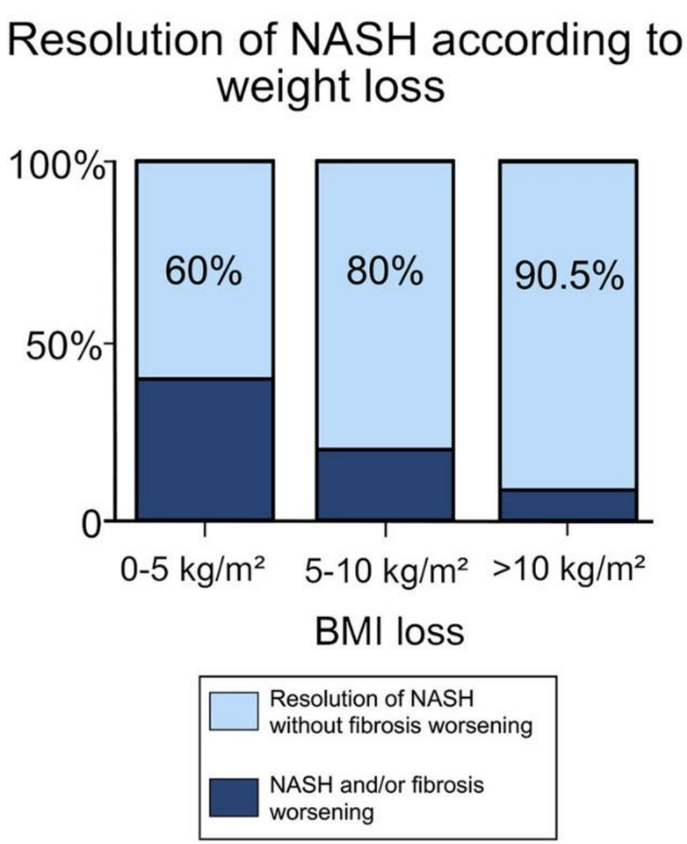
-Only 30% of the participants lost >5% of their weight

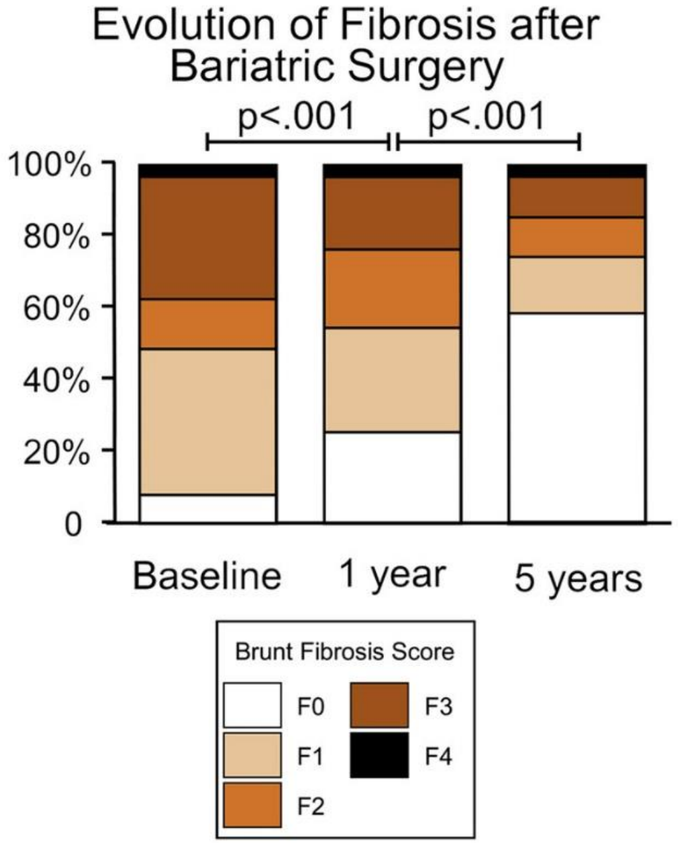


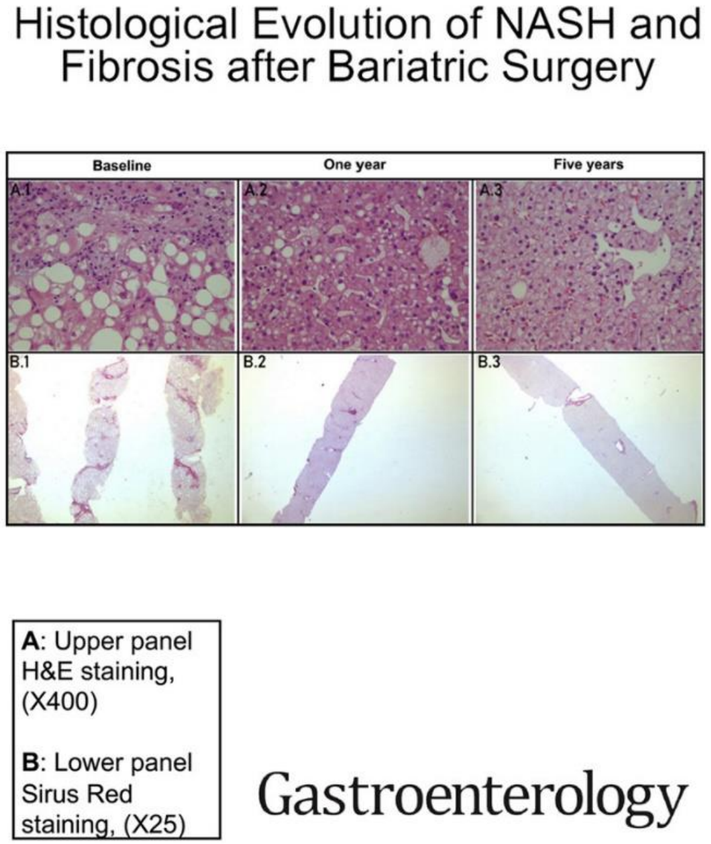
If >10% TBW weight loss achieved
81 % had histologic regression of disease

Martinez-Perez et al Gastroenterology 2015;149:367–378.e5

Bariatric Surgery for NASH







Lassailly et all. Gastroenterology 2020

Weight Loss Management

- Dietary Therapy
- Exercise
- Pharmacologic
  - Orlistat
  - Phentermine-topiramate
  - Naltrexone-bupropion
  - Liraglutide
- Surgical
  - Sleeve gastrectomy, RYGB, Duodenal Switch
  - Endoscopic balloon

