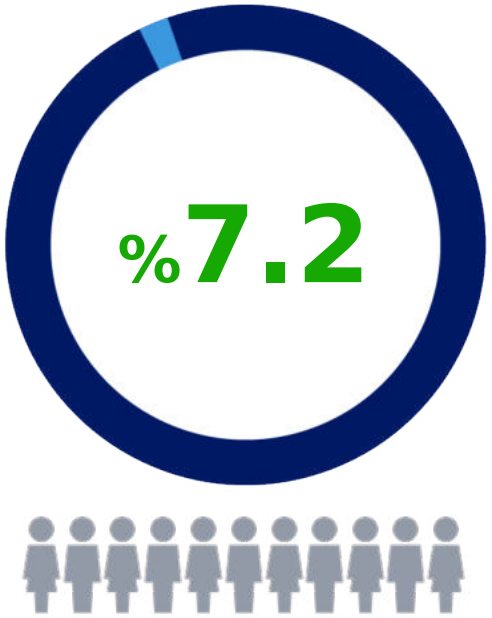
Tip 2 Diyabette 2 Yeni
Yeni Tanım, Yeni Komplikasyon

Prof.Dr. Kubilay UKİNÇ
Endokrinoloji ve Metab. Hast. Bölümü

Prof.Dr. Oğuzhan DEYNELİ
Endokrinoloji ve Metab. Hast. Bölümü

Diyabet Epidemisi

TURDEP 1



Türkiye'de Diyabet Prevalansı

TURDEP 2

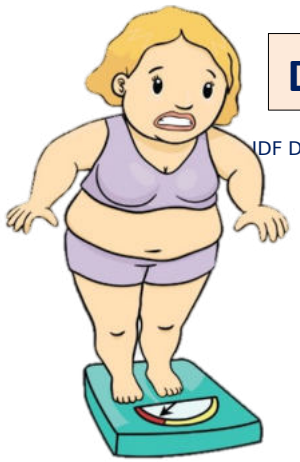
Türkiye'de Diyabet Prevalansı

TÜRKİYE

≥20 yaş, 9 Milyon Kişi

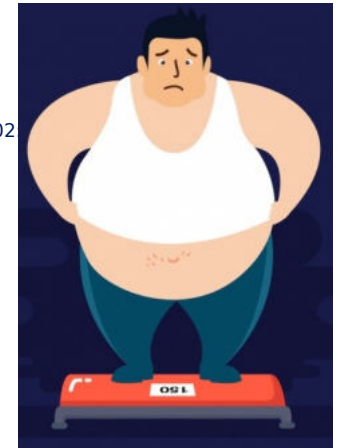
Türkiye'de diyabet artış hızı[2]

Kadınlarda 6 kg, bel çevresi 6 cm ↑;
Erkeklerde 8 kg, bel çevresi 7 cm ↑



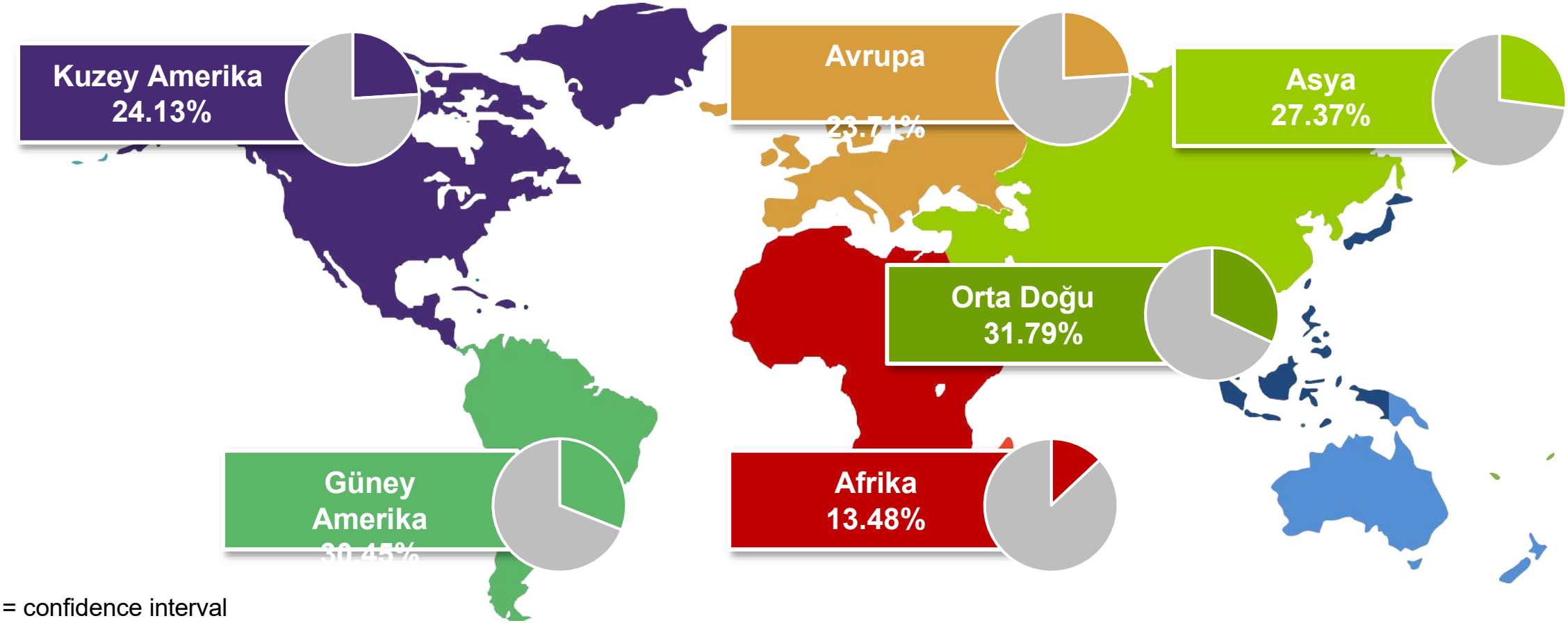
Diyabet başlangıcı 5 yıl erken

IDF Diabetes Atlas 8th Edition. 2. Satman İ et al. Diabetes Care, 25(9), 2002



NAFLD ve NASH Tüm Dünyada Yaygın

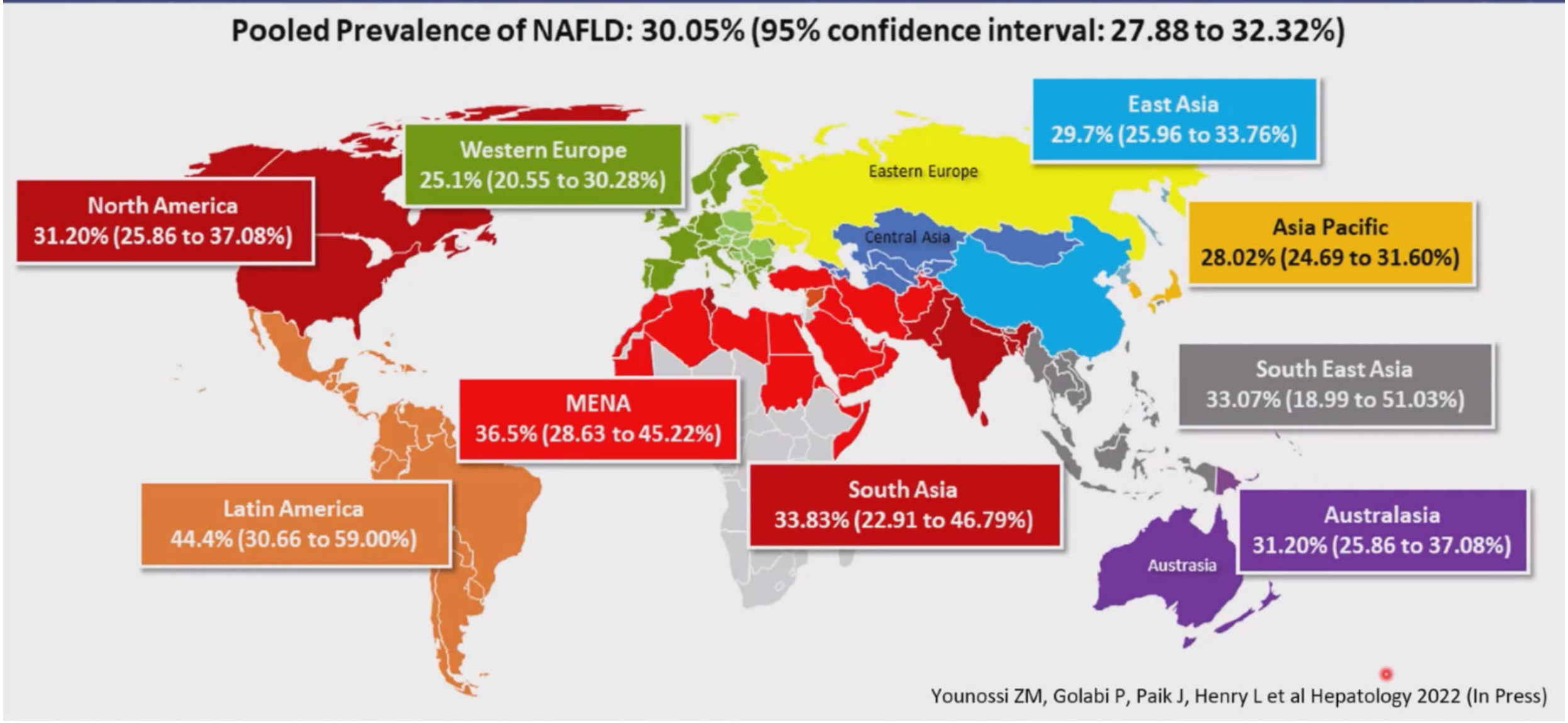
- NAFLD'ın Global prevalansı 25.24% (95% CI: 22.10-28.65)
- NASH'in genel toplumdaki prevalansının yaklaşık 1.5% - 6.45% arasında

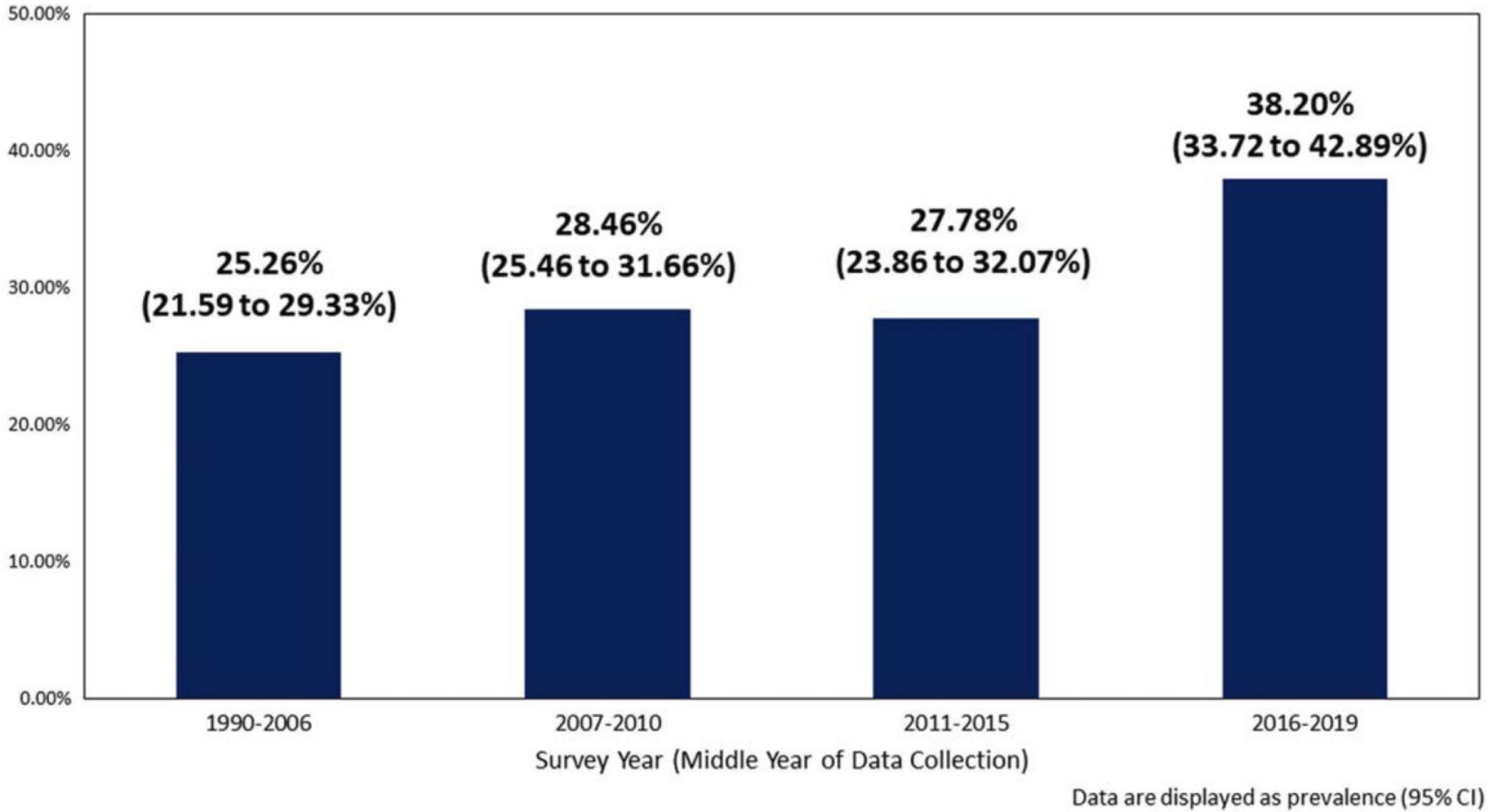


CI = confidence interval

Younossi ZM et al. *Hepatology.* 2016;64(1):73-84.

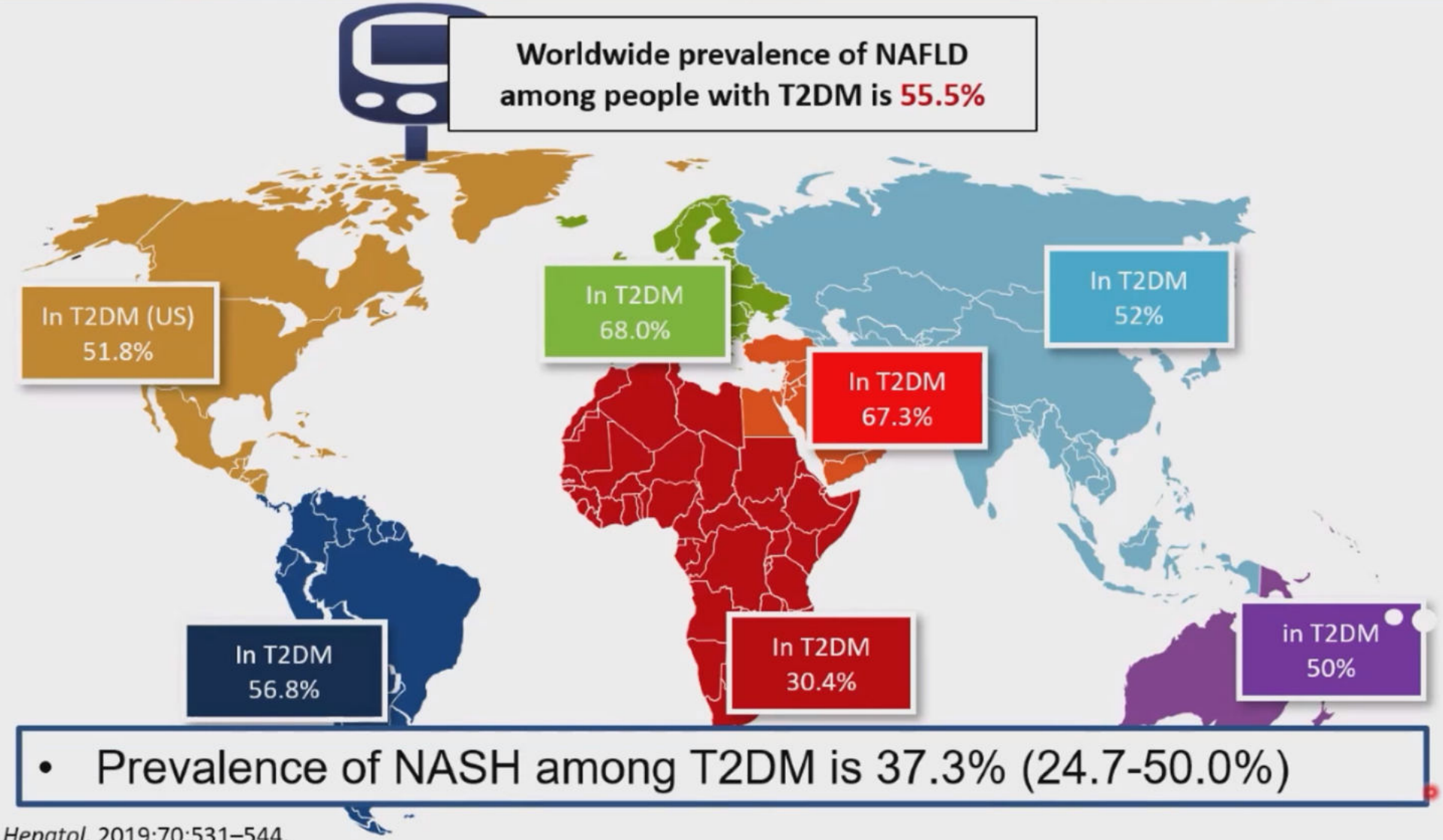
Yayınlanan Verilere Göre Meta Analitik Global ve Bölgesel NAFLD Oranları 2019





Younossi Z, Golabi P, Paik J et al. Hepatology. 2023;77:1335–1347

Tip 2 Diyabetli Hastalarda NAFLD ve NASH Prevalansları



- Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)

Younossi ZM. *J Hepatol*. 2019;70:531–544.

- Nonalcoholic fatty liver disease (NAFLD) tüm dünyada kronik karaciğer hastalığının en önemli nedenidir.
- NAFLD metabolik sendromun **karaciğer tutulumu** olarak değerlendirilmektedir ve sıklıkla obezite, dislipidemi, hipertansiyon ve diyabet gibi metabolik risk faktörleri ile ilişkilidir.
- Tüm dünyada artan obezite ve T2 DM oranları global olarak artan NAFLD prevalansı ile paralel seyretmektedir.

Nat. Rev. Gastroenterol. Hepatol. 2013; 10: 686-690; Nat. Rev. Gastroenterol. Hepatol. 2018; 15: 11-20; Cell 2021 184; 2537-2564
Younossi Z, Golabi P, Paik J et al. Hepatology. 2023;77:1335–1347

Alkolik olmayan yağlı karaciğer Spektrumu

YAĞLI KARACİĞER

Yağ karaciğerde depolanır

Karaciğerde en az %5 yağ depolanması/hepatoselüler zedelenme bulgusu olmaması (hepatosit balonlaşması)

Nonalkolik Steatohepatit

Yağ ve beraberinde inflamasyon ile skartis(nedbe) dokusu oluşması

Karaciğerde en az %5 yağ depolanması/inflamasyon var ve hepatoselüler zedelenme bulgusu var (hepatosit balonlaşması)
Fibrozis var veya yok. (az-orta-çok)

Siroz

Karaciğer hücrelerinin yerini skar dokusu kaplar

Nedbe, yıkıma uğramış dokuya benzer yeni bir doku yaratma olanağı bulunmadığında vücudun, doku yitimlerini onardığı sürecin son evresidir

Liver International. 2007;27(4):423-433.

