Management NAFLD and NASH in Patients with Type 2 Diabetes

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Disclosures

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- Other: None


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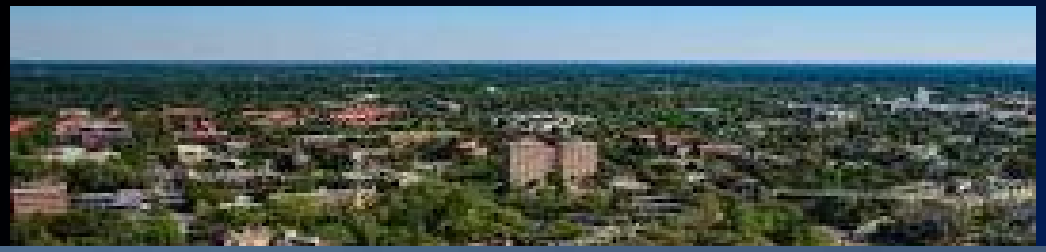

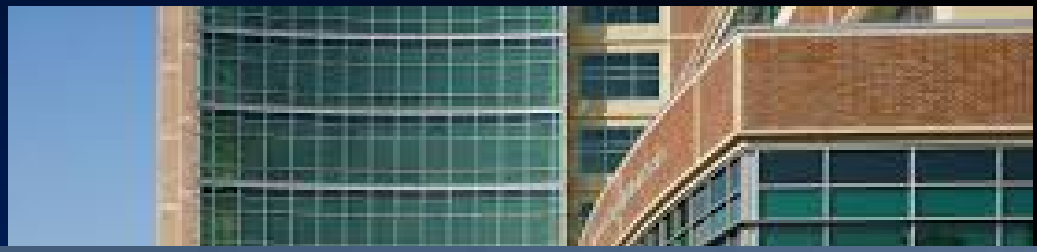

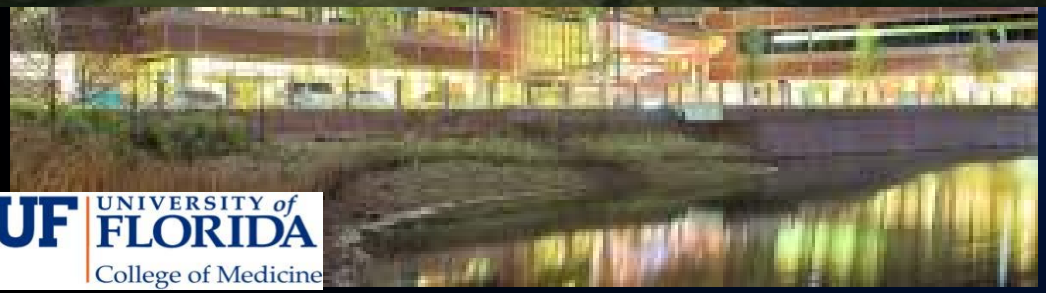

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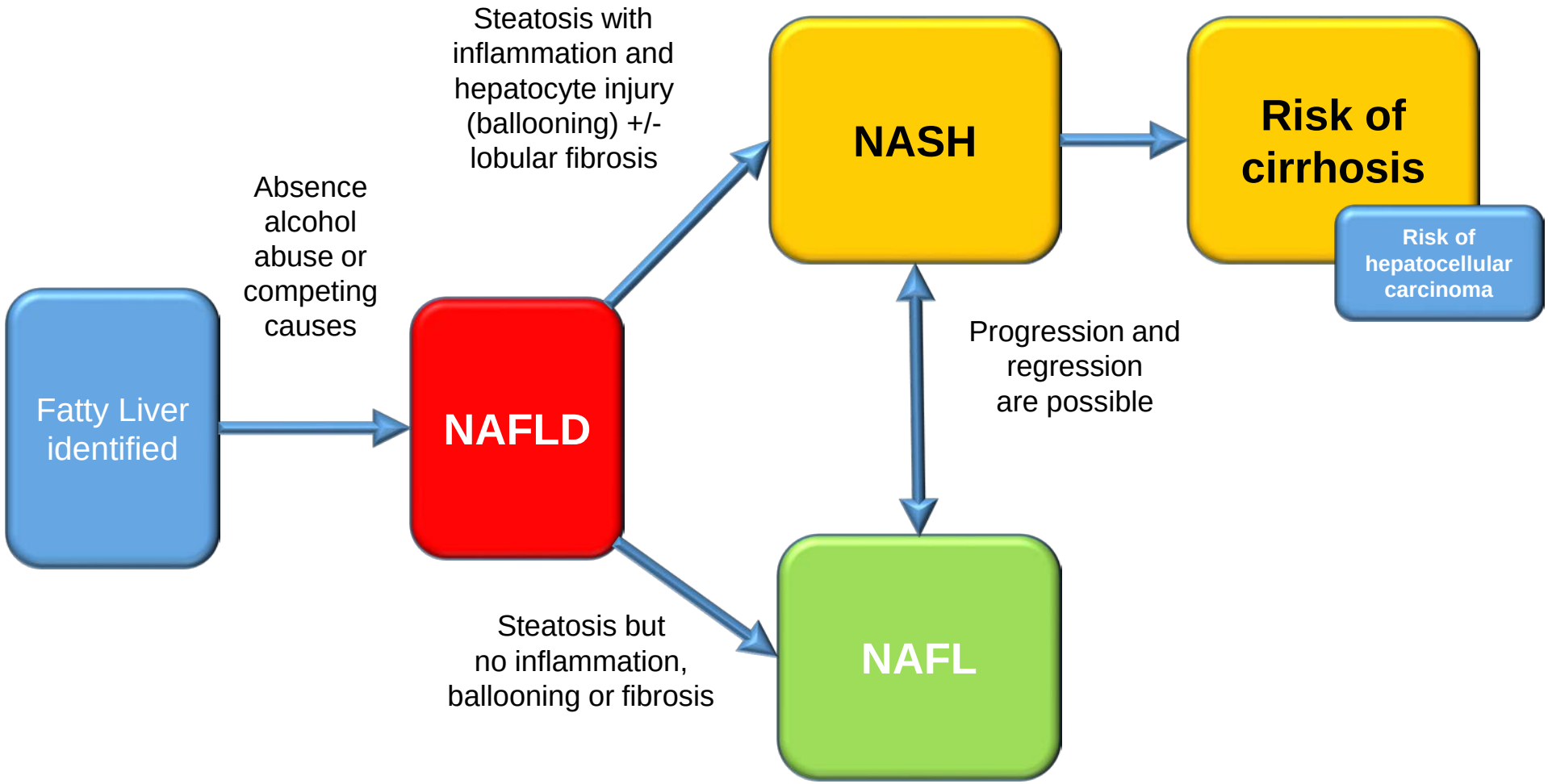
What is Non-Alcoholic Fatty Liver Disease?

- A chronic liver condition characterized by:
  - Hepatic fat accumulation (in the absence of ethanol abuse & other identifiable causes)
  - Insulin resistance
  - Frequently associated with impaired glucose intolerance or type 2 diabetes
- Steatosis may range from simple steatosis to steatohepatitis (NASH) with progressive liver damage with necrosis, inflammation and frequently fibrosis
- The natural history is poorly understood, no large long-term studies

Relationship between Fatty Liver, NAFLD, NAFL, and NASH



Budd & Cusi, American Journal of Medicine, 2020 *(in press)*

NAFLD in Type 2 Diabetes (T2DM)

1. Links between T2DM and NAFLD

- Prevalence and risk factors
- Mechanisms

2. Complications

- Liver: risk of cirrhosis, hepatocellular carcinoma
- Extra-hepatic: development of T2DM and of CVD