Low-Carb vs Low-Fat Diets in NAFLD

Study Population	N	Mos	Comparison	Results	Difference Between Diets?
Obese with insulin resistance[1]	52	4	60% carb + 25% fat vs 40% carb + 45% fat	▪ Significant reductions in weight, SSPG, circulating insulin, serum ALT ▪ **ALT reductions greater with 40% carb diet**	**Yes**
Overweight and obese, otherwise healthy[2]	170	6	Reduced carb vs reduced fat	▪ Similar reductions in weight, body fat, visceral fat, ALT, intrahepatic lipids	No
Obese with or without NAFLD[3]	162	3	Low fat vs low carb	▪ Reductions in weight, BP, cholesterol ▪ In patients with NAFLD, similar reductions in glucose, triglycerides, transaminases	No

Inconsistent results: unclear whether type of diet is important

1. Ryan. Diabetes Care. 2007;30:1075. 2. Haufe. Hepatology. 2011;53:1504. 3. de Luis. Nutr Hosp. 2010;25:730 Slide adapted from: clinicaloptions.com

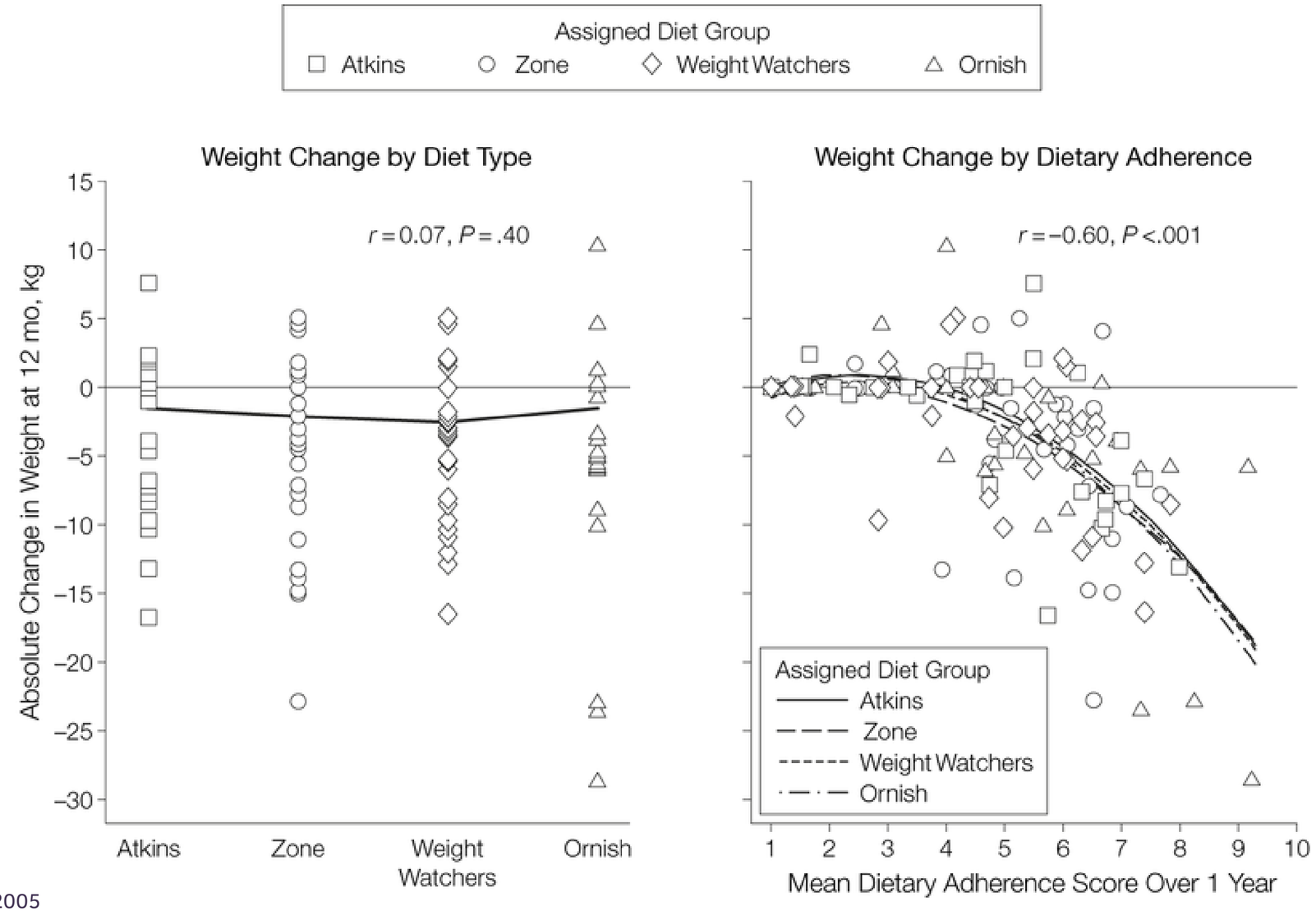
Low-Carb vs Low-Fat Diets for CVD Prevention

- Meta-analysis of randomized, controlled trials comparing **low-carb** vs **low-fat** diets in overweight and obese subjects for ~ 1 yr (17 trials; N = 1797)
- **Low-carb** diets superior for metabolic syndrome components (weight loss, HDL, TG, and BP)
- **Low-fat** diets superior for lowering LDL and total cholesterol
- ASCVD risk reduced by both diets but **more by low carb**

	Low Carb		Low Fat		Between Group Differences*	
	Mean (95% CI)	*P* Value	Mean (95% CI)	*P* Value	Mean (95% CI)	*P* Value
BMI, kg/m^2	-2.8 (-3.3 to -2.2)	< .0001	-2.1 (-2.5 to -1.7)	< .0001	-0.7 (-1.1 to -0.3)	.0016
Cholesterol, mg/dL	-4.2 (-9.4 to 1.1)	.11	-13.8 (-21.6 to -5.9)	.002	9.1 (2.6 to 15.7)	.006
HDL, mg/dL	4.4 (2.3 to 6.5)	.0004	-1.0 (-3.2 to 1.2)	.35	5.1 (3.5 to 6.7)	< .0001
LDL, mg/dL	-1.8 (-6.1 to 2.6)	.39	-10.9 (-17.3 to -4.4)	.0025	8.6 (3.6 to 13.7)	.0008
TG, mg/dL	-41.1 (-54.7 to -27.5)	< .0001	-11.3 (-18.8 to -3.7)	.006	-28.8 (-39.1 to -18.5)	< .0001
Systolic BP, mm Hg	-6.7 (-9.0 to -4.3)	< .0001	-4.4 (-7.2 to -1.5)	.006	-1.7 (-3.5 to 0.2)	.08