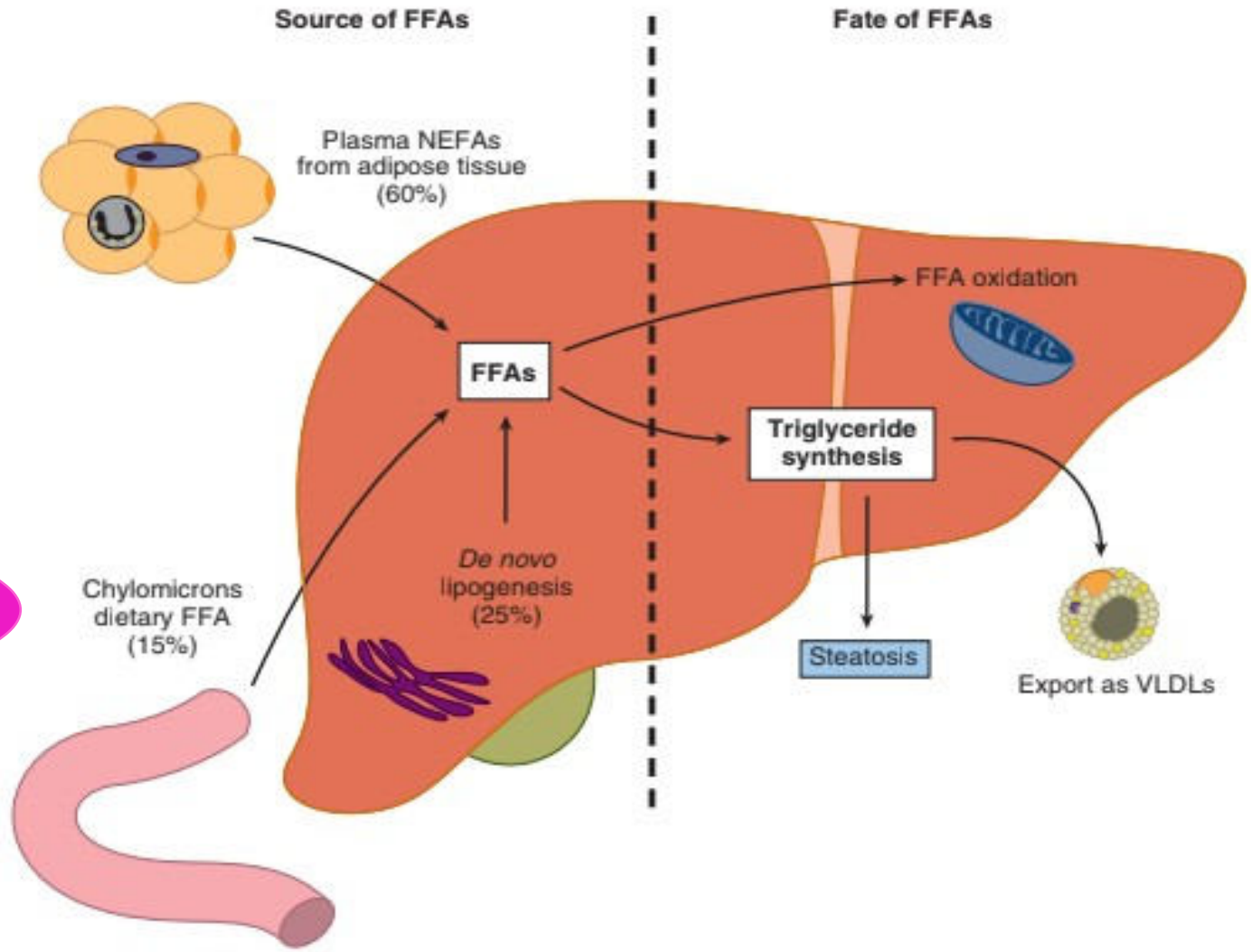
Karaciğer'in yağ kaynakları nelerdir?

Diyetteki SYA leri

IR nin şiddetine bağlı..adiposit kaynaklı SYA

Hepatosit denovo lipogenez

NAFLD de normalde '<%5 iken. %26kadar çıkar



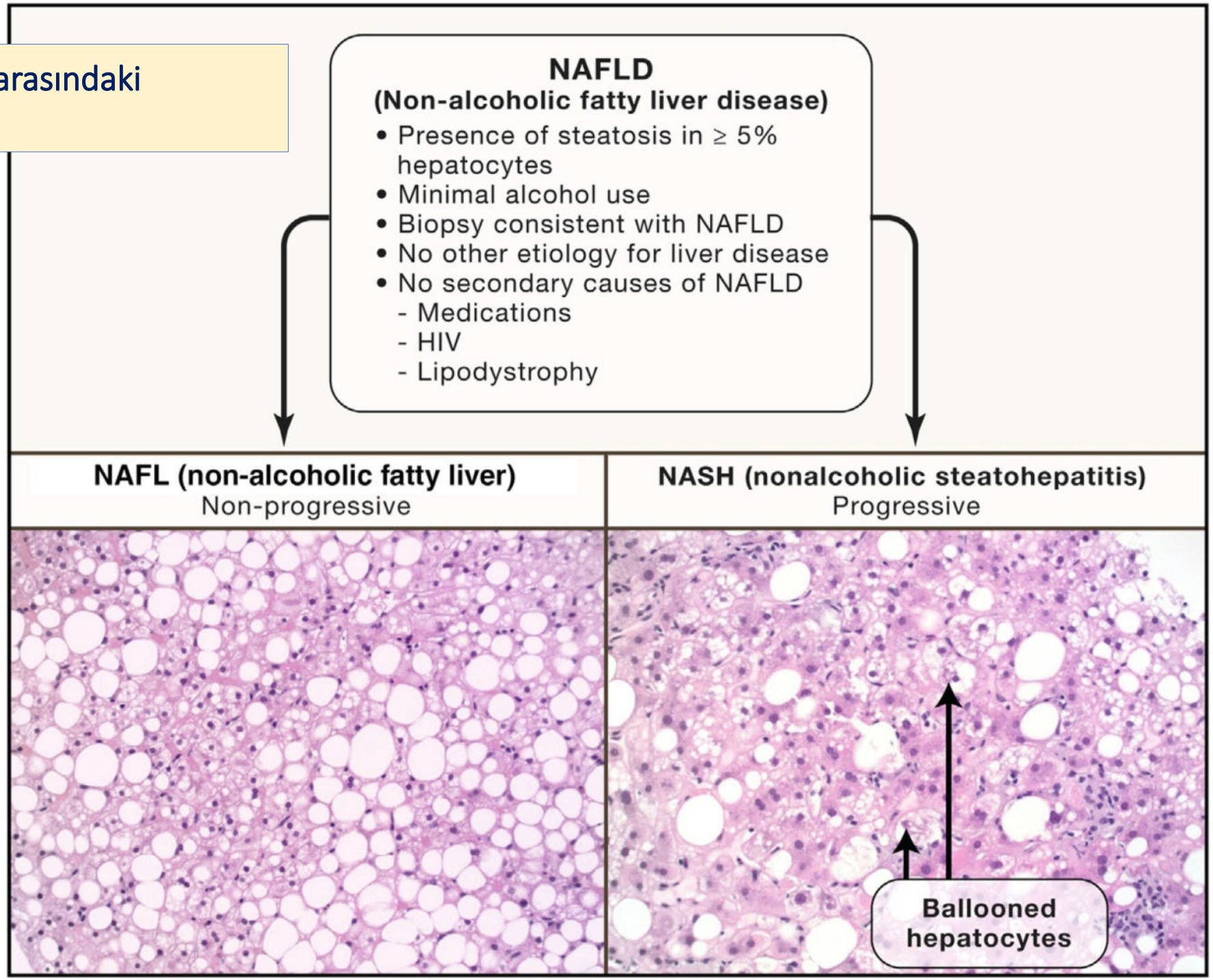
Epidemiyoloji: NAFLD'ın Yükü

- **Global olarak, nonalcoholic fatty liver disease (NAFLD) her 3 kişiden 1'inde mevcut**[1]
- **Etnik yatkınlık**
  - Asyalı Hintliler>İspanikler>Beyaz Irk>Afrika orjinli Amerikalılar
- **Risk faktörleri MetS**
  - Obezite, hipertansiyon, hipertrigliseridemi, insülin direnci ve diyabet
  - PNPLA3, TM6SF2, MBOAT7 genotip
  - HSD17B13

- NAFLD teşhisinde
  – Biyopsi veya görüntülemede hepatik yağlanma bulguları (Hepatositlerin ≥ 5% steatoz) alkol tüketmeyen veya çok az tüketen bireylerde bir başka sekonder nedene bağlı olmaksızın(Örneğin Wilson, Lipodistrofiler, ilaçlar ....)

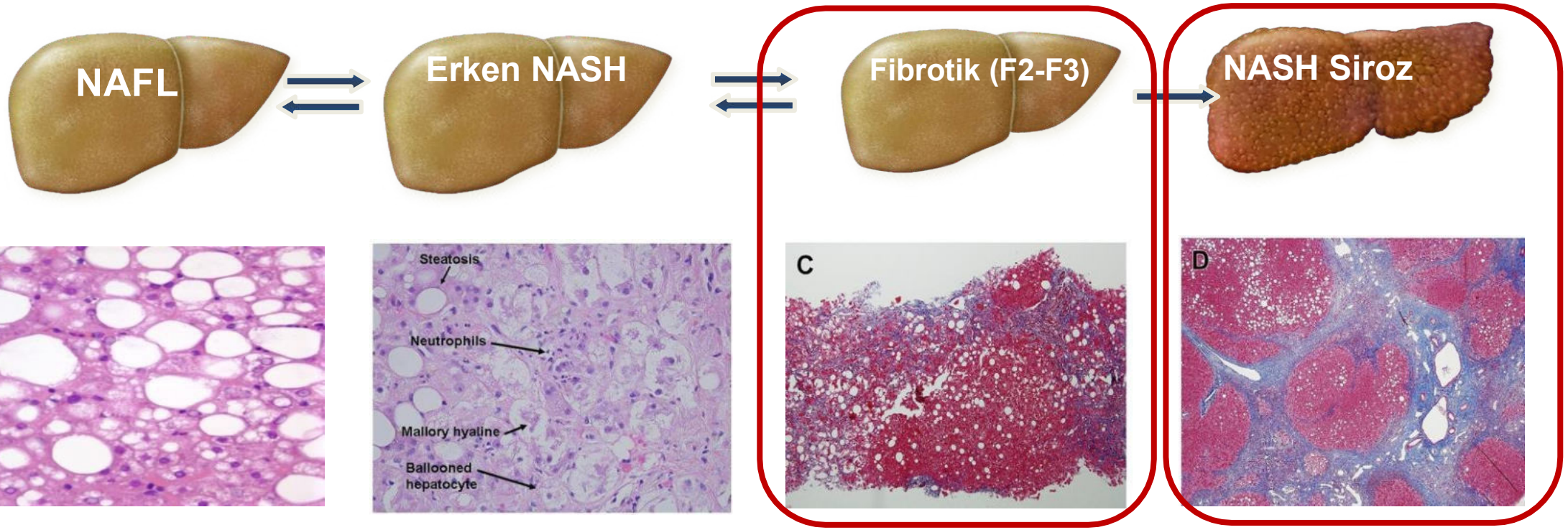
1. Younossi Z, Golabi P, Paik J et al. Hepatology. 2023;77:1335–1347

NAFLD ve NASH arasındaki histolojik farklılık



Loomba R, Friedman SL, Shulman GI. Cell 2021 184; 2537-2564

Olağan Süreç

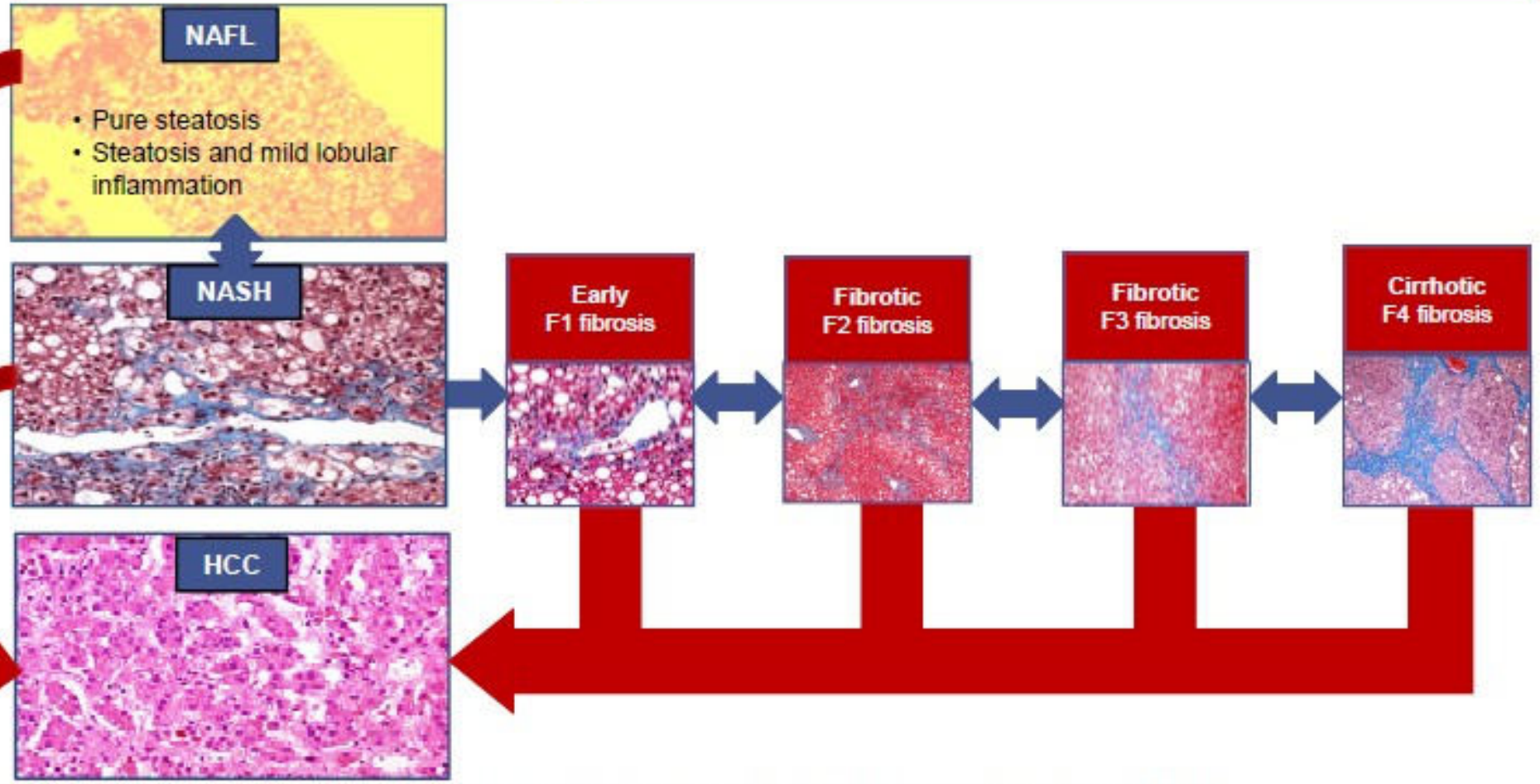


NAFLD ve NASH

NAFLD Spektrumu

Diagnosis of NAFLD requires

- Steatosis in >5% of hepatocytes
- NASH requires specific pathologic criteria
- Exclusion of secondary causes and AFLD
- Associated metabolic risk factors

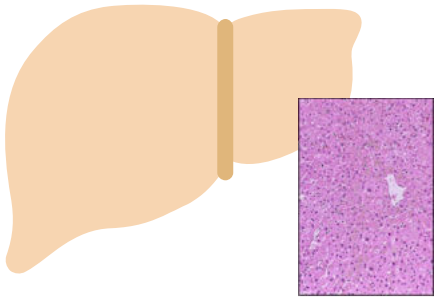


1. Younossi ZM. *Hepatology*. 2018;68(1):349-360; 2. Chalasani N, et al. *Hepatology*. 2018;67(1):328-35; 3. Younossi ZM, et al. *Hepatology*. 2011;53(4):1874-1882;
4. Younossi ZM, et al. *Hepatol Commun*. 2017;1(5):421-428; 5. Anstee QM, et al. *Gastroenterology*. 2016;150(8):1728-1744, 6. EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

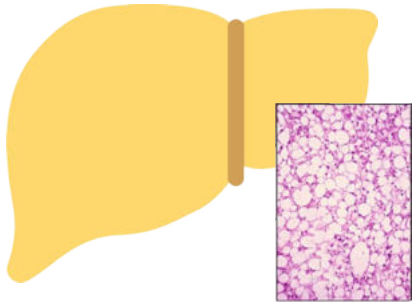
NAFLD Olağan Süreç

NAFLD

Normal Liver

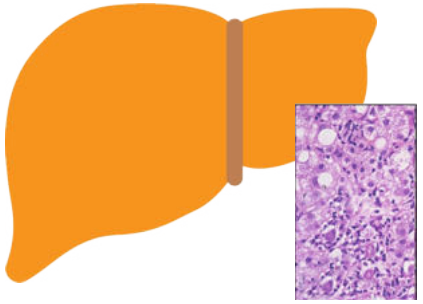


Steatosis "NAFL"



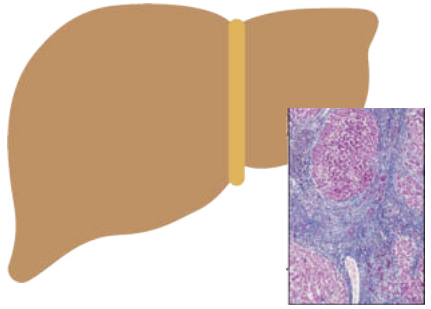
Fat infiltration ≥ 5% without ballooning, with or without inflammation

Steatohepatitis "NASH"



Fat infiltration ≥ 5% with necroinflammation and hepatocellular injury (ballooning, hepatocyte degeneration, Mallory bodies, or megamitochondria)