3. Management

- Diagnosis
- Treatment: a) Liver disease

  b) Extra-hepatic: T2DM prevention and CVD

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2019*

Diabetes Care 2019;42(Suppl. 1):S34–S45 | https://doi.org/10.2337/dc19-S004

Recommendation

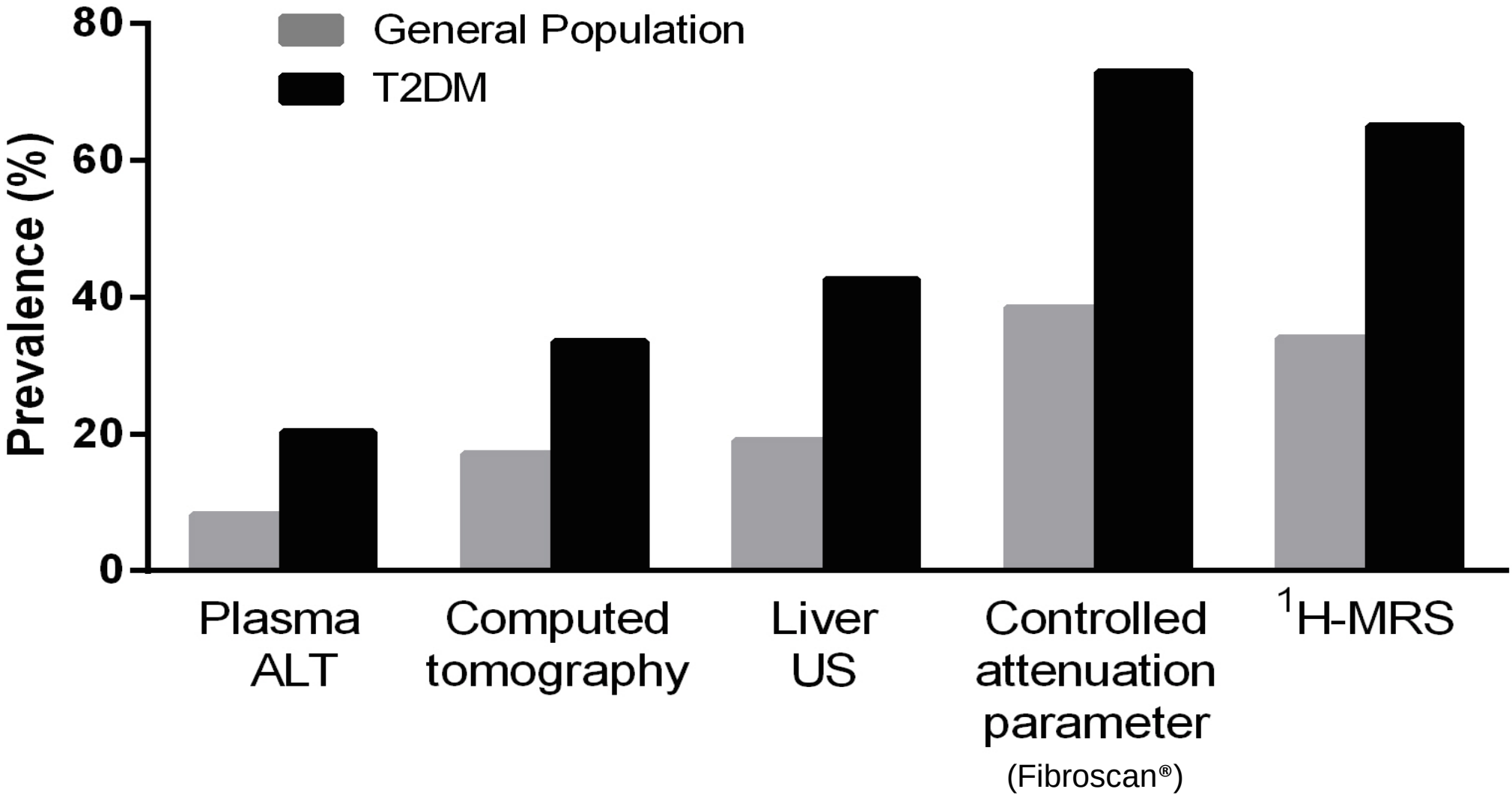
4.14 Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

(page S40)