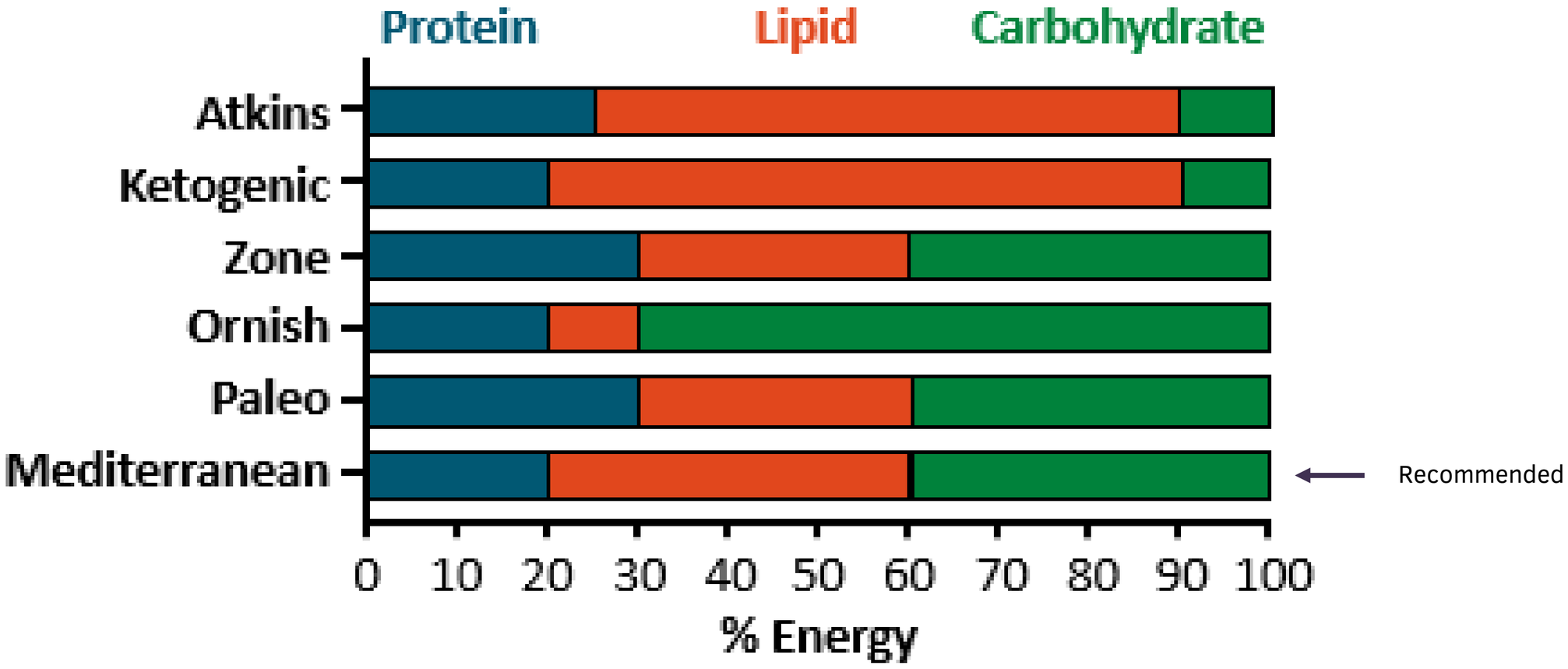
Sackner-Bernstein. PLoS One. 2015;10:e0139817. Slide adapted from: clinicaloptions.com

Diets for Active Weight loss (adherence matters)

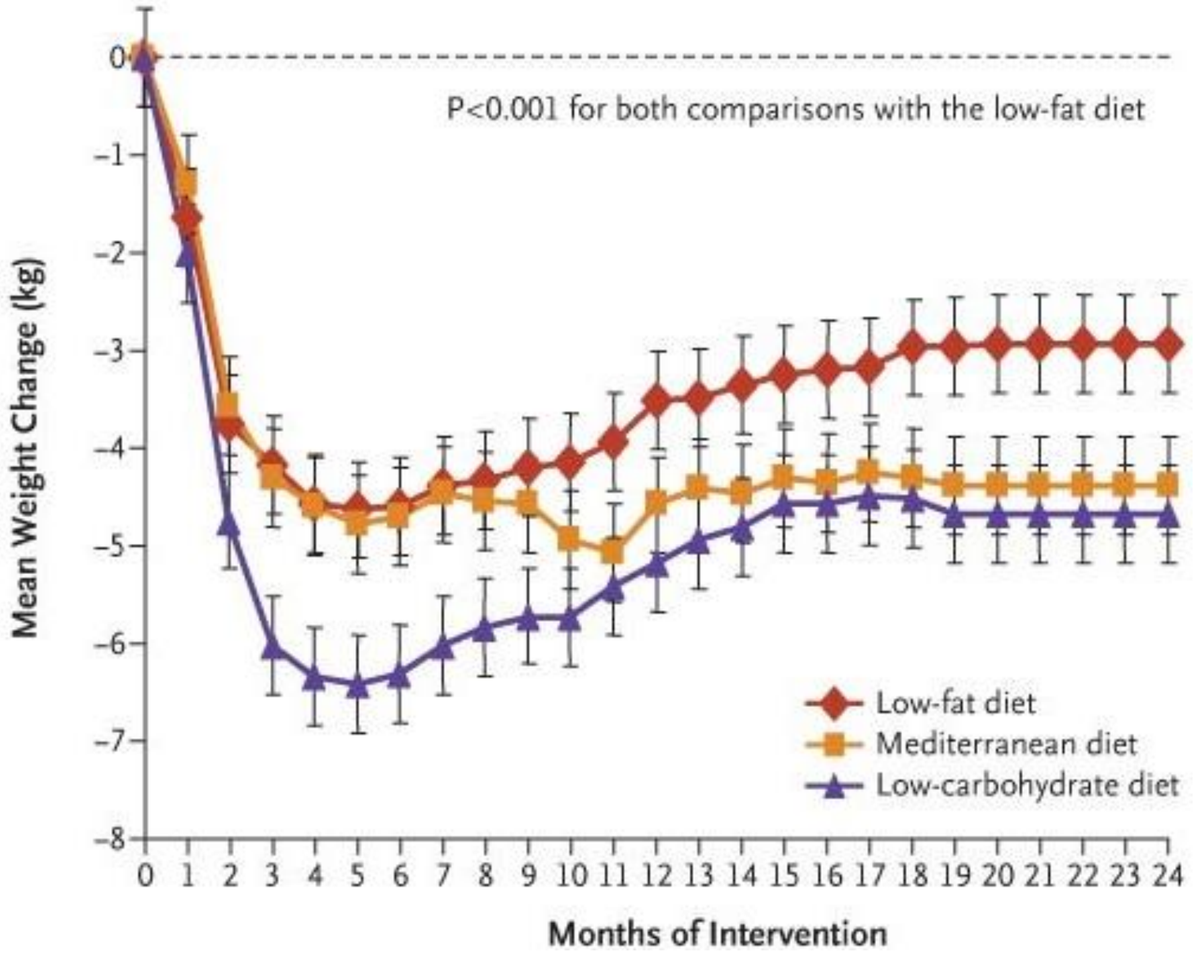


Dansinger et al JAMA 2005

Weight loss diets



Weight loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet



- 322 moderately obese subjects
- Mean BMI 31
- Randomized to 1 of 3 diets:
  - low-fat, restricted-calorie
  - Mediterranean, restricted-calorie
  - low-carbohydrate, non–restricted-calorie