Cirrhosis

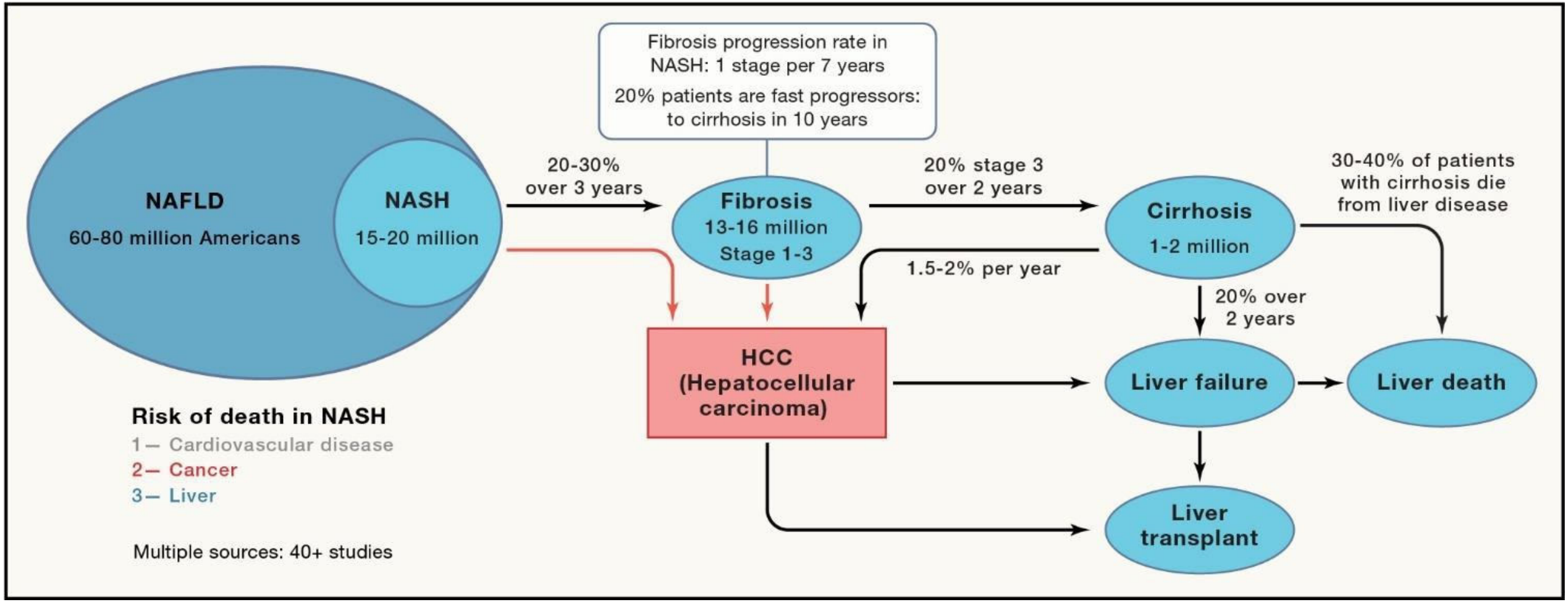


Increasing fibrosis, leading to cirrhosis

HCC

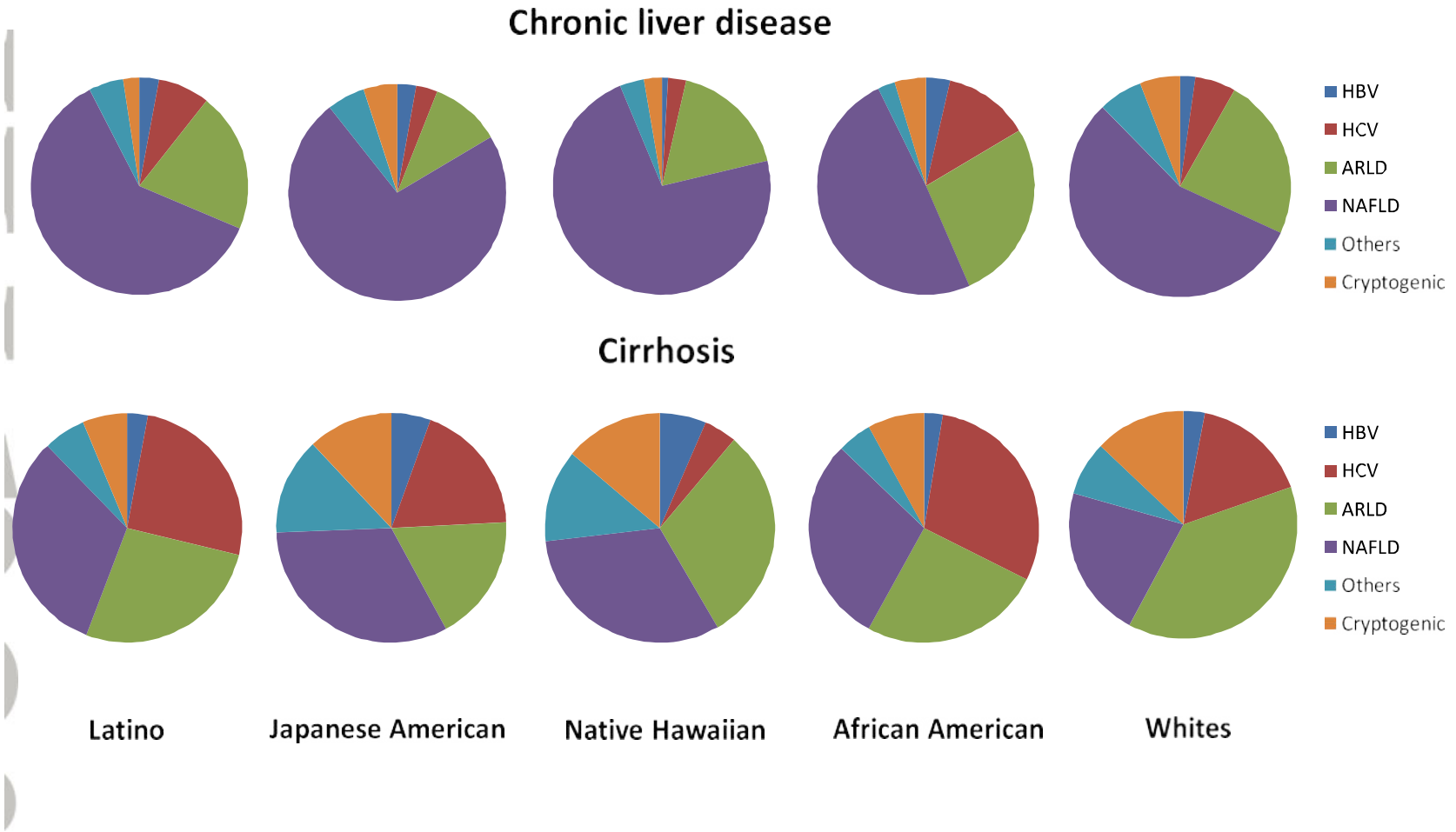
Chalasani. Hepatology. 2018;67:328.

NAFLD Olağan Süreç



Loomba, Friedman and Shulman. Cell. 2021

NAFLD: En sık KKH ve Siroz nedenidir

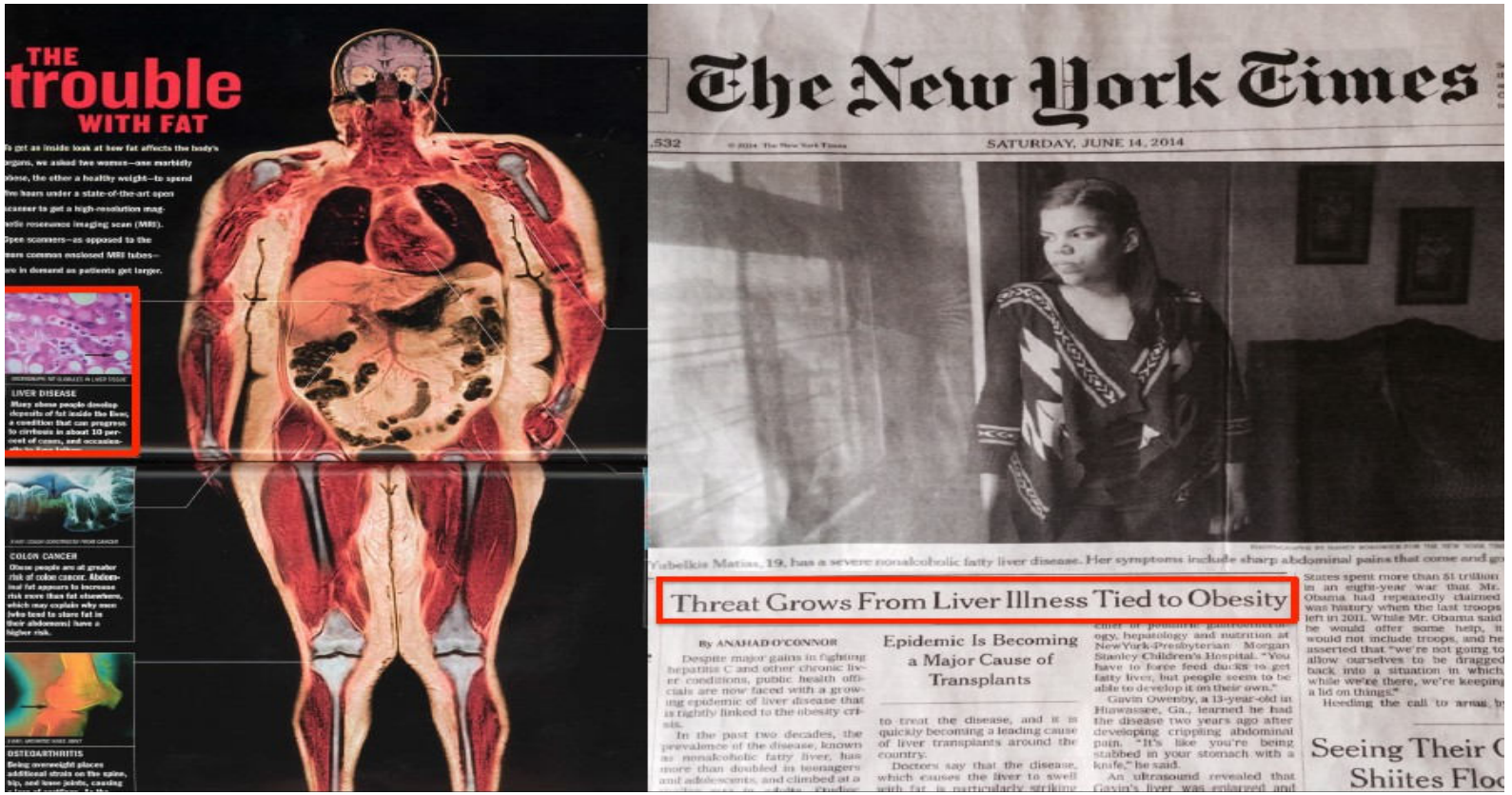


Setiawan VW, et al Noureddin. Hepatology 2016

Neden Nonalkolik yağlı Karaciğer Hastalığı?

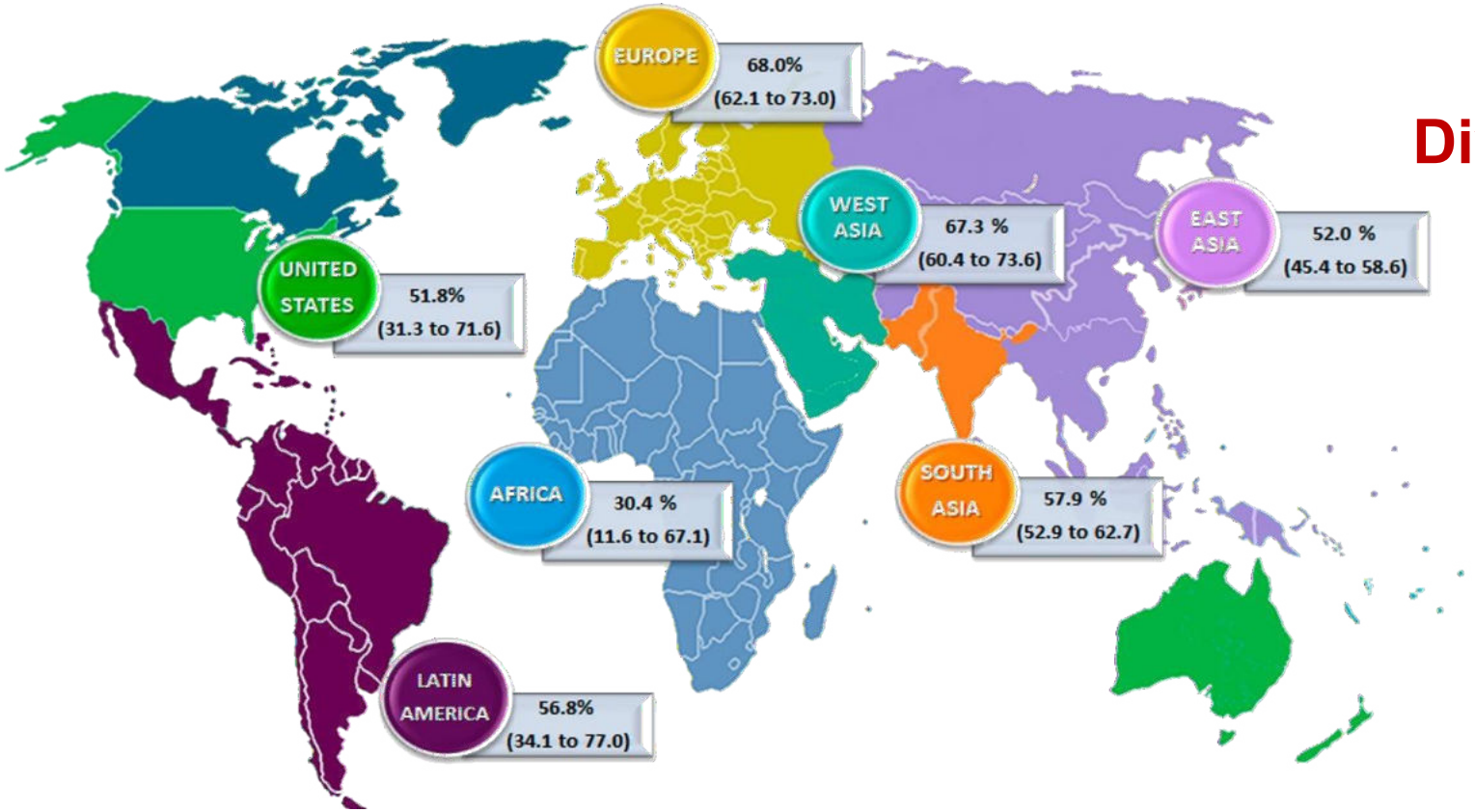
NAYKH Epidemisi!

Artan obezite/diyabet trendine bağlı olarak NAFLD dünya genelinde en yaygın görülen kronik karaciğer hastalığıdır ve karaciğer transplantasyonunun ve HCC'nin en önemli nedenidir[1].



1.Zobair M. Younossi Linda Henry. Economic and Quality-of-Life Implications of Non-Alcoholic Fatty Liver Disease. PharmacoEconomics, Springer International Publishing 2015

NAFLD ve NASH için En Önemli Risk Faktörü Metabolik Sendromdur



Diyabet varlığı olumsuz etkiler

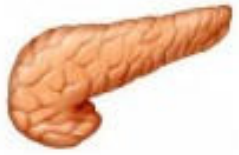
- Diyabetlilerde global NAFLD prevalansı 73%
- İleri(advanced) fibroz prevalansı (fibrosis ≥ F3) 17.2%
- Siroz, HCC, veya Karaciğer transplantasyonunda mortalitede ~2X artış

Nasrin Amiri A, et al. *Gastroenterol Hepatol Bed Bench*. 2017. 10:S1-S7. Younossi Z, et al. *Diabetes Care*. 2020.43:283-289

NAFLD Bağlantılı Non Hepatik Hastalıklar

Vasküler Hastalık

Diyabet



Obstruktif Uyku Apnesi

Serebrovasküler Hastalık

Kardiyak Hastalık

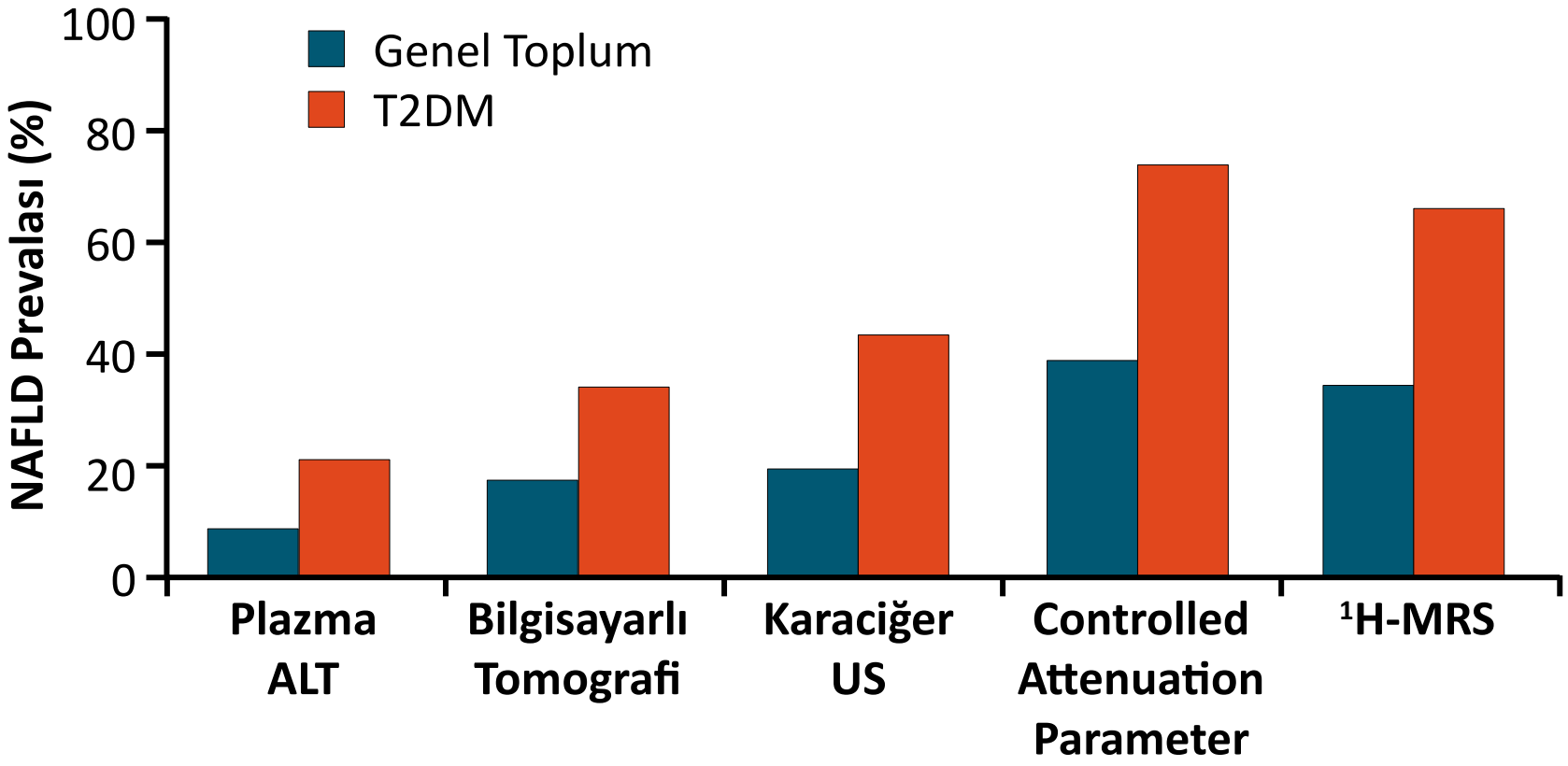
Author	N	FU (yr)	CVD Death	Findings
Angulo, 2015	619	12.6	38.3%	CVD most common COD Fibrosis predicts death
Söderberg, 2010	118	24	30%	↑Death in NASH, CVD most common COD
Ekstedt, 2006	129	13.7	16%	↑CVD death NASH CVD most common COD in NASH but no SS
Dam-Larsen, 2009	170	20.4	38%	No difference between SS and control
Rafiq, 2009	173	18.5	12.7%	CVD most common COD

Patient Characteristic	NAFLD (n=3869)	Control (n=15,209)	Fold Increase
Median age, yrs	53	NR	
Women, %	52	NR	
Diagnosed with malignancy, n (%)	580 (15)	1521 (10)	
Site of malignancy, incidence/100,000 PY			
• **Liver**	26.8	6.6	4
• **Stomach**	9.8	2.8	3.5
• **Pancreas**	19.6	7.2	2.7
• **Lung**	34.1	16.9	2

COD, cause of death; CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SS, simple steatosis

Angulo P, et al. *Gastroenterology*. 2015;149(2):389-397; Söderberg C, et al. *Hepatology*. 2010;51(2):595-602; Ekstedt M, et al. *Hepatology*. 2006;44(4):865-873; Dam-Larsen S, et al. *Scand J Gastroenterol*. 2009;44(10):1236-1243; Rafiq N, et al. *Clin Gastroenterol Hepatol*. 2009;7(2):234-238, Hicks. AASLD 2018. Abstr 31

Tip 2 DM Olan ve Olmayan Hastalarda Farklı Teşhis Yöntemlerinde NAFLD



Bril. Diabetes Care. 2017;40:419.