Shai et al. NEJM 2008

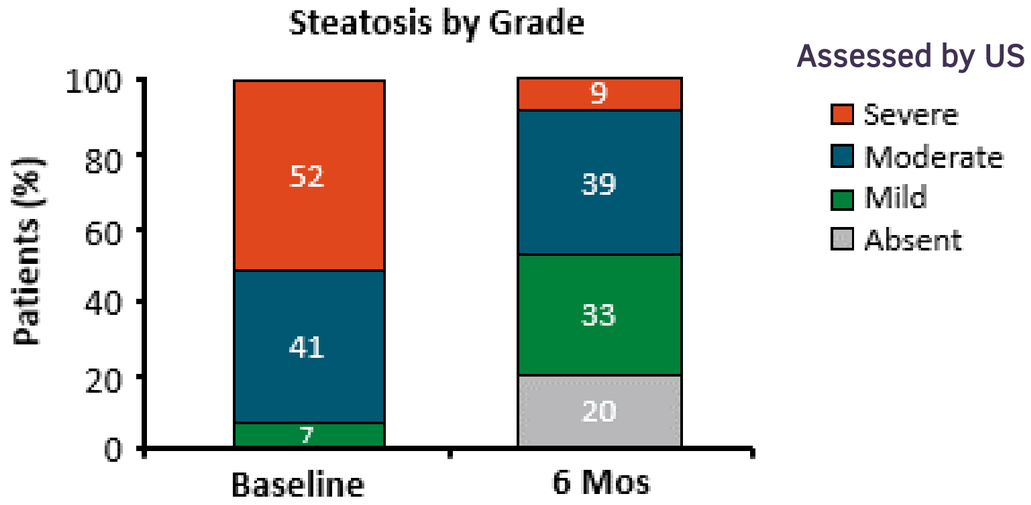
Mediterranean Diet in MAFLD: Observational Study

Design

- 6-mo observational study of **Mediterranean diet** intervention with monthly nutrition counseling in patients with NAFLD (N = 46)

Results

- Frequency of grade ≥ 2 steatosis decreased in > 80%, with resolution in 20%
- Caveat: Fibrosis not assessed



Gelli. World J Gastroenterol. 2017;23:3150.

Slide adapted from: clinicaloptions.com

Role of Exercise: Prospective Study of 346627 UK Biobank participants

1 point for meeting targets

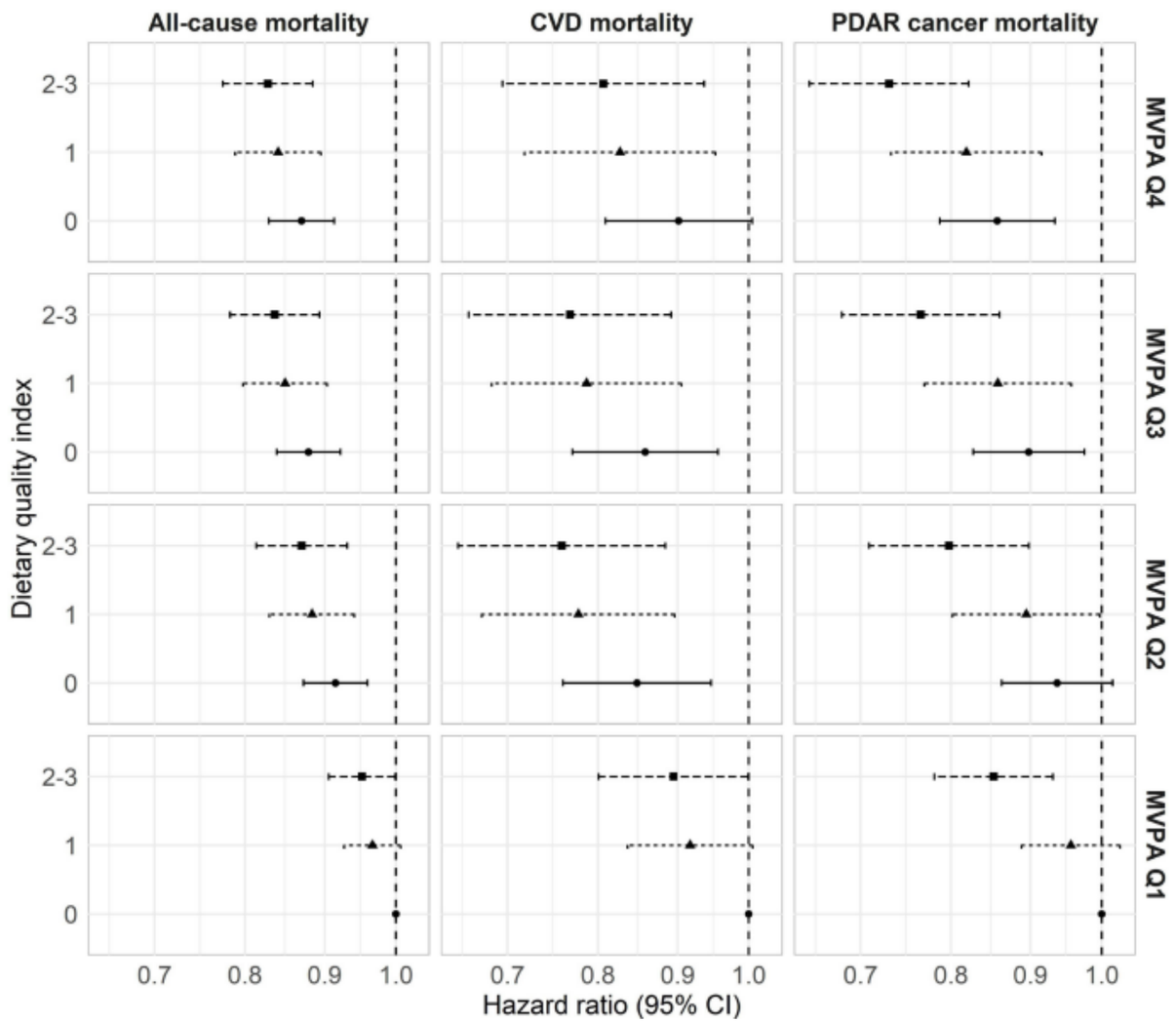
≥4.5 cups/day of fruit and vegetables

≥2 serves/week of fish

≤2 times/week intake of processed meat and ≤5 times/ week of red meat intake

Scoring

0 (lowest diet quality),
1 (medium diet quality)
2–3 (high diet quality).



total minutes of walking, MPA and VPA (x2)

921–5040 min

451–920 min

211–450 min

0–210 min

Ding D, et al. Br J Sports Med 2022;0:1–10. doi:10.1136

Case Presentation

A 51 year old man presents to the clinic for routine follow up

PMH: Hypertension, Hyperlipidemia

Meds: Lisinopril, metformin, simvastatin, fenofibrate

SH: Rare social alcohol

FH: Father has T2 DM and CAD

Exam: BMI 36, Otherwise normal

Fibroscan: CAP 312 dB/M, 9.6 Kpa ~F3; FAST = 0.54

Liver biopsy: NAS score 5, Stage 2 fibrosis (Brunt)

Lab Test	Patient Results	Normal Range
BMI	36.0	18.5-24.9
Fasting glucose, mg/dL	144	< 100
A1C, %	6.9	≤ 5.6
ALT, IU/mL	60	7-40
AST, IU/mL	45	7-40
Albumin, g/dL	3.9	3.4-5.4
Platelets, cells/mm^3	190	150-450
Lipids, mg/dL ▪ LDL ▪ HDL ▪ Triglycerides	 93 31 170	 < 100 > 60 < 150

Advise weight loss via healthy eating/exercise

Case Presentation

A 51 year old man presents to the clinic for 3 month follow up

He states that he decided to use an online/App based weight loss program

Walking 30-60 minutes 4-5x per week

He has lost 20 lbs and “feels great”

Now what?

Lab Test	Patient Results	Normal Range
BMI	33.1	18.5-24.9
A1C, %	5.8	≤ 5.6
ALT, IU/mL	29	7-40
AST, IU/mL	25	7-40
Albumin, g/dL	3.9	3.4-5.4

Losing weight and keeping it off

- Study of Successful Weight Loss Maintainers: The National Weight Control Registry
- Compared to weight-matched but non-reduced individuals:
  - Diet: About 100-150 calories/day less
  - Exercise: About 45 minutes/day (200 calories/day more)
  - TV: Average < 10 hrs/week vs. 28 hours national average
  - Cognitive response to food: higher dietary restraint

Wing et al, AJCN, 82:222S, 2005; Phelan et al, Ann. Behav. Med., 38:94, 2009; Raynor et al, Obesity, 14:1816, 2006; Bond et al, IJO, 33:173, 2009; Klem et al, AJCN, 66: 239, 1997; Gorin et al, Prev. Med.39:612, 2004; McCafferey et al, AJCN, 90:928, 2009

Weight Loss and Weight Regain in Individuals MAFLD

- Enrolled in TARGET-NASH, receiving care in usual clinical practice in the United States, who were either overweight or obese with at least 2 weight measurements over a 6-month period
- Weight loss was defined as ≥5% reduction compared with baseline
- Weight regain as return to baseline weight or greater
- **32%** of overweight or obese adults with NAFLD receiving usual care in the United States **achieved ≥5% weight reduction** during a median follow-up of 39 months
- Among those with initial weight loss, **21.2% had regained weight** back to baseline during a median follow-up of 32.3 months
- **Independent Predictors of Weight loss: Insurance status, number of encounter providers per year**

Malespin et al. Clinical Gastroenterology and Hepatology 2021.

Case – 6-month follow-up

A 52-year-old man presents to the clinic for MAFLD follow up

He stopped regularly using his weight loss App and “things got busy” ay work so he has been “walking less”.

Exam: BMI 35, Otherwise normal – has gained back 15 lbs.

Lab Test	Patient Results	Normal Range
BMI	35.0	18.5-24.9
Fasting glucose, mg/dL	144	< 100
A1C, %	6.3	≤ 5.6
ALT, IU/mL	**50**	**7-40**
AST, IU/mL	**48**	**7-40**
Albumin, g/dL	**3.9**	**3.4-5.4**
Platelets, cells/mm^3	**190**	**150-450**
Lipids, mg/dL ▪ LDL ▪ HDL ▪ Triglycerides	 107 31 190	 < 100 > 60 < 150

The patient is asks if medications are available and what can be prescribed now?

Indications for MAFLD Pharmacotherapy

AASLD (2018)	EASL (2016)	ADA (2022)
Limit to those with biopsy proven NASH with fibrosis	Offer to NASH with F2 or higher fibrosis or high risk for progression -DM -MetS -Persistently elevated ALT -High necroinflammation on biopsy	No Fibrosis thresholds discussed Clinicians must manage persons with NAFLD for obesity, metabolic syndrome, prediabetes, diabetes mellitus, dyslipidemia, hypertension, and CVD based on the current standards of care Pioglitazone and GLP-1 RAs are recommended for persons with T2D and biopsy-proven NASH.