Fibrozis Teşhisi İçin En Sık Kullanılan Noninvasif Testler

Vibration-controlled transient elastography (FibroScan)

Serologic Markers

- **Simple**
  - FIB-4
  - NFS
- **Complex**
  - ELF
  - Pro-C3

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

AASLD

Imaging

- **Elastography**
  - VCTE
  - MRE
  - Multiparametric
  - ARFI

Liver stiffness

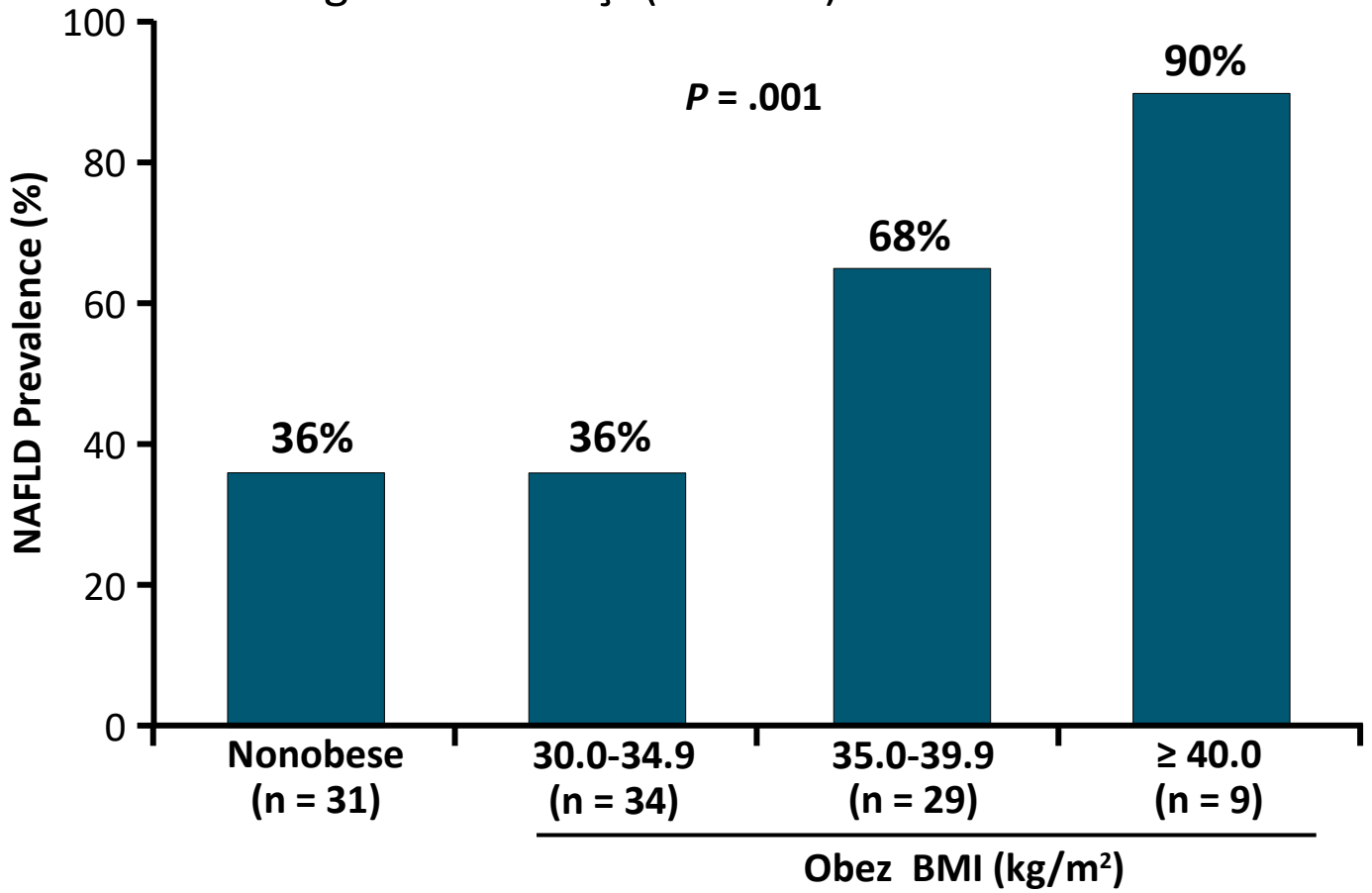
- Obtained through a VCTE measurement
- Correlated to extent of fibrosis

CAP

- Quantification of ultrasound attenuation obtained in VCTE measurement
- Correlated to liver steatosis

Normal AST veya ALT Değerleri olan Tip 2 DM'lu Hastalarda NAFLD ve NASH Prevalansı

- Normal AST veya ALT Değerleri olan Tip 2 DM'lu Hastalar karaciğer Trig içeriğini değerlendirmek için H-MRS ile değerlendirilmiş. (N = 103)

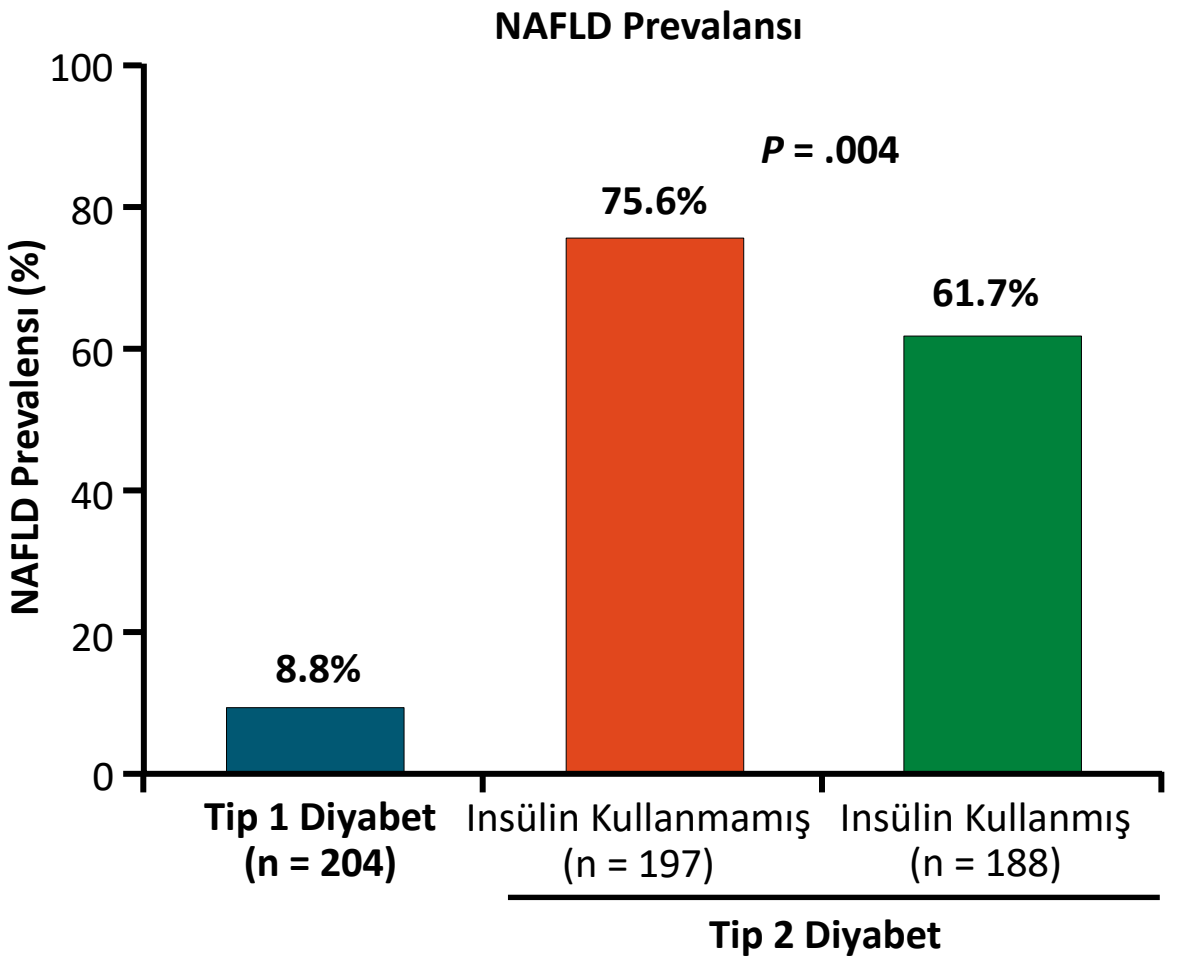


- NAFLD Prevalansı: 50%
  - Bunların içinde NASH prevalansı: 56%

Portillo-Sanchez. J Clin Endocrinol Metab. 2015;100:2231. Stål. World J Gastroenterol. 2015;21:11077.

Tip 1 ve 2 Diyabetli Hastalarda NAFLD Prevalansı

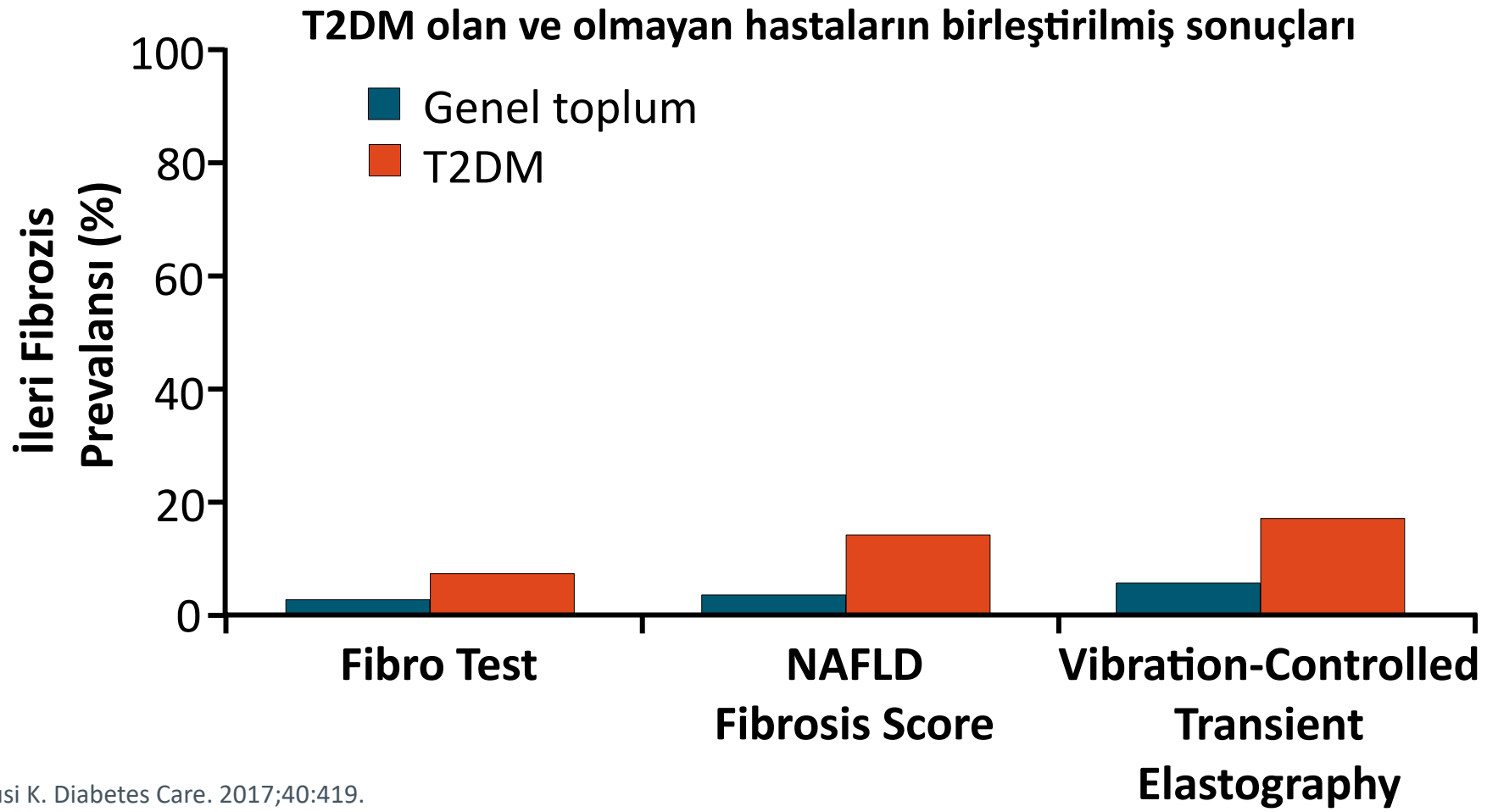
- Dört faz III çalışmadan elde edilen temel verilerin post hoc analizi(N = 589)
- Hariç tutma kriterleri: trigliseritler> 400 mg/dL ve ALT/AST > 2.5 x ULN



Cusi. Diabetes Obes Metab. 2017;19:1630.

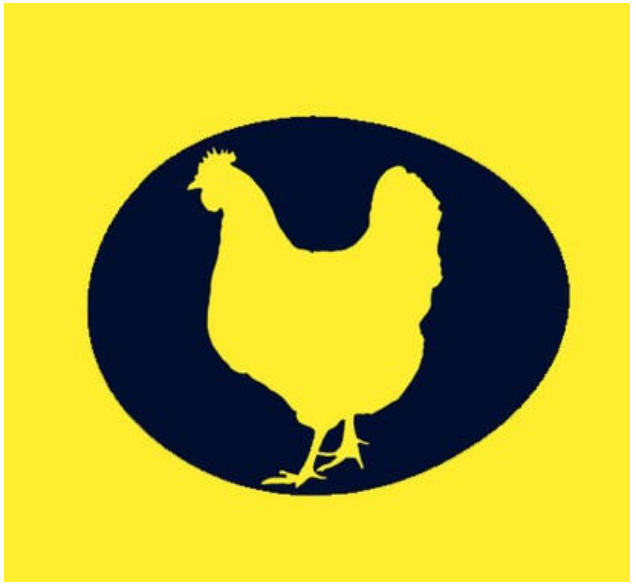
Farklı Tanısal Yöntemler ile T2DM Olan ve Olmayan Hastalarda İleri Fibrozis

- Meta-analiz (N = 3229)

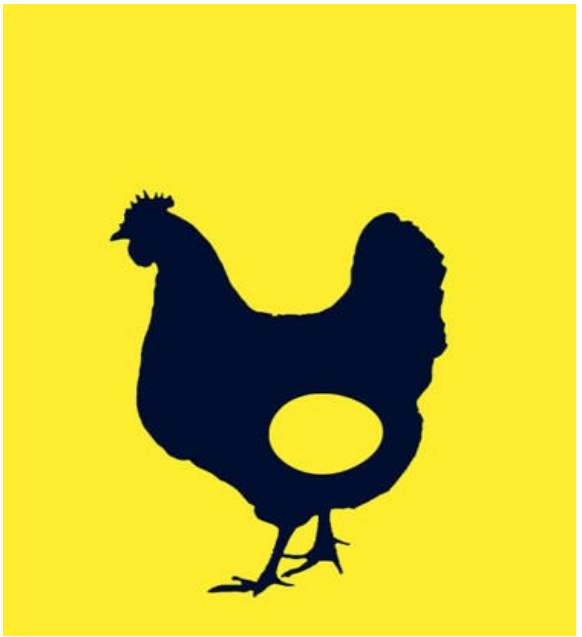


Neden Tip 2 Dm'nin Artan/Yeni Komplikasyonu?

Non-Alkolik Yağlı Karaciğer Hastalığı ve Tip2 DM tedavisi birlikte yönetilmelidir



Non-Alkolik Yağlı Karaciğer Hastalığı yeni tanılı Tip2 DM görülme sıklığını arttırır.[1]



Tip2 DM varlığı, Non-Alkolik Yağlı Karaciğer Hastalığının ileri formlarına ilerlemesinde anahtar rol oynar.(Nash, fibrozis, HCC)[2,3,4]

1. Ballestri S et al. Nonalcoholic fatty liver disease is associated with an almost two-fold increased risk of incident type 2 diabetes and metabolic syndrome. J Gastroenterol Hepatol 5;31:936
ossain N, Afendy A, Stepanova M, et al. Independent predictors of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7: 1224–9.e1-
dams LAet al. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. J Hepatol 2005;42:132–8.
4. Wang Cet al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. Int J Cancer 2012;130:1

Neden Tip Dm’nin Artan/Yeni Komplikasyonu?

NAYKH Tip2 Dm’nin yeni komplikasyonudur!

- NAFLD Tip2 DM’li hastalarda artarak yaygınlaşı
- NAFLD'nin varlığı daha kötü aterojenik dislipidemiye yol açarken ve hiperglisemi kontrolünü zorlaştırırken, T2DM varlığı ise NAF hastalarında karaciğer hastalıklarının progresyonunu hızlandırıyor.
- Özellikle plazma aminotransferazlarının NAFLD’li hastalarda karaciğer hasarının markerı olmadığı düşünülürse, Tip2 DM’li hastalarda sağlık hizmeti sağlayıcılarının NAFLD tanısı noktasında daha şüpheci olmaları gerekmektedir.

Neden Tip 2 Dm'nin Artan/Yeni Komplikasyonu?

Tip2 DM'li hastaların %80-90'nda Non-Alkolik Yağlı Karaciğer Hastalığı vardır.

Time to Include Nonalcoholic Steatohepatitis in the Management of Patients With Type 2 Diabetes

Kenneth Cusi[1,2]

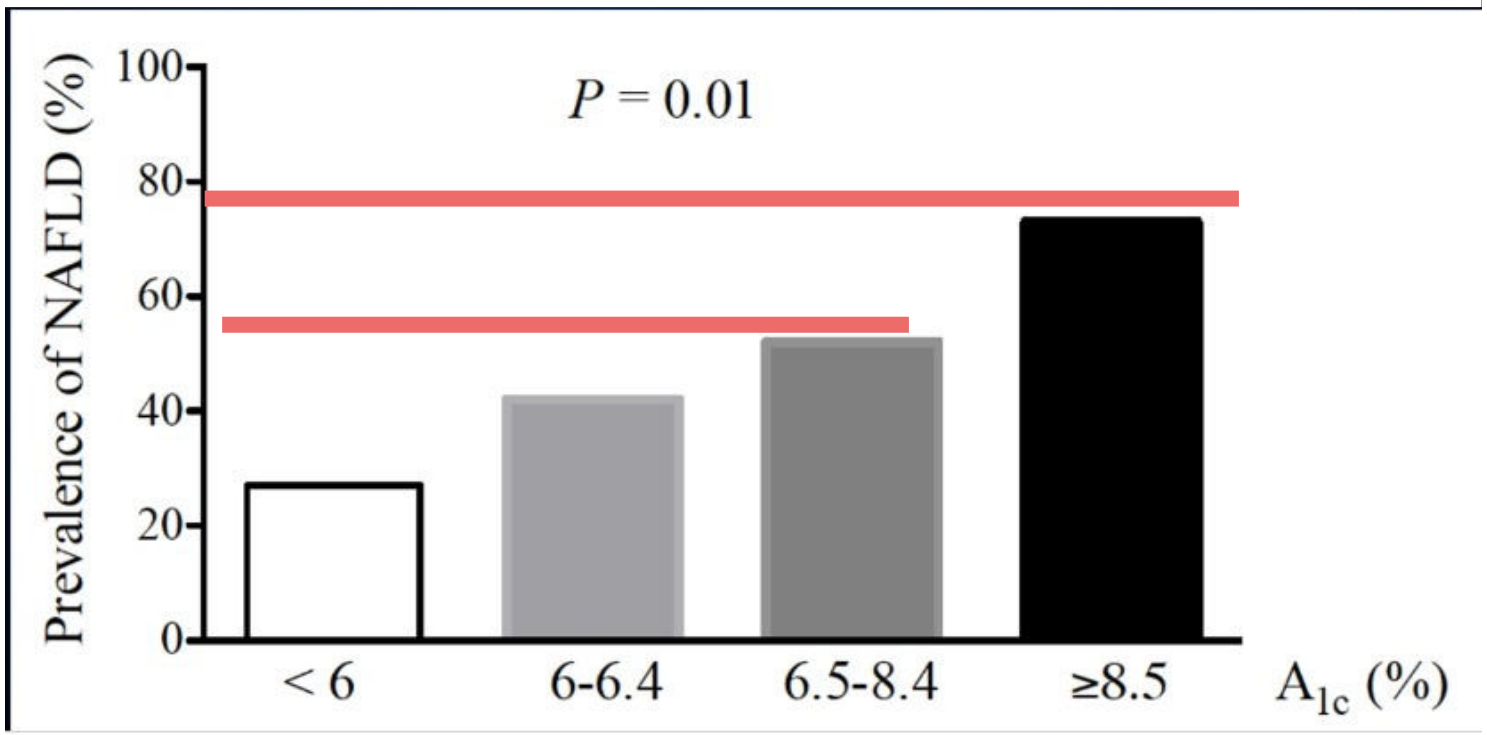
Diabetes Care 2020;43:275–279 | https://doi.org/10.2337/dci19-0064

- In summary,
  - it is time to include NASH in the management plan of patients with T2D in the same way as today it includes diabetic retinopathy or nephropathy.
  - The American Diabetes Association in the 2019 Standards of Care guidelines recommends that “patients with type 2 diabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for the presence of nonalcoholic steatohepatitis and liver fibrosis” (recommendation 4.14) (58).

Neden Tip 2 Dm'nin Artan/Yeni Komplikasyonu?

Her iki Tip2 DM hastasının birinde Non-Alkolik Yağlı Karaciğer Hastalığı bulunmaktadır[1]

AST/ALT seviyeleri normal T2DM'li hastalarda hiperglisemiye bağlı olarak Non-Alkolik Yağlı Karaciğer Hastalığı prevelansı artmaktadır.[2] N=103



1. **Nash Çalıştayı Sonuç Raporu 2018**
2. Paola Portillo-Sanchez et al, High Prevalence NAFLD in Patients With Type 2 DM and Normal Plasma Aminotransferase Levels J Clin Endocrinol Metab, June 2015, 100(6):2231–2238

2020 YILINDAN İTİBAREN ARTIK DİYABET KILAVUZLARINDA

American Diabetes Association®

Nonalcoholic Fatty Liver Disease

Recommendation

4.14 Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. C

Tip2 DM'li Hastalarda NAYKH Bakılmalıdır

Tip2 Dm ya da prediyabeti olanlar ve yüksek karaciğer enzimleri veya yağlı karaciğeri olanlar;

NASH ya da karaciğer fibrozisi için değerlendirilmelidir/ölçülmelidir.

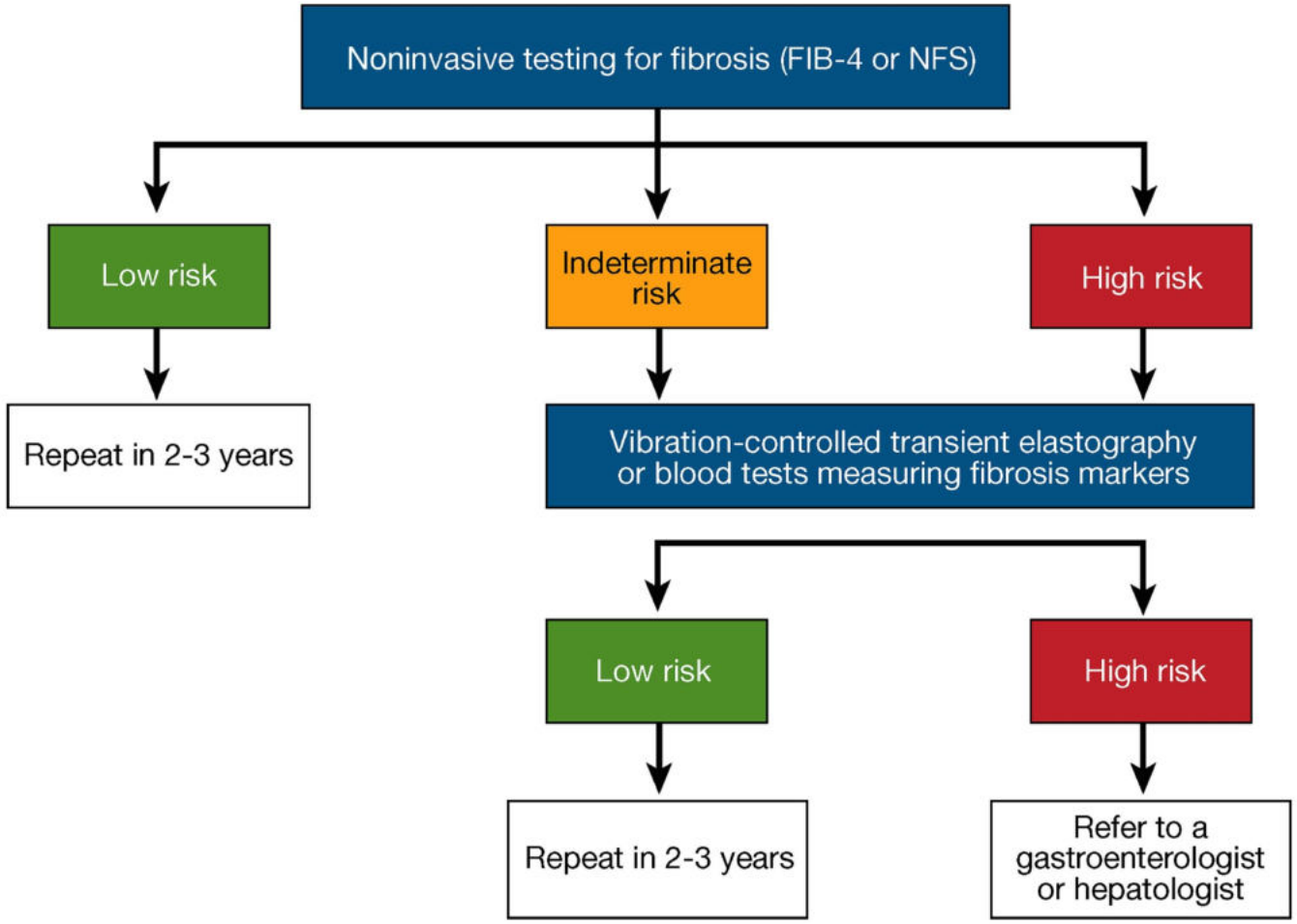
COMPREHENSIVE MEDICAL EVALUATION AND ASSESSMENT OF COMORBIDITIES

American Diabetes Association®

Nonalcoholic Fatty Liver Disease

Recommendation

4.10 People with type 2 diabetes or prediabetes with cardiometabolic risk factors, who have either elevated liver enzymes (ALT) or fatty liver on imaging or ultrasound, should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**



Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Care in Diabetes - 2023*. *Diabetes Care* 2023;46(Suppl. 1):S49-S67

Sık kullanılan noninvazif testler

Klinik veya Laboratuar Skorlar

Basit

- Fibrosis-4 (FIB-4) index
- NAFLD fibrosis score (NFS)
- AST/platelet ratio index

Proprietary

- Enhanced liver fibrosis panel (not available in US)
- NIS4
- ADAPT/Pro-C3 (not available in US)
- *FibroSure*
- Hepascore

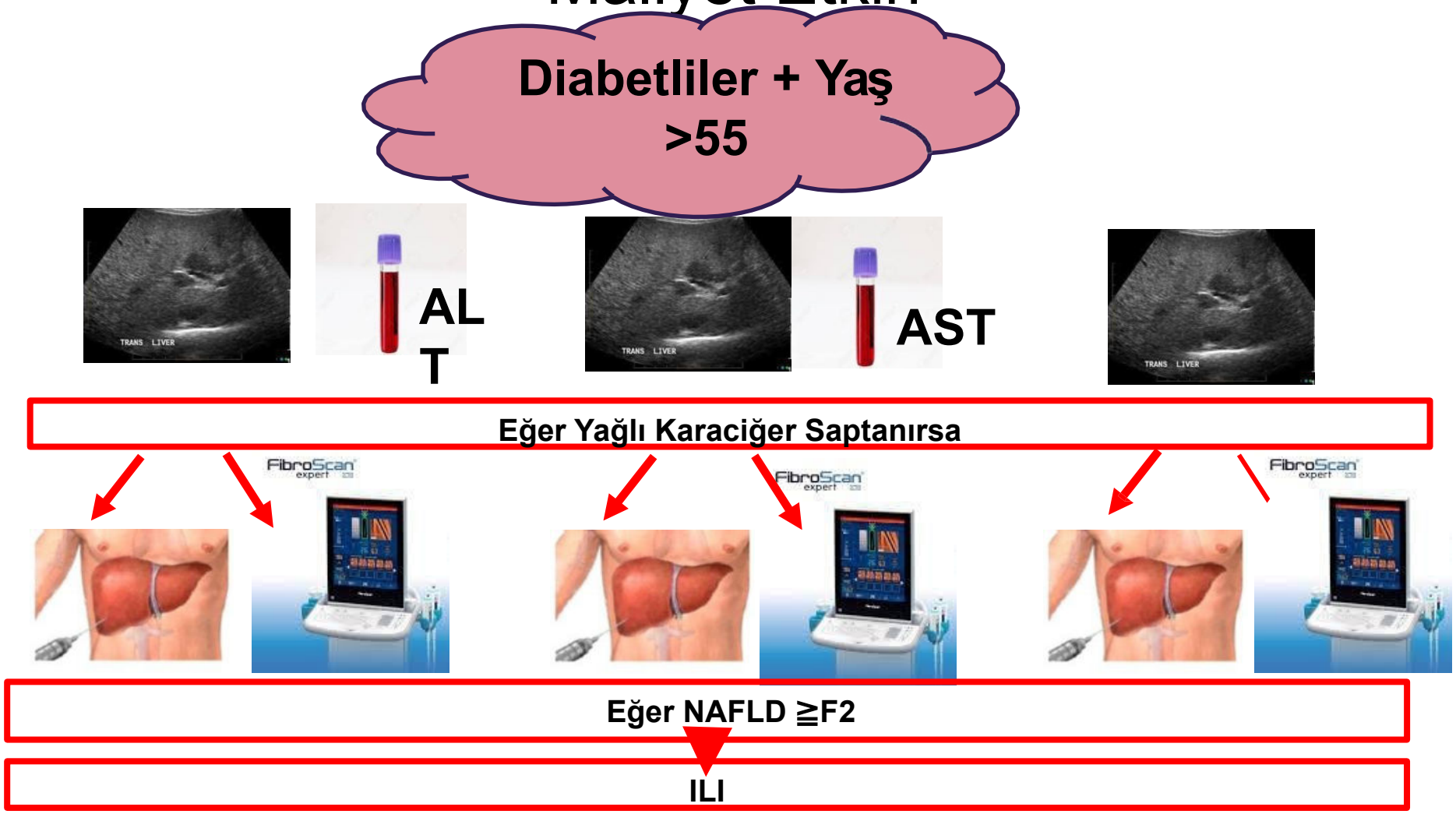
Görüntüleme

Elastography

- Transient elastography (eg, *FibroScan*)
- 2D shear wave elastography
- Magnetic resonance elastography
- Corrected T1 (*Liver MultiScan*)
- MRI-PDFF
- FAST score

Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. Daniels. Hepatology. 2019;69:1075. EASL. J Hepatol. 2015;63:237. Idilman. Radiology. 2013;267:767. Jayaswal. AASLD 2018. Abstr 1042. Jayaswal. Liver Int. 2020;40:3071. Newsome. Lancet Gastroenterol Hepatol. 2020;5:362. Sigrist. Theranostics 2017;7:1303. Harrison. Lancet Gastroenterol Hepatol. 2020;5:970.

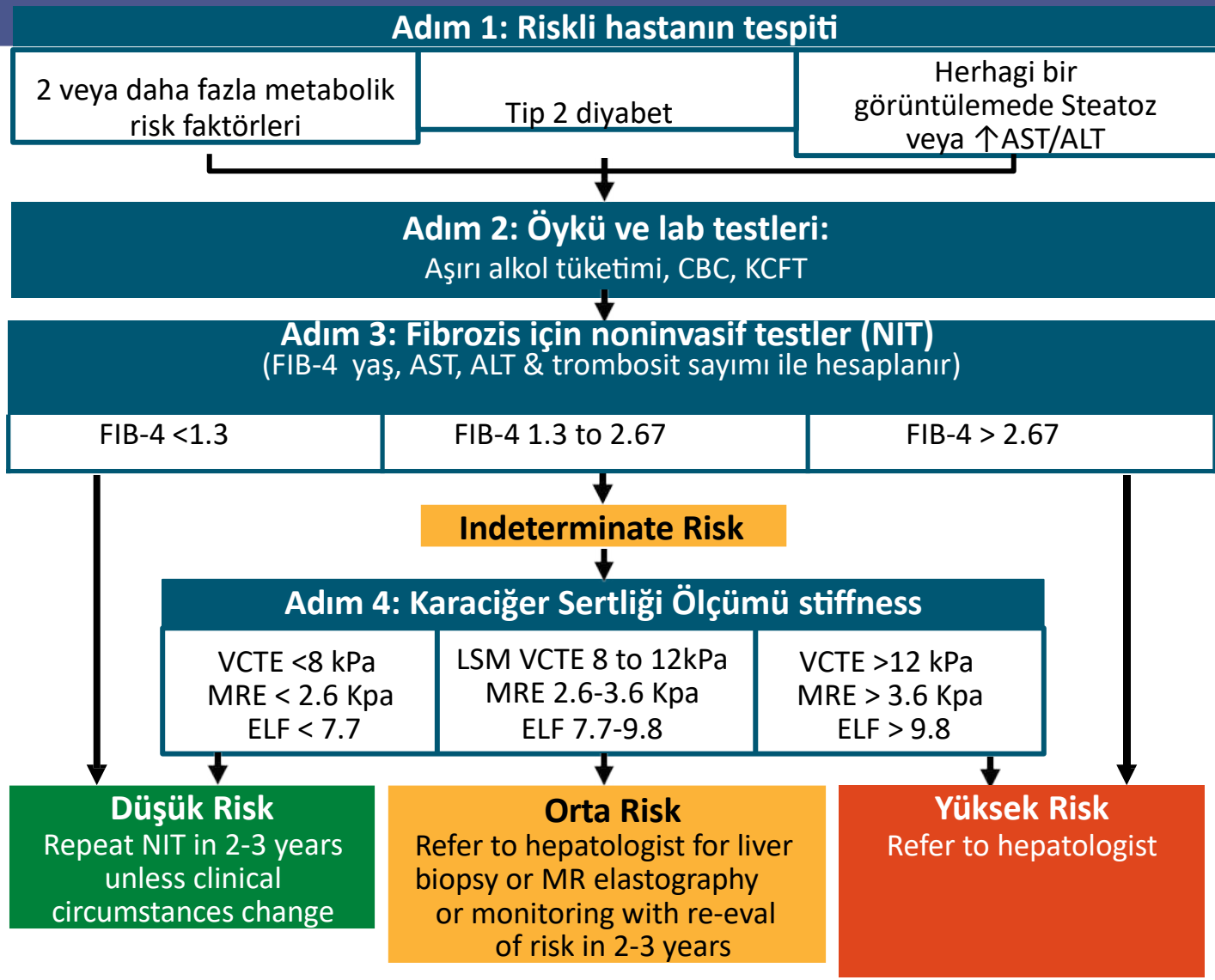
T2 Diyabetli kişilerde NAFL Taraması: Maliyet Etkin



Noureddin M, et al. Gastroenterology. 2020.

AGA: Klinik Bakım Süreci- modifiye

Primer bakım, endokrinologlar, gastroenterologlar, iç hastalıkları uzmanları İleri Fibrozisli NAFLD'ı taramalılar

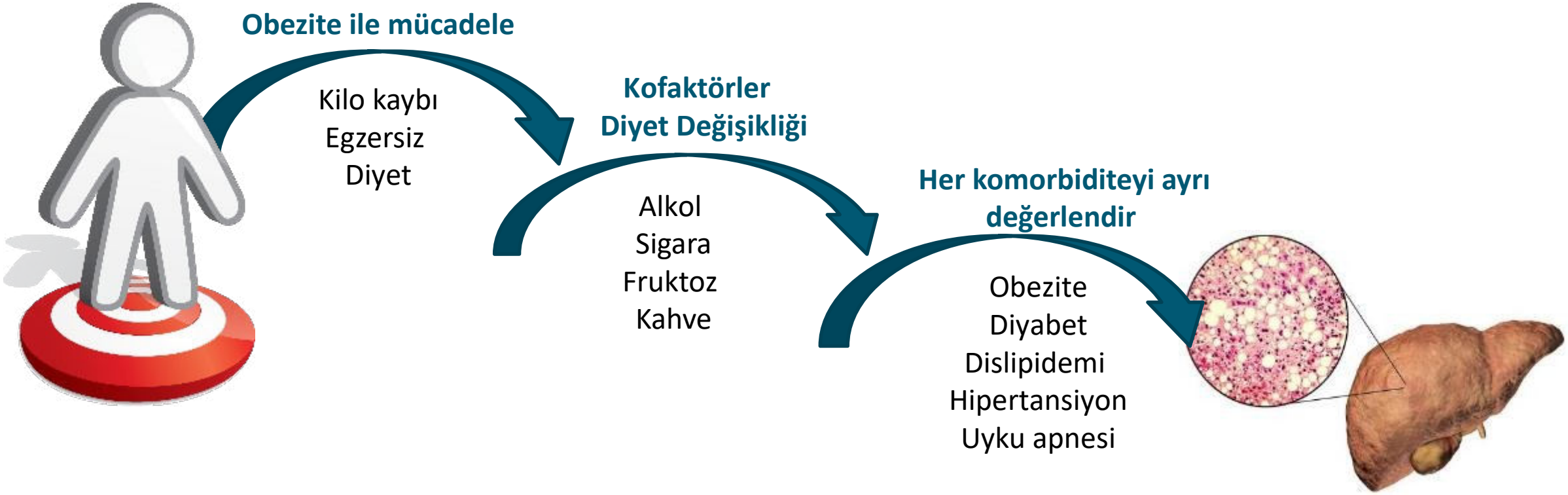


Midified Kanwal. Gastroenterology 2021;161:1657–1669

Hasta Merkezli/Bireyselleştirilmiş Tedavi

FDA-onaylı tedavi yokluğunda,

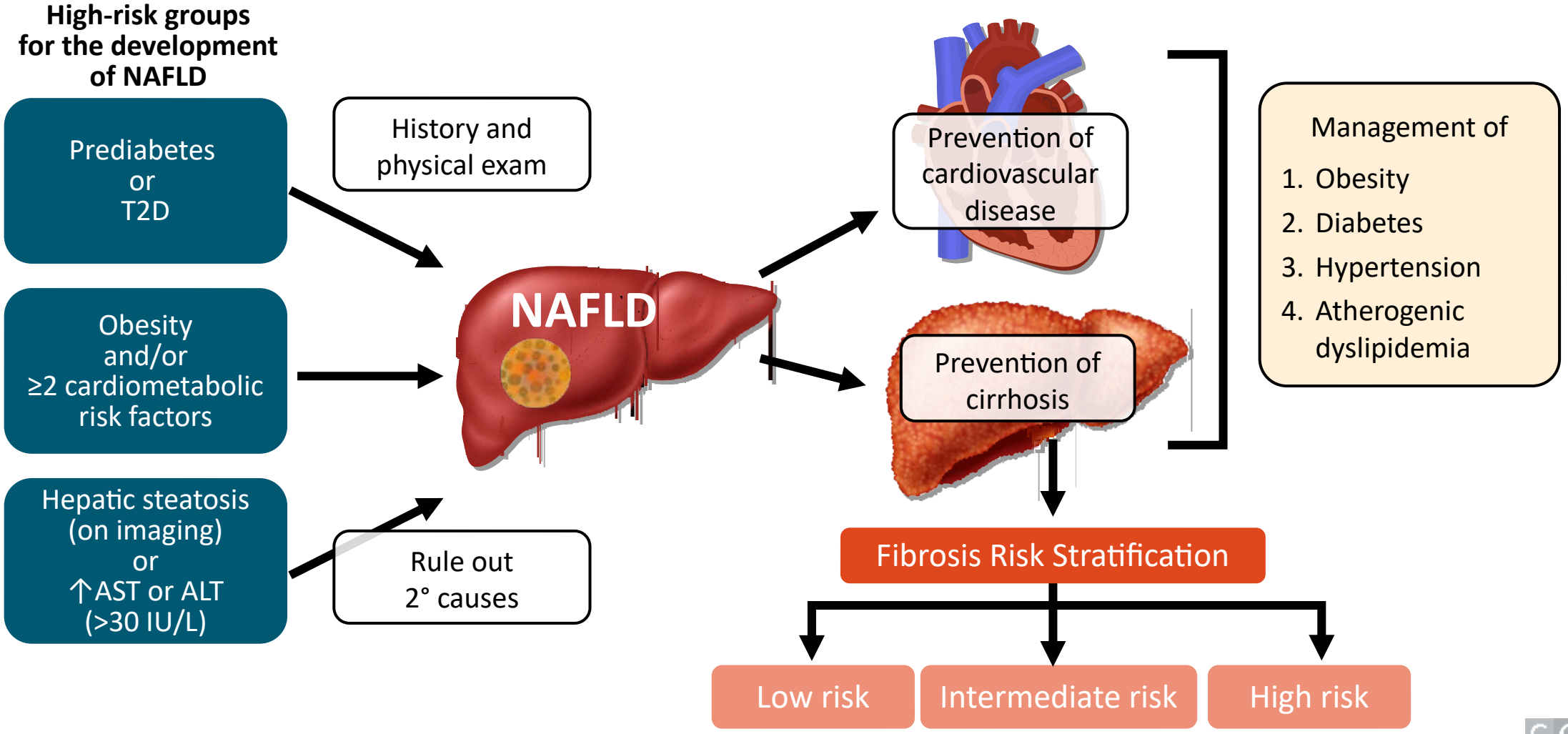
Metabolik sendrom parçalarının erken teşhis ve tedavisi karaciğer ilişkili mortaliteyi azaltmak için KRİTİK



Chalasani. Hepatology. 2018;67:328. Ando. Clin Liver Dis (Hoboken). 2021;17:23.