1. Chalasani et al. Hepatology 2018 2. J Hep 2016 3. Eslam Hep International 2020

- Slide credit – figure adapted from www.clinicaloptions.com

Summary of Guideline Pharmacologic Recommendations for NASH

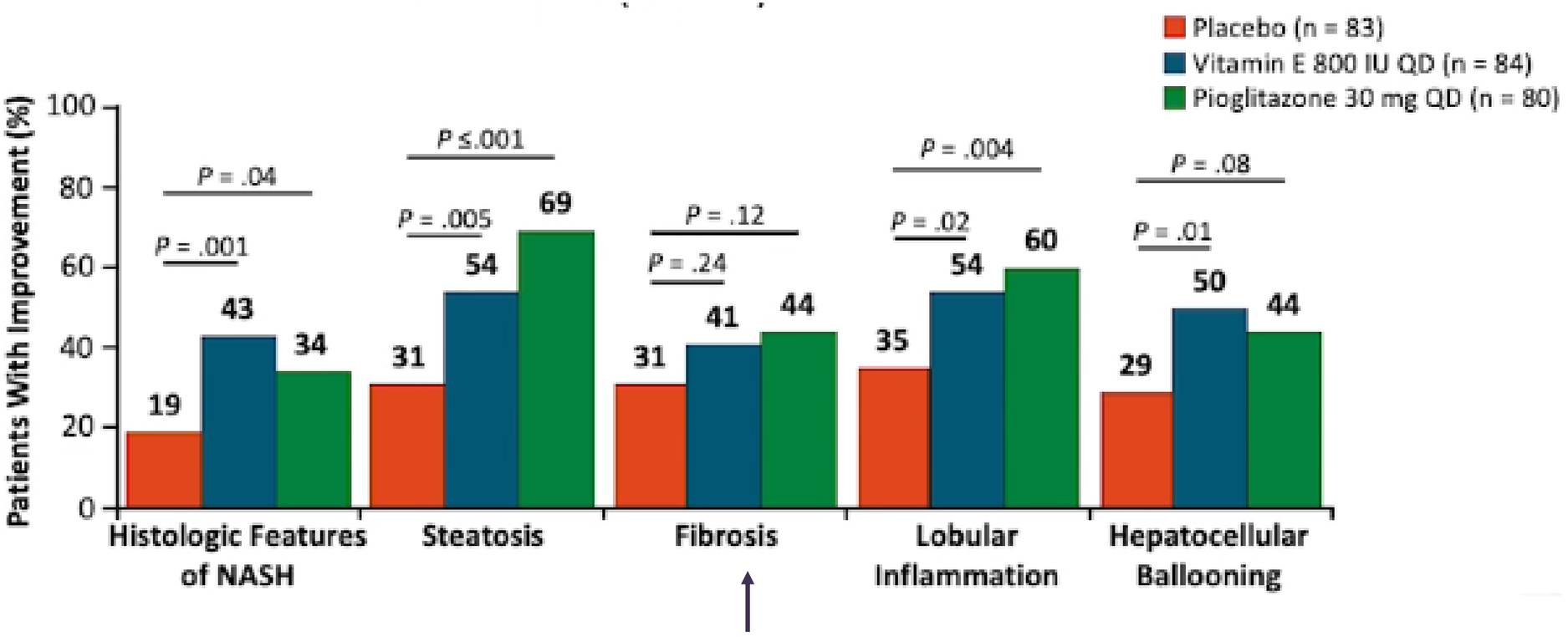
	AASLD (2018)	EASL (2016)	ADA (2022)
Vitamin E	800 IU/day in patients with biopsy proven NASH without T2D	800 IU/day in NASH without T2D	
Pioglitazone	Biopsy proven NASH with or without T2DM	Biopsy proven NASH with T2DM	NASH patients with T2DM
Metformin	Not recommended as treatment, but acceptable for management of DM		
Statins	Use to treat for CVD risk reduction or dyslipidemia, but NOT specifically for NASH		
Ursodeoxycholic acid	Not recommended		
Omega-3 Fatty acids	Can be used for dyslipidemia, but NOT specifically for NASH		Not discussed.
Obetacholic Acid	Not recommended, further data needed.		
GLP-1 receptor agonists	No Recommendation		NASH patients with T2D or obesity
SGLT2 inhibitors	Not discussed		Further data needed, but acceptable for DM management

1. Chalasani et al. Hepatology 2018 2. J Hep 2016 3. Cusi et al. Endocrine Practice 2022

Slide credit – figure adapted from www.clinicaloptions.com

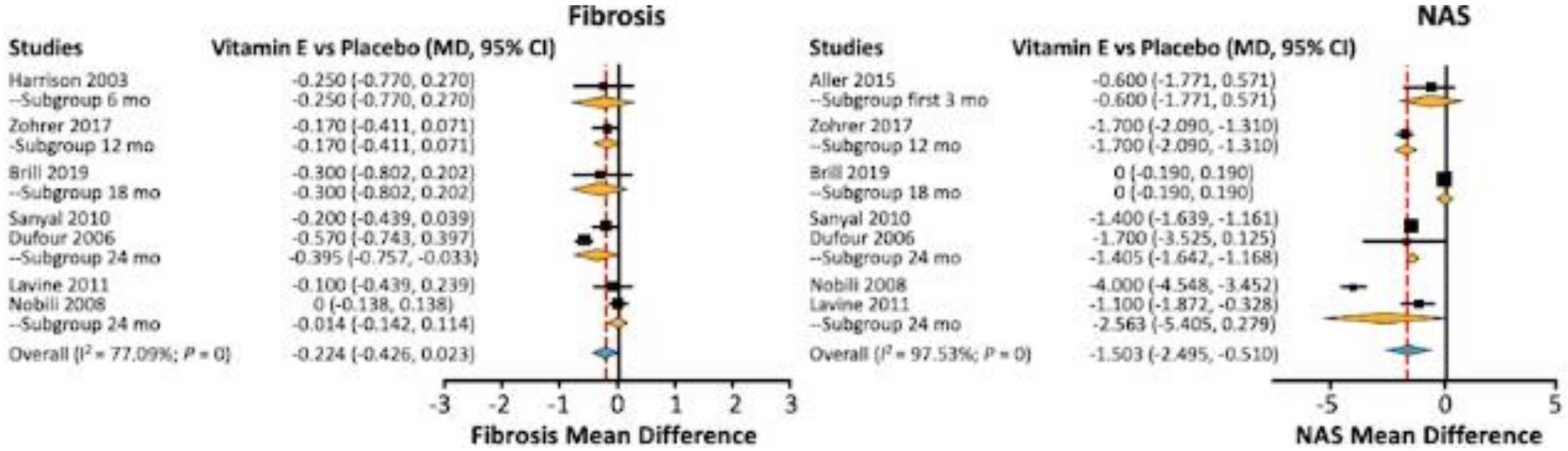
PIVENS Trial – Vitamin E and Pioglitazone

Vitamin E vs. Pioglitazone vs. Placebo in biopsy proven NASH with no diabetes or cirrhosis N=247, 96-week follow-up



Sanyal et al. NEJM 2010

Vitamin E – Updated results and Meta-analysis



N=1317 in 15 Randomized controlled trials
Definition of NAFLD not uniform across all studies
AST levels had a significant effect on NAS, and patients with a baseline AST > 50 IU/l showed more promising results.
Changes in weight and body mass index (BMI) were strongly associated with changes in NAS.

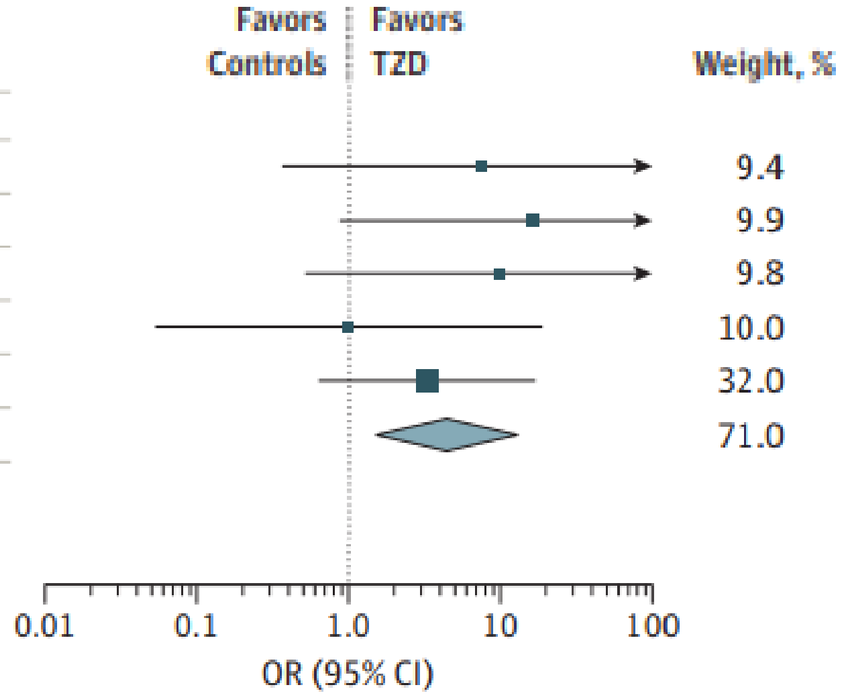
Abdel-Maboud et al. Therapeutic Advances in Gastroenterology 2020