Slide credit: clinicaloptions.com

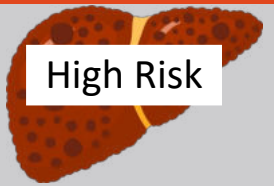
Management Algorithm for NAFLD: Recommendations from AACE 2022



Cusi. Endocr Pract. 2022;28:528.

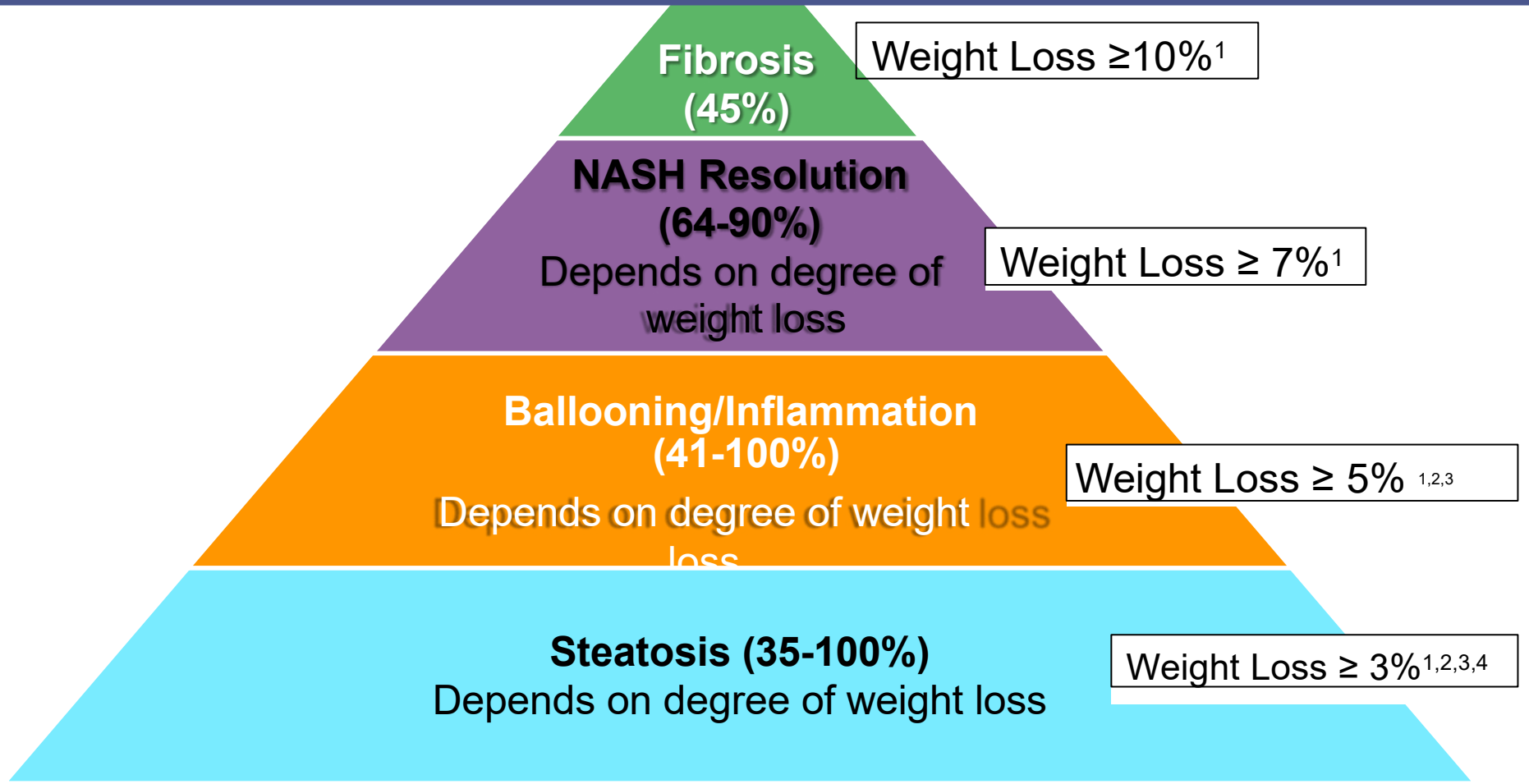
Slide credit: clinicaloptions.com

Weight Management in NAFLD

	Fibrosis Risk Stratification		
	 Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	 Indeterminate Risk FIB-4: 1.3-2.67 LSM 8-12 kPa ELF 7.7-9.8	 High Risk FIB-4: >2.67 LSM >12 kPa ELF >9.8
General lifestyle changes	Decrease sedentary time and increase daily movement; stress reduction through exercise and other methods		
Dietary recommendations	Creating an energy deficit is the priority with reduction of saturated fat, starch, and added sugars Persons with cirrhosis need an individualized nutritional assessment and treatment plan		
Exercise	To improve cardiometabolic health support weight loss and mitigate sarcopenia, aerobic exercise for 30-60 min (3-5 days/wk) + resistance training 20-30 min (2-3 times/wk)		
Alcohol intake	Minimize	Minimize	Avoid if F3 or cirrhosis (F4)
Weight loss goal to treat NAFLD (if overweight or obesity)	Greater weight loss associated with greater liver and cardiometabolic benefit		
Weight loss tools	Behavioral modification counseling, in-person or remote programs	Greater intensity of weight loss to reverse steatohepatitis and fibrosis	Specialized obesity management, with a structured program, antiobesity medications, bariatric surgery
Medical therapy to treat obesity	Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liraglutide 3 mg/day, semaglutide 2.4 mg/wk	GLP-1 RA preferred for NASH	GLP-1 RA preferred for NASH
Bariatric surgery	Consider to treat obesity and comorbidities	Strong consideration to treat steatohepatitis and fibrosis	Stronger consideration to treat steatohepatitis and fibrosis; avoid in decompensated cirrhosis

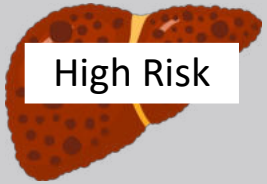
Cusi. Endocr Pract. 2022;28:528.

Kilo Kaybı Piramidi



1 Vilar-Gomez. Gastroenterology 2015;
2 Promrat. Hepatology 2010;
3 Harrison. Hepatology 2009;
4 Wong. J Hepatol 2013

NAFLD’da Hipertansiyon Yönetimi

	Fibrosis Risk Stratification		
	 Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	 Indeterminate Risk FIB-4: 1.3-2.67 LSM 8-12 kPa ELF 7.7-9.8	 High Risk FIB-4: >2.67 LSM >12 kPa ELF >9.8
General goal	Optimize BP control and improve cardiovascular health using preferred agents, whenever possible Assess every 3 mo and intensify therapy until goal achieved		
Goal (individualize)	Systolic <130 mm Hg Diastolic <80 mm Hg	Systolic <130 mm Hg Diastolic <80 mm Hg	Systolic <130 mm Hg Diastolic <80 mm Hg Individualize of decompensated cirrhosis
Dietary recommendations	In addition to general dietary recommendations, reduce sodium & increase high potassium foods (eg, DASH diet)		
Pharmacotherapy for hypertension	First-line therapy: ACEIs and ARBs	First-line therapy: ACEIs and ARBs	Same but avoid ACEI or ARB if decompensated cirrhosis
Intensification of therapy	Second agent: CCB, BB or thiazide diuretic (as additional agents as needed)		Same but individualize if decompensated cirrhosis. Use diuretics with caution (risk of excessive diuresis)
Additional options	Additional BP medication choices: alpha-blockers, central agents, vasodilators, aldosterone antagonist		Same but individualize if decompensated cirrhosis

Cusi. Endocr Pract. 2022;28:528.

Slide credit: clinicaloptions.com

Dislipidemi ve Kardiyovasküler Risk Azaltımı

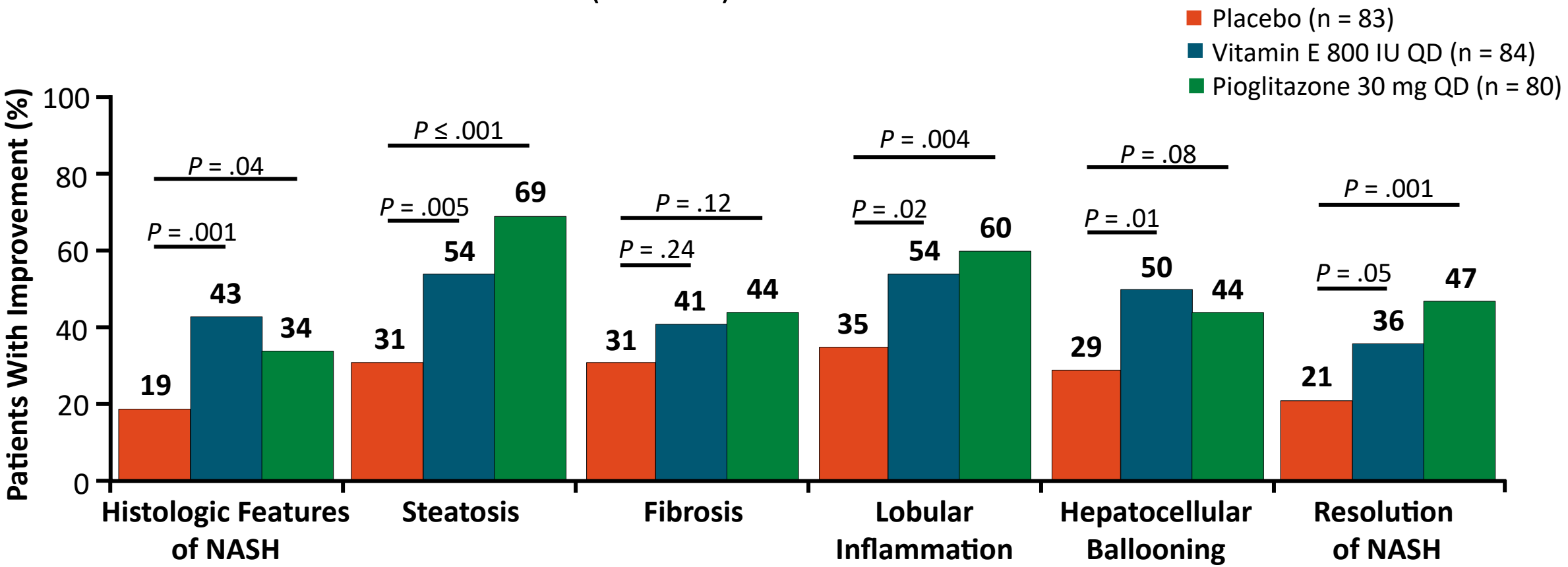
Lipid risk levels are similar in the presence of NAFLD or NASH			
General goal	Early intensive management of dyslipidemia needed to reduce cardiovascular risk; intensify therapy until lipid goal is reached		
Dietary recommendations	Increase fiber intake (>25 g/day), prioritize vegetables, fruits whole grains, nuts, reduce saturated fat and added sugars (eg, Mediterranean diet)		
Lipid risk levels	**High CV Risk** ≥2 risk factors and 10-yr risk 10%-20% Diabetes or CKD ≥3 with no other risk factors	**Very high CV Risk** Established CVD or a 10-yr risk >20% Diabetes with >1 risk factor, CKD ≥3, HeFH	**Extreme CV Risk** Progressive CVD CVD + diabetes or CKD≥3 or HeFH FHx premature CVD (>55 yr male, <65 yr female)
LDL-C goal (mg/dL)	<100	<70	<55
Non–HDL-C goal (mg/dL)	<130	<100	<80
Triglycerides goal (mg/dL)	<150	<150	<150
ApoB goal (mg/dL)	<90	<80	<70
First line pharmacotherapy: statins	Use a moderate- to high-intensity statin, unless contraindicated Statins are safe in NAFLD or NASH but do not use in decompensated cirrhosis (Child C)		
If LDL-C not at goal: intensify statin therapy	Use higher dose or higher potency statin		
If LDL-C not at goal (or statin intolerant): add 2nd agent, then add 3rd agent	Ezetimibe, PCSK9 inhibitor, bempedoic acid, colesevelam, inclisiran		
If triglycerides >500 mg/dL	Fibrates, Rx grade omega 3 FA, icosapent ethyl (if diabetes, optimize glycemic control and consider pioglitazone)		
If TG 135-499 mg/dL on max statin dose	Emphasize diet (as above)	Add icosapent ethyl	Add icosapent ethyl

Cusi. Endocr Pract. 2022;28:528.

Slide credit: clinicaloptions.com

PIVENS: NASH olan Hastalarda 96-Hafta Pioglitazone ve Vitamin E Tedavisi

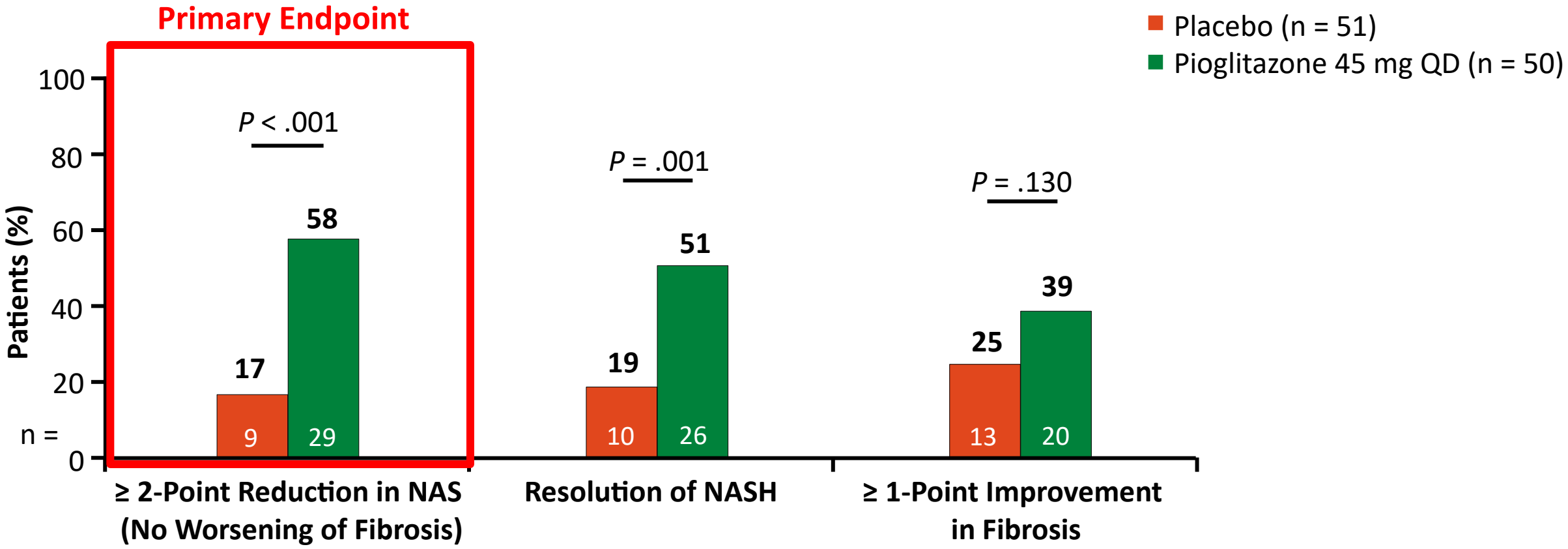
- Double-blind, placebo-controlled, randomized phase III study in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)



Sanyal. NEJM. 2010;362:1675.

NASH ve Prediyabet veya Tip 2 Diyabette Pioglitazon: 18-Aylık Sonuçlar

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



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

JAMA Internal Medicine | Original Investigation

Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis

A Meta-analysis

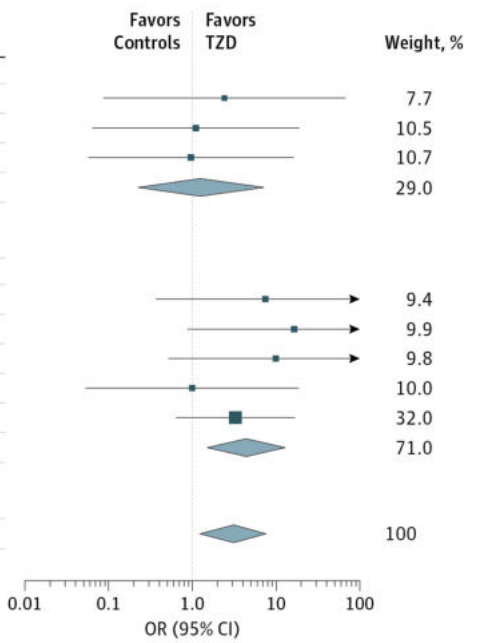
Giovanni Musso, MD; Maurizio Cassader, PhD; Elena Paschetta, MD; Roberto Gambino, PhD

Thiazolidinedione Therapy (TZD) and Improvement in Advanced Fibrosis, Improved Fibrosis of Any Stage, and Nonalcoholic Steatohepatitis (NASH) Resolution

JAMA Intern Med. 2017 May 1;177(5):633-640

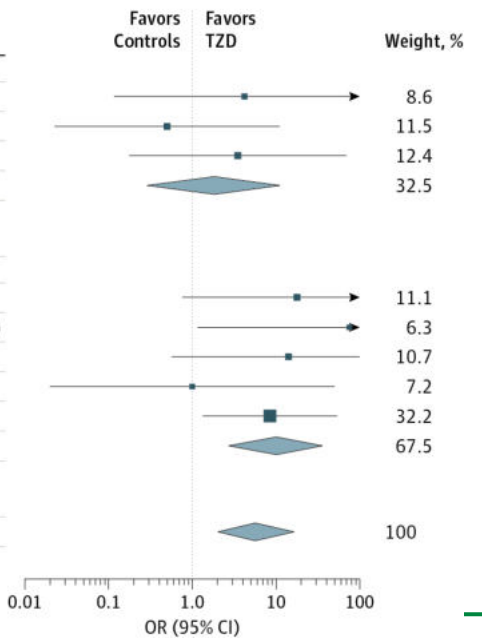
A All patients with NASH

Source	TZD No. of Events	TZD No. of Patients	Control No. of Events	Control No. of Patients	Odds Ratio (95% CI)	Weight, %
Rosiglitazone maleate						
Idilman et al,[19] 2008	1	11	0	8	2.43 (0.09-67.57)	7.7
Omer et al,[21] 2010	1	20	1	22	1.11 (0.06-18.93)	10.5
Ratziu et al,[18] 2008	1	32	1	31	0.97 (0.06-16.19)	10.7
Total (95% CI)	3	63	2	61	1.30 (0.23-7.20)	29.0
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=0.19$; $P=.91$; $I^2=0\%$ Overall effect: $z=0.30$; $P=.77$						
Pioglitazone hydrochloride						
Aithal et al,[17] 2008	3	31	0	30	7.49 (0.37-151.50)	9.4
Belfort et al,[16] 2006	7	26	0	21	16.54 (0.89-308.98)	9.9
Cusi et al,[12] 2016	4	50	0	51	9.97 (0.52-190.16)	9.8
Sanyal et al,[15] 2004	1	10	1	10	1.00 (0.05-18.57)	10.0
Sanyal et al,[20] 2010	6	80	2	83	3.28 (0.64-16.78)	32.0
Total (95% CI)	21	197	3	195	4.53 (1.52-13.52)	71.0
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=2.39$; $P=.66$; $I^2=0\%$ Overall effect: $z=2.71$; $P=.007$						
Total (95% CI)	24	260	5	256	3.15 (1.25-7.93)	100
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=4.12$; $P=.77$; $I^2=0\%$ Overall effect: $z=2.44$; $P=.01$						

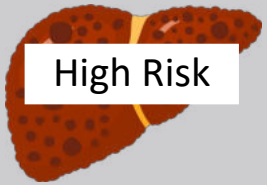


B Patients with NASH with advanced fibrosis at baseline

Source	TZD No. of Events	TZD No. of Patients	Control No. of Events	Control No. of Patients	Odds Ratio (95% CI)	Weight, %
Rosiglitazone maleate						
Idilman et al,[19] 2008	1	3	0	3	4.20 (0.12-151.97)	8.6
Omer et al,[21] 2010	1	7	1	4	0.50 (0.02-11.09)	11.5
Ratziu et al,[18] 2008	1	5	1	15	3.50 (0.18-69.34)	12.4
Total (95% CI)	3	15	2	22	1.84 (0.29-11.66)	32.5
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=1.06$; $P=.59$; $I^2=0\%$ Overall effect: $z=0.65$; $P=.52$						
Pioglitazone hydrochloride						
Aithal et al,[17] 2008	3	7	0	11	17.89 (0.76-420.49)	11.1
Belfort et al,[16] 2006	7	7	0	2	75.00 (1.16-4868.64)	6.3
Cusi et al,[12] 2016	4	7	0	5	14.14 (0.57-352.00)	10.7
Sanyal et al,[15] 2004	1	2	1	2	1.00 (0.02-50.40)	7.2
Sanyal et al,[20] 2010	6	12	2	19	8.50 (1.33-54.13)	32.2
Total (95% CI)	21	35	3	39	10.17 (2.83-36.54)	67.5
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=2.43$; $P=.66$; $I^2=0\%$ Overall effect: $z=3.55$; $P<.001$						
Total (95% CI)	24	50	5	61	5.84 (2.04-16.71)	100
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=5.71$; $P=.57$; $I^2=0\%$ Overall effect: $z=3.29$; $P=.001$						



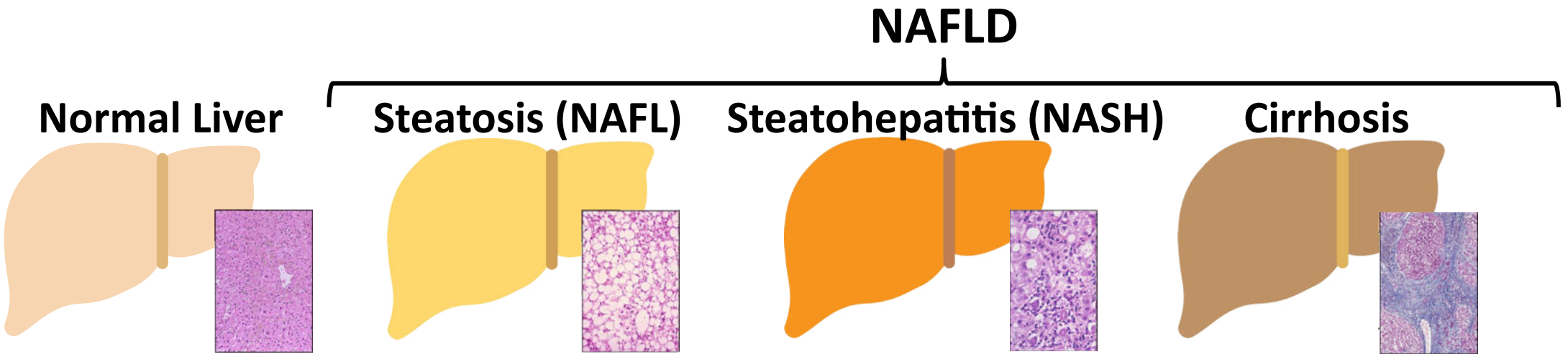
NAFLD’da Diyabet Yönetimi

	Fibrosis Risk Stratification		
	 Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	 Indeterminate Risk FIB-4: 1.3-2.67 LSM 8-12 kPa ELF 7.7-9.8	 High Risk FIB-4: >2.67 LSM >12 kPa ELF >9.8
General goal	Optimize glycemic control using preferred agents that reverse steatohepatitis, whenever possible Prefer GLP-1 RA and SGLT2i in CVD Prefer SGLT2i in CKD and HF		
Dietary recommendations	Glycemic load reduction via emphasis on whole food carbohydrates (vegetables, legumes, fruit) versus sugar/processed carbohydrates		
Individualize A1c target	≤6.5% for persons without concurrent serious illness and at low hypoglycemic risk (>6.5% otherwise)		In advanced cirrhosis, caution with risk of hypoglycemia and avoid oral agents
Preferred diabetes pharmacotherapy	Consider agents that reduce liver fat (pioglitazone, GLP-1 RA, SGLT2i)	Strongly consider agents with efficacy in NASH: pioglitazone and/or GLP-1 RA No evidence that SGLT2i improve steatohepatitis	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA No efficacy data in cirrhosis
Metformin, sulfonylurea, DPP-4i, acarbose, and insulin	May continue but limited benefit on liver histology in NAFLD	May continue but limited benefit on liver histology in NAFLD	May continue (F2-F3) but avoid oral agents if advanced cirrhosis present Cannot avoid insulin in patients with advanced liver cirrhosis; often only option

Cusi. Endocr Pract. 2022;28:528.

Slide credit: clinicaloptions.com

Patofizyolojik Süreçleri Hedefleme



Targets related to insulin resistance and/or lipid metabolism

PPARγ: Pioglitazone
GLP-1: Liraglutide, Semaglutide
ACC: GS-0976
SCD1: Aramchol
FGF21: BMS-986036
THR-β: MGL-3196, VK 2807

Targets related to lipotoxicity and oxidative stress

PPARα/∂: Elafibranor
FXR: OCA, GS-9674, Tropifexor
FGF19: NGM282
Vitamin E

Targets related to inflammation and immune activation

CCR2/5: Cenicriviroc
TLR4: JKB-121

Targets related to cell death (apoptosis and necrosis)

ASK1: Selonsertib

Targets related to fibrogenesis and collagen turnover

Galectin: GR-MD-02

TABLE 1. Comparison of NAFLD Management Guidelines in Adults From the United States (AASLD), Europe (EASL-EASD-EASO), and United Kingdom (NICE)[3,4,18,19]

Guidelines	Diagnostic criteria	Screening strategy; diagnostic tests and prognostic scores	Evaluation and monitoring of fibrosis; liver biopsy	Lifestyle interventions	Pharmacotherapy
AASLD 2018[3]	Evidence of HS (≥5%) by imaging or histology Exclusion of secondary causes of HS (no significant alcohol consumption, no existing liver disease) Alcohol consumption threshold (weekly): >21 drinks in men or >14 drinks in women (United States standard drink, 14 g of alcohol)	No systematic screening No screening in high-risk groups; but "vigilance" for chronic liver disease in T2D HS imaging: US; MRI is better but routine availability limited Assess risk of CVD and T2D Presence of metabolic disease most potent predictor of adverse outcome	Serum biomarkers Clinical decision aids: NFS or FIB-4 Imaging: TE or MRE Monitoring: no information Liver biopsy with advanced liver fibrosis suggested by serum or noninvasive imaging tools Liver biopsy with MetS + risk liver inflammation	Structured programs: weight loss, healthy diet, regular physical activity 500-1000 kcal deficit; 3%-5% weight loss improves HS; 7%-10% weight loss improves NASH (including fibrosis) Moderate-intensity exercise Macronutrients/diet: no information	For NASH + fibrosis Metformin: not recommended Pioglitazone: may be used in adult T2D + biopsy-proven NASH GLP-1 RAs: insufficient data Vitamin E: may be used in nondiabetic adult + biopsy-proven NASH UCDA: not recommended Omega-3 fatty acids: may be used in adult hypertriglyceridemia + NAFLD Statins: may be used in adults + dyslipidemia + NAFLD or NASH
EASL-EASD-EASO 2016[4]	HS in >5% hepatocytes by imaging or histology Associated with insulin resistance Exclusion of secondary causes (no significant alcohol consumption) Alcohol consumption threshold (daily): >30 g in men or >20 g in women	No community screening Screening in high-risk groups by US or liver enzymes HS imaging: US; MRI is "gold standard," but availability and cost issues HS score: FLI (SteatoTest) or NAFLD liver fat score Assess risk of CVD and T2D	Serum biomarkers Clinical decision aids: NFS or FIB-4 Imaging: TE (in combination with biomarkers/scores, as less reliable with high BMI) Monitoring for progression: NASH ± fibrosis, yearly; NASH cirrhosis, every 6 months Liver biopsy when medium/high risk of advanced liver fibrosis suggested by serum or noninvasive imaging tools	Structured programs: weight loss, healthy diet, regular physical activity 500-1000 kcal deficit; 7%-10% weight loss to improve HS and NASH 150-200 min/wk moderate-intensity aerobic and resistance training (split into shorter sessions) Diet: low to moderate fat + moderate to high carbohydrates; low-carbohydrate ketogenic or high protein	For NASH + fibrosis For early NASH + high risk of progression Metformin: insufficient evidence Pioglitazone: may be used in adult NASH with T2D (off-label outside T2D) GLP-1 RAs: initial data favorable; insufficient evidence Vitamin E: may be used in noncirrhotic nondiabetic adult + NASH; more data needed UCDA: no effect observed Omega-3 fatty acids: insufficient data to support use Statins: no benefit or harm to liver disease

Mayo Clin Proc. 2022;97(9):1700-1716

Guidelines	Diagnostic criteria	Screening strategy; diagnostic tests and prognostic scores	Evaluation and monitoring of fibrosis; liver biopsy	Lifestyle interventions	Pharmacotherapy
NICE[18]	Excessive fat in liver Exclusion of secondary causes (no significant alcohol consumption) Alcohol consumption threshold (daily): >30 g in men or >20 g in women	No community screening Consider that NAFLD is common in T2D and MetS	ELF blood test Monitoring: ELF negative, reassess every 3 years; ELF positive, referral to hepatologist Liver biopsy is the gold standard for diagnosis but impractical to use widely in at-risk patients	Consider NICE guidelines for obesity excessive weight gain	For NASH + fibrosis Metformin: not mentioned Pioglitazone: consider use regardless of diabetes status GLP-1 RAs: not mentioned UCDA: not mentioned Omega-3 fatty acids: not recommended Statins: continue use if already taking statins; stop if liver enzymes elevate (×2 within 3 months) Vitamin E: consider use regardless of diabetes status

AASLD, American Association for the Study of Liver Diseases; BMI, body mass index; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; FLI, fatty liver index; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HS, hepatic steatosis; MetS, metabolic syndrome; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NICE, National Institute for Health and Care Excellence; T2D, type 2 diabetes; TE, transient elastography; UCDA, ursodeoxycholic acid; US, ultrasound.

Mayo Clin Proc. 2022;97(9):1700-1716

Uygun Tedavilerin Güvenlik ve Tolere Edilebilirlikleri (Off Label)

Vitamin E (800 IU/day)

- Possible all-cause mortality risk at > 800 IU/day[1]
- Increased hemorrhagic stroke risk[2]
  - Also shows reduced ischemic stroke risk
- Increased prostate carcinoma risk (HR vs placebo: 1.17; 99% CI: 1.004-1.36; *P* = .008)[3]

Pioglitazone

- Edema, weight gain (~ 2-3 kg over 2-4 yrs)[4]
- Risk of osteoporosis in women[5]

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. Schurks. BMJ. 2010;341:c5702. 3. Klein. JAMA. 2011;306:1549.
4. Bril. Diabetes Care. 2017;40:419. 5. Yau. Curr Diab Rep. 2013;13:329. 6. Tuccori. BMJ. 2016;352:i1541.
7. Lewis. JAMA. 2015;314:265. 8. Davidson. Diabetes Complications. 2016;30:981.

Pioglitazone: Mesane Kanseri ?

Original Investigation

Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons With Diabetes

James D. Lewis, MD, MSCE; Laurel A. Habel, PhD; Charles P. Quesenberry, PhD; Brian L. Strom, MD, MPH; Tiffany Peng, MA; Monique M. Hedderson, PhD; Samantha F. Ehrlich, PhD; Ronac Mamtani, MD, MSCE; Warren Bilker, PhD; David J. Vaughn, MD; Lisa Nessel, MSS, MLSP; Stephen K. Van Den Ee

193,099 patients
10 yıllık izlem
HR 1.06 (95% CI 0.89-1.26)

IMPORTANCE St

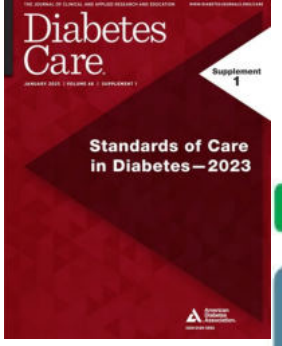
OBJECTIVE To e k of bladder and 10 a

DESIGN, SETTING, AND PARTICIPANTS Cohort and nested case-control analyses among persons with diabetes. A bladder cancer cohort followed 193 099 persons aged 40 years or older in 1997-2002 until December 2012; 464 case patients and 464 matched controls were surveyed about additional confounders. A cohort analysis of 10 additional cancers included 236 507 persons aged 40 years or older in 1997-2005 and followed until June 2012. Cohorts were from Kaiser Permanente Northern California.

Editorial pages 233 and 235

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and CME Questions page 293



USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit **EITHER/OR** SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If A1C above target

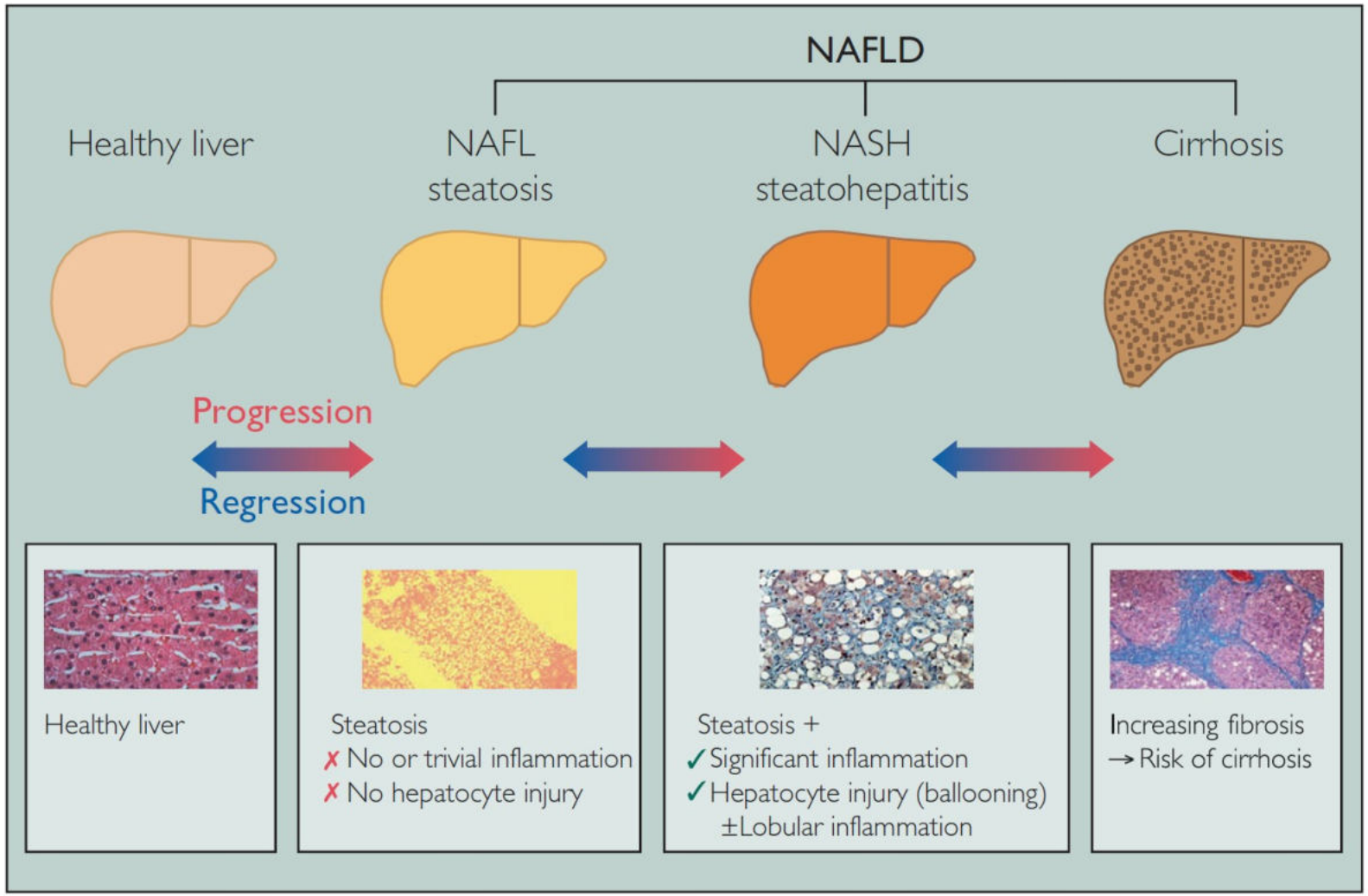
Identify barriers to goals:

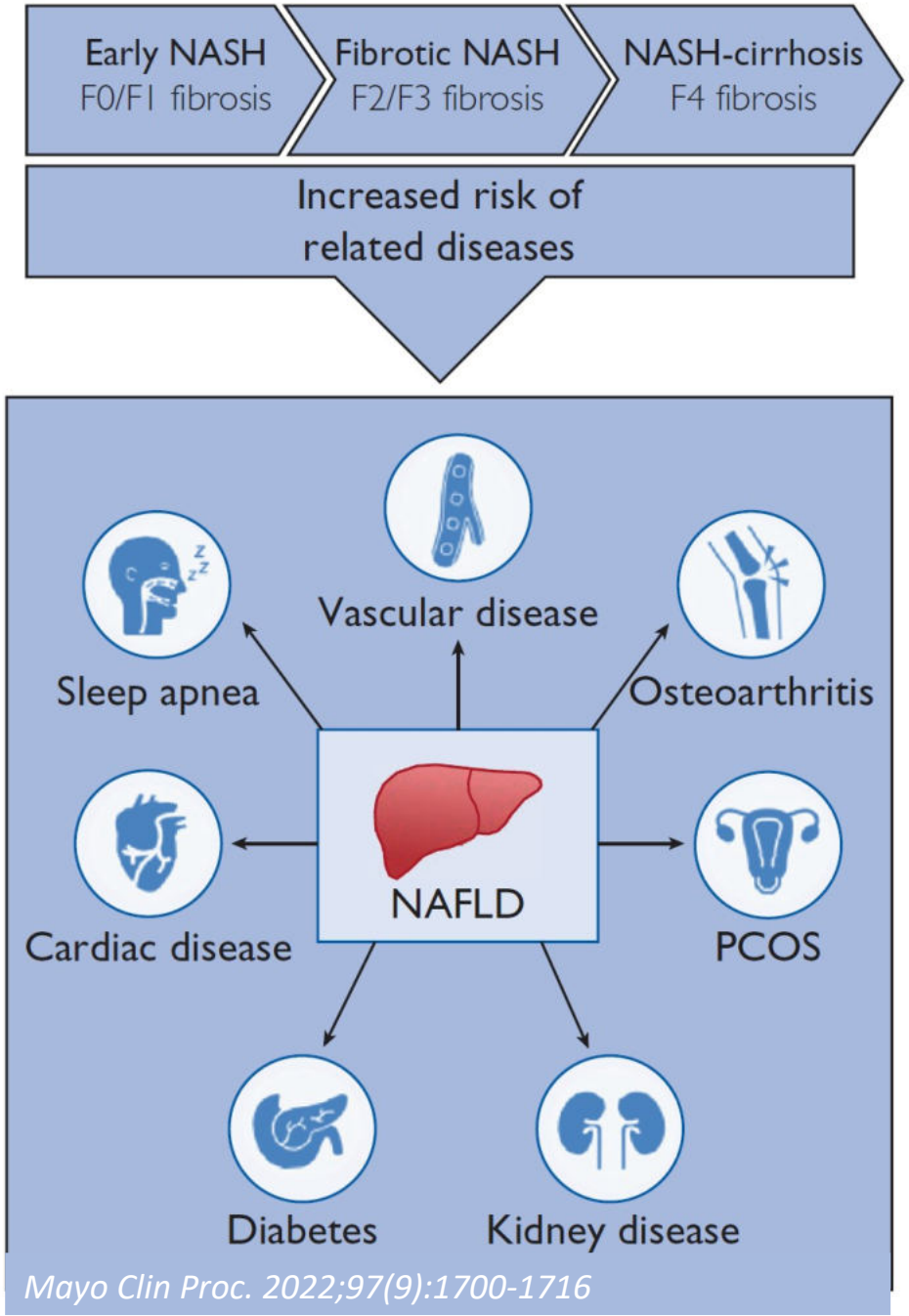
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