Pioglitazone – Updated results and Meta-Analysis

Source	TZD No. of Events	TZD No. of Patients	Control No. of Events	Control No. of Patients	Odds Ratio (95% CI)
Pioglitazone hydrochloride					
Aithal et al,[17] 2008	3	31	0	30	7.49 (0.37-151.50)
Belfort et al,[16] 2006	7	26	0	21	16.54 (0.89-308.98)
Cusi et al,[12] 2016	4	50	0	51	9.97 (0.52-190.16)
Sanyal et al,[15] 2004	1	10	1	10	1.00 (0.05-18.57)
Sanyal et al,[20] 2010	6	80	2	83	3.28 (0.64-16.78)
Total (95% CI)	21	197	3	195	4.53 (1.52-13.52)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_5 = 2.39$; $P = .66$; $I^2 = 0\%$
Overall effect: $z = 2.71$; $P = .007$

Pioglitizone trials in biopsy proven NASH N=516



Improved Fibrosis of Any Stage

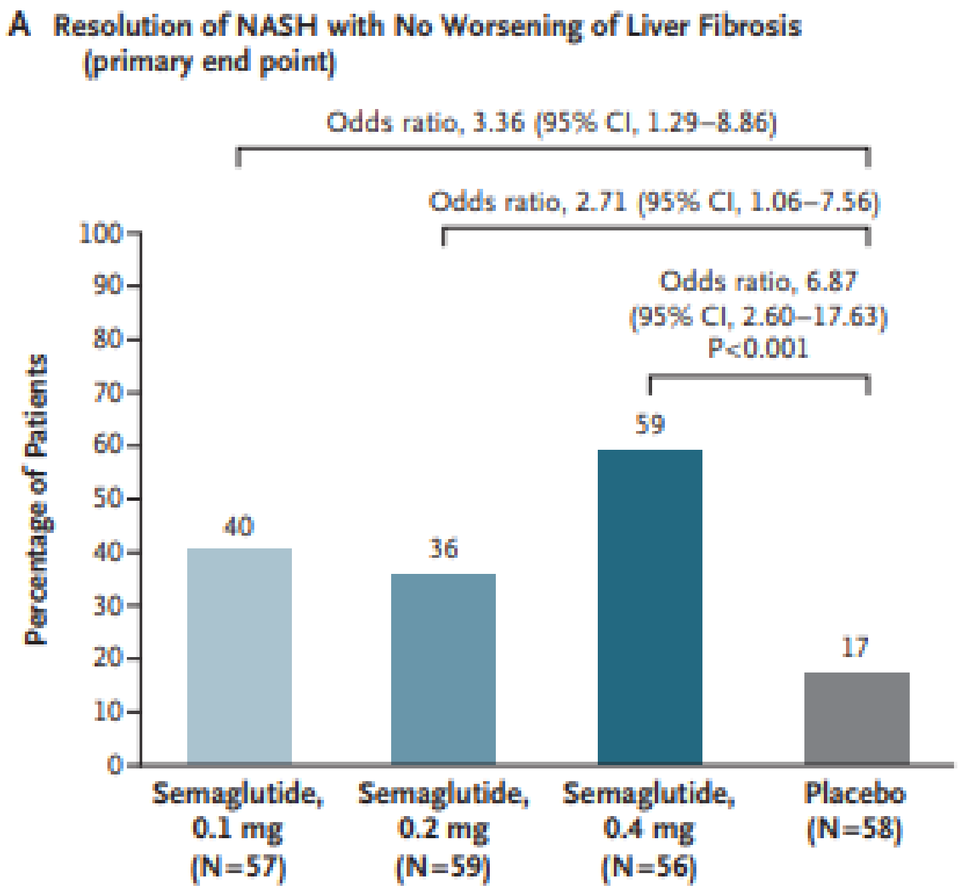
Musso et al. JAMA Internal Medicine 2017

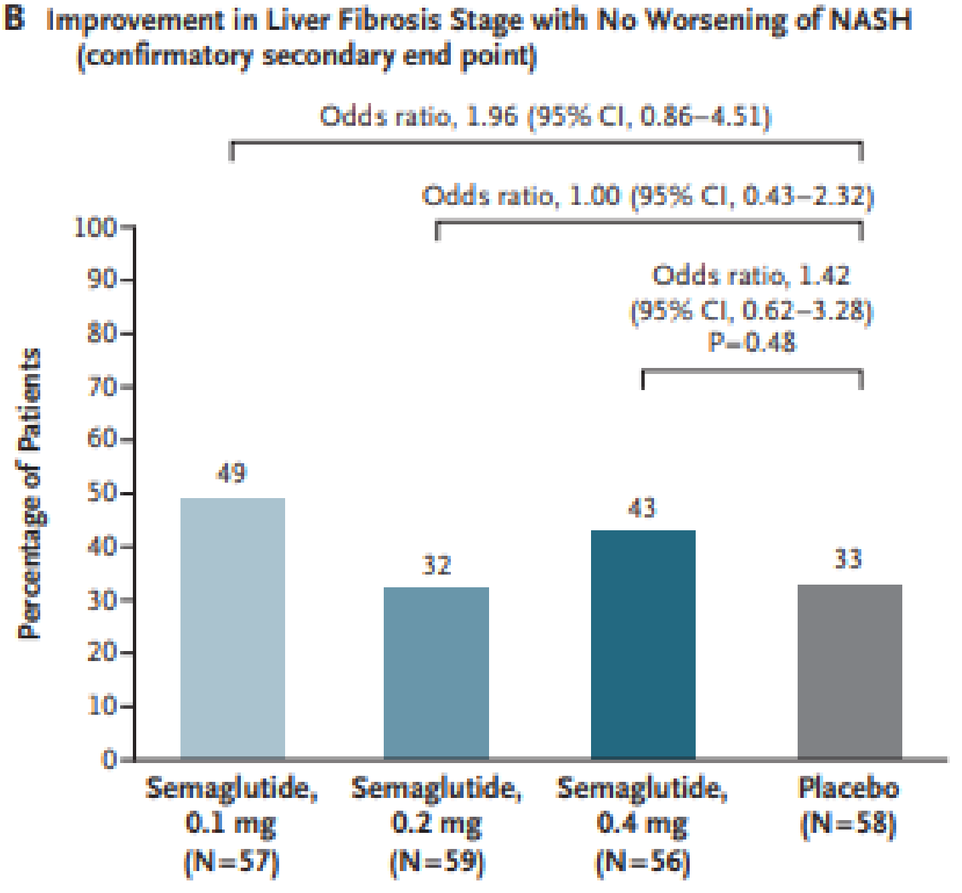
Safety and Tolerability

Vitamin E 800 IU / day	Pioglitazone 45mg / day
Possible all-cause mortality risk (1), not confirmed by a recent meta-analysis (2) Increased hemorrhagic stroke risk (3) Increased prostate carcinoma risk (HR 1.17, 4)	Edema, weight gain: 2-3 kg over 2-4 years (5) Risk for CHF exacerbation Increased risk of osteoporosis (6) Equivocal bladder cancer risk (7,8)

• 1. Miller et al. An Int Med 2005, 2. Abner et al. Curr Aging Sci 2011 3. Schurks et al. BMJ 2010 4. Klein et al. JAMA 2011 5. Brill et al. Diabetes Care 2017 6. Yau et al. Curr Diab Rpe 2013 7. Tuccorri BMJ 2016 8. Lewis et al. JAMA 2015

Semaglutide for Nonalcoholic Steatohepatitis – Phase 2 Study





>50% of the cohort had F3 fibrosis

Newsome et al. 2021

MAFLD Therapeutics – Phase 3 Studies

Agent	Class / Mechanism	Status
Obeticholic acid	FXR Agonist	Initial FDA application failed
Cenicriviroc	CCR2/CCR5 antagonist	Negative study
Elafibranor	PPARα/δ agonist	Stopped early due lack of efficacy
Selonsertib	Apoptosis signal-regulating kinase 1	Negative study
Resmetirom	Selective thyroid hormone receptor-β agonist	Submitted to FDA for approval
Aramchol	Stearoyl coenzyme A desaturase 1 modulator	Ongoing

Thank you!

Cardiometabolic teleECHO™ Clinic

Patient Recommendation Form

Presentation Date: August 3, 2022 **Presenter name:** Olesya Mykulyn, PA-C

Presenter Facility: Sea Mar CHC

Recap: 51-year-old man with new diagnosis of T2D (a1c 10.6), random sugar 298mg/dl, new hypertension (original blood pressure 190/120's/ hypertensive urgency/ no end organ issues), possible M/NASH, BMI 35(103kg), and just started on therapy plan below with close follow up in 4 days, and 1 weeks with titration of medications as noted below

- Current Diabetes regimen:
  - Metformin 1000mg and recent increase to BID
  - Glipizide 10mg BID
- Hypertension – amlodipine, lisinopril, chlorthalidone- with resent transition from amlodipine to nifedipine
- Limited but teaching on diabetes and meter use

Case Recommendations:

1. Follow up in 2-4 weeks as schedule permits
2. Attempt to ask patient to photograph all food with meals and in between meals and all drinks/liquid intake for 24 hours prior to the appointment
3. Ask patient to try to check fasting glucose in AM if possible every day, but at least every other day. If able, have the patient check 1 sugar prior to dinner/bedtime, alternating to look at patterns but no more than 2 fs a day. Limit fs if this is a barrier for the patient.
4. Check CBC for platelets and risk calculation for M/NASH
5. May defer Hepatology referral for now as focus on other metabolic issues. Agree with sleep referral, but you may want to defer in short term
6. Reconsider in 6-12 months based a re-risk stratification for Hepatology and Sleep referral (both may improve with weight loss)
7. Agree with nutrition referral. Try to position with your 2-3 month follow-up. However, given 2-3 months prior to appt, attempt to partner with patient for small changes in nutrition at each visit. Start with limiting sugared beverages. Then review with patient their photos of meals taken to discuss portion sizes or specific foods to limit change. Targeting just 1-2 small changes at a time can be more effective.
8. Simple handout/ discussion on DASH diet for blood pressure improvement (see attached DASH handout in Spanish)
9. Check in on mental health and consider diabetes distress score and PHQ-9 (consider partnering with a Sea mar health educator for this assessment after visit at 1 month and for additional lifestyle support
10. If schedule permits, consider an in-person check in 2 weeks rather than a phone check-in to assess any GI issues on metformin and glucose. vs phone check in
11. Consider conversion to metformin 750mg XR twice a day if sig GI issues

12. At one-month check-in, low threshold to initial insulin in short term for fasting glucose >250mg/dL or if persist glucose > 300mg/dl with consideration of replacing or adding GLP- RA at follow up appointment. A 0.1-0.3 u/kg would be an appropriate start for insulin based on patient comfort
13. Consider 18-20 units as an "effective but safe" starting dose given weight of 103kg and normal renal function in setting of stopping glipizide
14. If there is moderate improvement and GI issues are stable, at 1-month visit consider GLP-RA over basal insulin. (Review of formulary showed weekly semaglutide and dulaglutide covered with PA after on metformin)
15. Continuation of glipizide would be based on current glucose levels and held if insulin started.
16. If fasting sugars are still in 180-200 would likely convert just to 10mg XR glipizide or 2mg glimiperide- for pill burden and start weekly GLP-1 RA.
17. Instruct patient if having any sugars less than 70mg/dl or fasting sugars 100-110mg/dl for 2 or more occasions in AM to reduce glipizide or glimiperide, or if on insulin to reduce insulin by 4 units.
18. Monitor blood pressure on 3 drug therapies. We agree nifedipine conversion is more effect than amlodipine, but current levels are safe/acceptable for BP so no further escalation is indicated in next 1-2 months. If blood pressure remains >130/80 (so outside of goal on 3 agents) then consider aldosterone/renin fasting screening and next step would be to consider spironolactone.
19. Consider combination of medication and XR to minimize twice a day dosing of medications and pill burden. Review of united formulary by pharmacy showed chlorthalidone/azilsartan (in place of Lisinopril) combination covered per pharmacy.
20. Continue partnership with patient and complete an assessment of their distress over multiple new chronic disease diagnoses. Check in is important to limit any barriers to taking medications.

Nicole Ehrhardt, MD

Physician Signature: *Nicole Ehrhardt*
Please Re-present this case: September 2022