NAFLD prevalence
Global: 25.2% (33.5% by 2030)
United States: 24.1% (~100M adults by 2030)

NASH prevalence
Global: 1.5%–6.45%





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Most Common Tests in Noninvasive Diagnosis of Fibrosis in NAFLD

Serologic Markers

- **Simple**
  - FIB-4
  - NFS
- **Complex**
  - ELF
  - Pro-C3

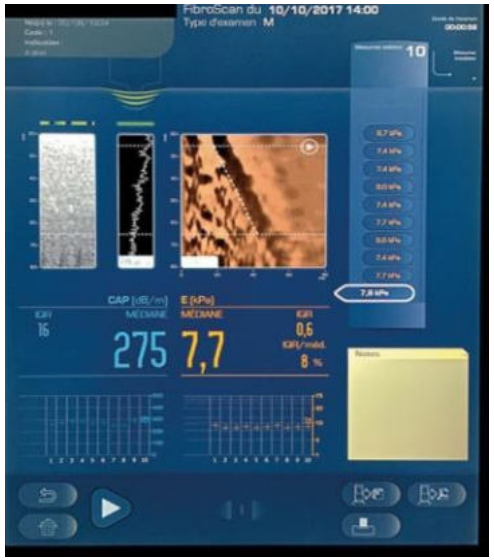
Imaging

- **Elastography**
  - VCTE
  - MRE
  - Multiparametric
  - ARFI

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}}$$

AASLD

Pro-C3



“Simple Scores” for Predicting Presence of Advanced (F3/4) Fibrosis

NAFLD Fibrosis Score

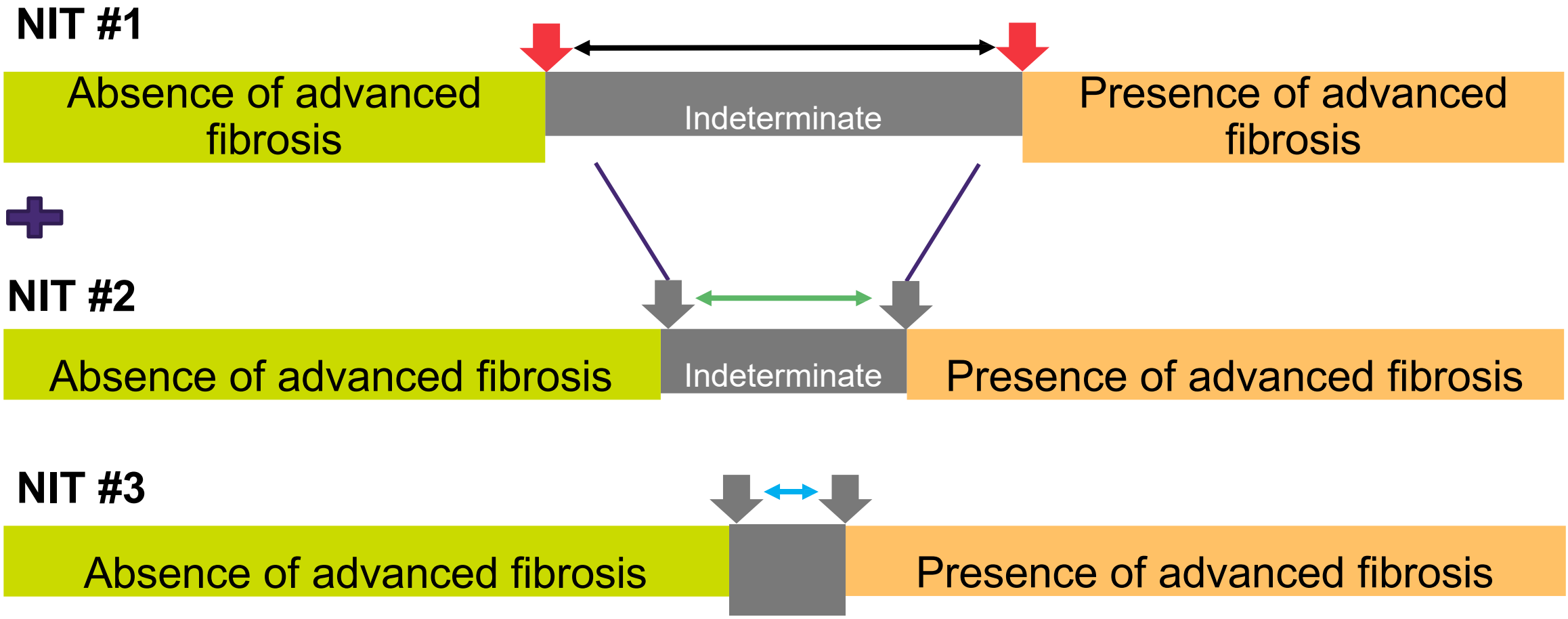
- = -1.675 + 0.037 x **Age** + 0.094 x **BMI** + 1.13 x **IFG/diabetes** + 0.99 x **AST/ALT ratio** - 0.013 x **Platelets** - 0.66 x **Albumin**.
- A score of less than -1.455 excludes fibrosis (NPV 88-93%).
- A score of greater than 0.676 predicts fibrosis (PPV 82-90%)

FIB-4 Score

- = (**Age** * **AST**) / (**Platelets** * Sqrt (**ALT**))
- A score of less than 1.3 excludes fibrosis (NPV 95%)
- A score greater than 3.25 predicts fibrosis (PPV ~70%)

Angulo et al. Hepatology. 2007; Sterling et al. Hepatology. 2006; McPherson et al. Gut. 2010

The use of Sequential NITs



Anstee et al ;Hepatology 2019

VCTE(Vibration-controlled transient elastography) (FibroScan)

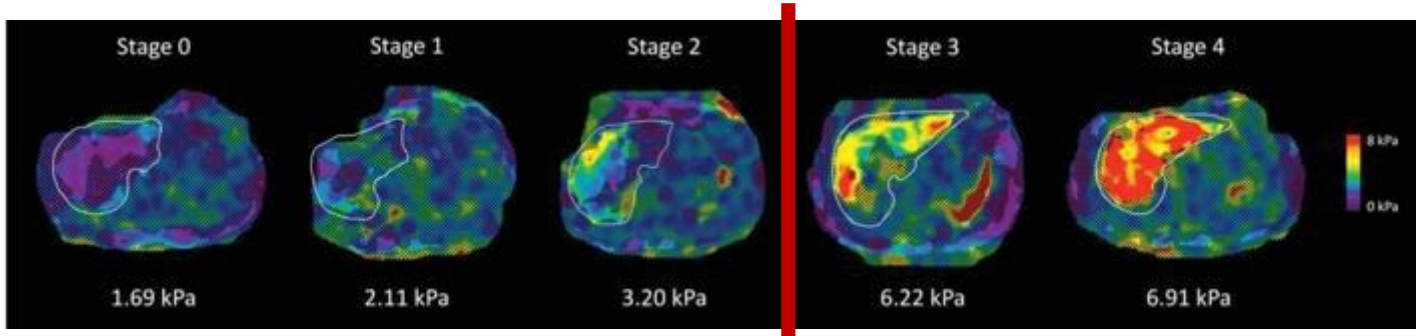
Non-invasive quantification of two physical biomarkers of the liver within a 10-minute examination:

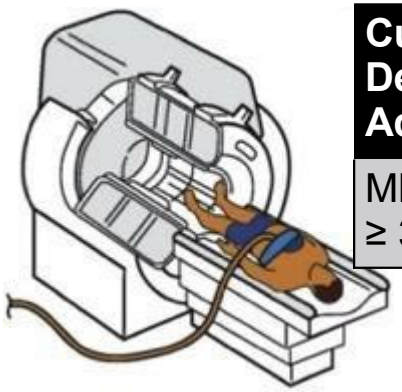
Liver stiffness	CAP
• Obtained through a VCTE measurement • Correlated to extent of fibrosis	• Quantification of ultrasound attenuation obtained in VCTE measurement • Correlated to liver steatosis

Both biomarkers can be used to assess disease severity in different etiologies including NASH

MRE

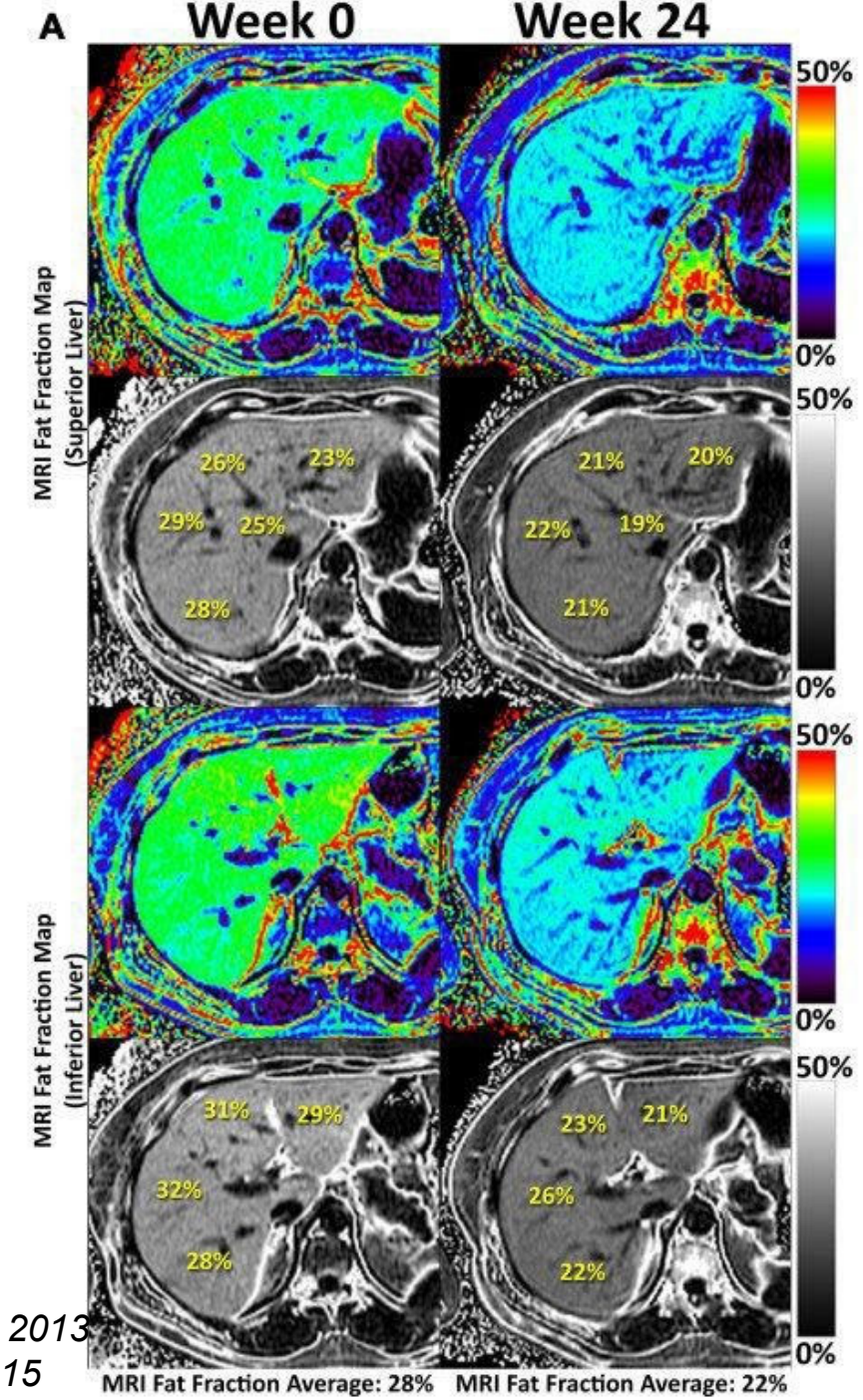
Modified phase-contrast pulse sequence to visualize rapidly propagating mechanical shear waves (~60 Hz)





Cutoff for Detecting Advanced Fibrosis	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
MRE stiffness ≥ 3.64 kPa	0.86 (0.65-0.97)	0.91 (0.83-0.96)	0.68 (0.48-0.84)	0.97 (0.91-0.99)

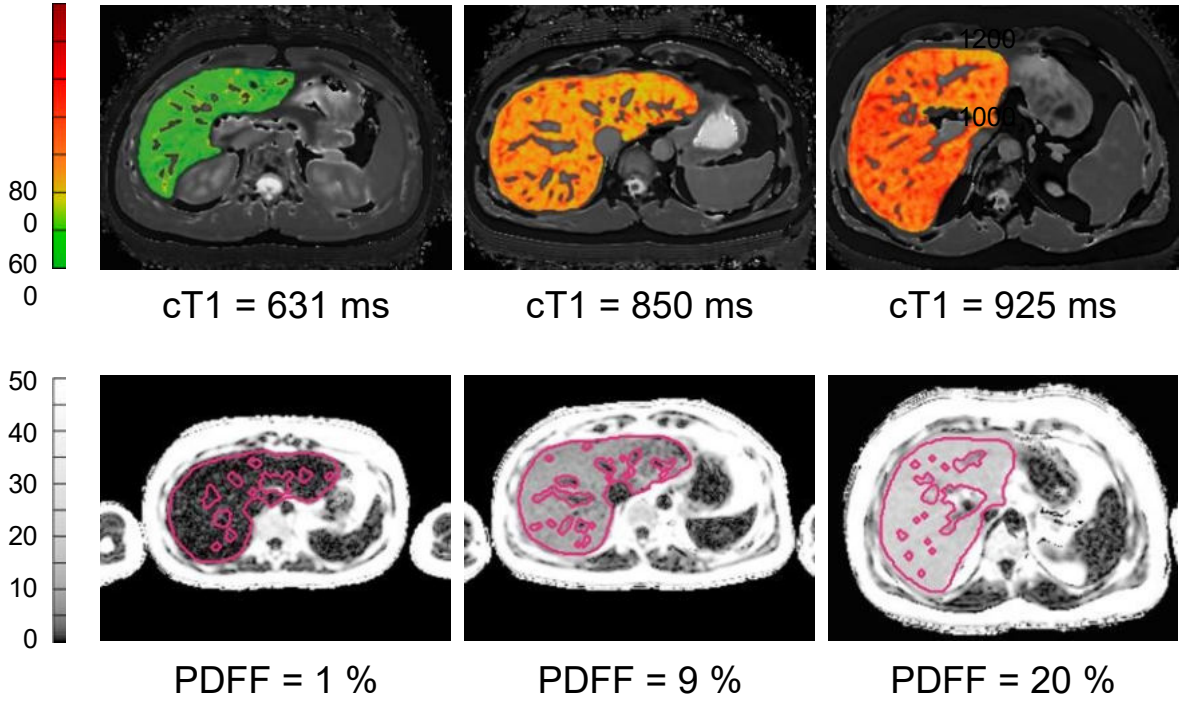
Loomba et al. Hepatology. 2014;
Patel et al. Ther Adv Gastroenterol.. 2016



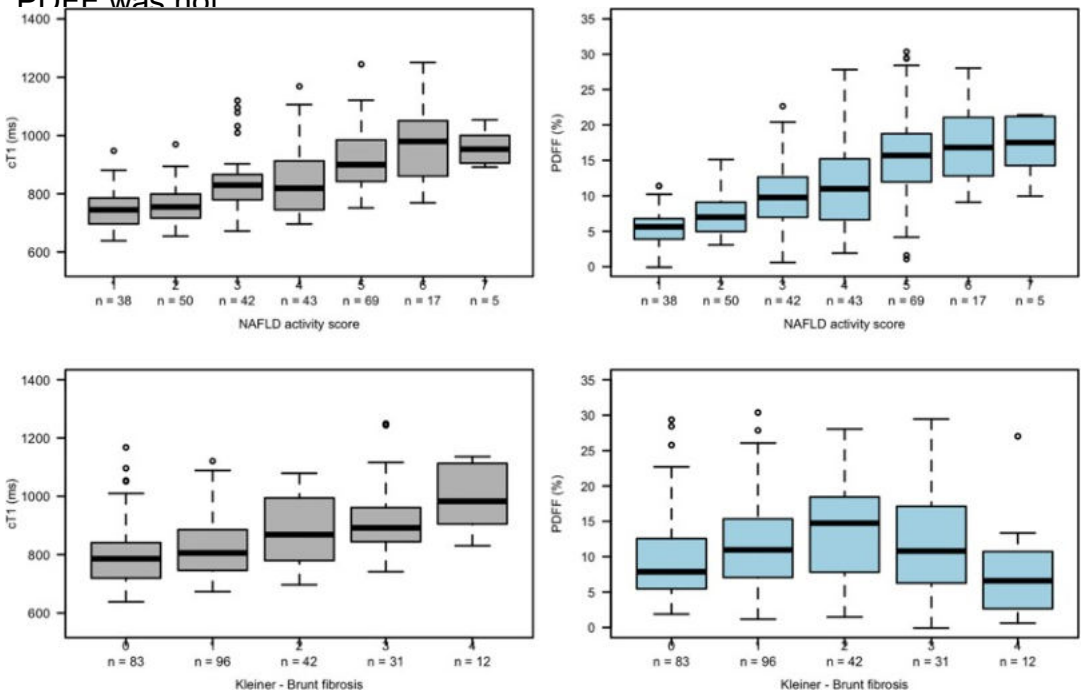
Noureddin, Hepatology 2013
Loomba Hepatology 2015

LiverMultiScan® – cT1 and PDFF Have Potential as Non-Invasive Biomarkers for NASH

Example cT1 and PDFF maps for range of values based NAFLD



cT1 and PDFF were both strongly correlated with all features of the biopsy-activity score. cT1 was strongly correlated with fibrosis, but PDFF was not



cT1 and PDFF were both correlated with all features of the NAFLD activity score (NAS); cT1 was also correlated with fibrosis.

Dennis, et al. *Frontiers of Endocrinology*. 2021.

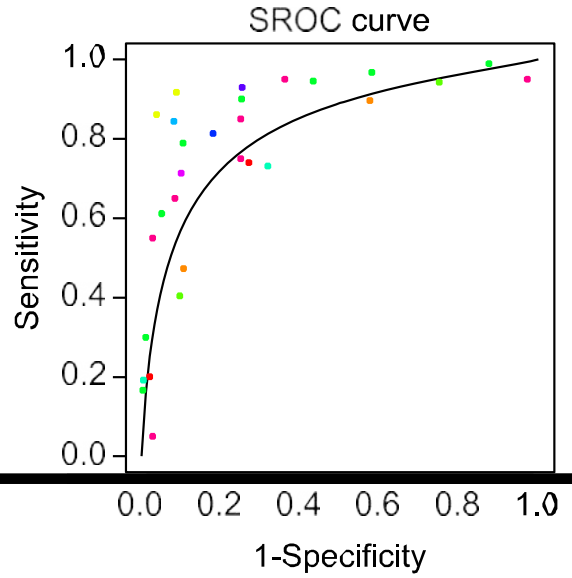
ELF

Hyaluronic acid (HA)

Procollagen III amino terminal peptide (PIIINP)

Tissue inhibitor of metalloproteinase 1 (TIMP-1)

- Meta-analysis of 11 studies
- ELF test had a sensitivity of >0.90 for excluding fibrosis at a threshold of 7.7
- To achieve a specificity of 0.90 for advanced and significant fibrosis, thresholds of 10.18 (sensitivity: 0.57) and 9.86 (sensitivity: 0.55) were required, respectively



11 studies were included in the meta-analysis of advanced fibrosis
AUC: 0.83 (0.71, 0.90)
Sensitivity: 0.73 (0.60, 0.83)
Specificity: 0.80 (0.68, 0.88)

Vali et al. *J Hep*. 2020.