NASH in 2020 as a Public Health Problem

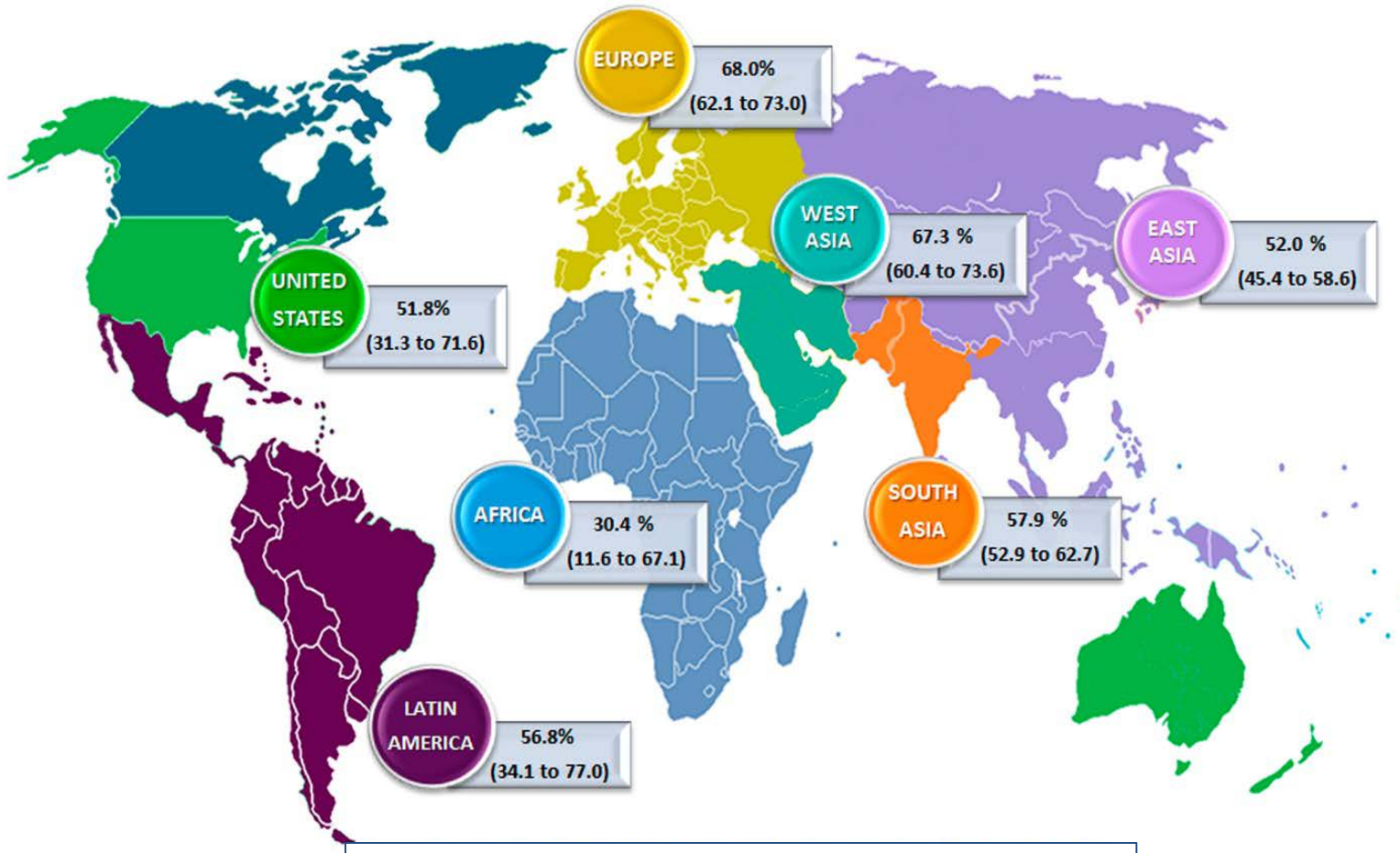
	DM nephropathy in the 80s	Osteoporosis in the 90s	NASH in 2020
Long natural history	Yes	Yes	Yes
High prevalence?	Yes	Yes	Yes
Major cause of morbidity?	Yes	Yes	Cirrhosis, HCC, + CVD
Increased mortality?	Yes	Yes	Yes
Diagnosis	Microalbuminuria	Bone mineral density	No simple, “great” test yet for fibrosis
Adequate treatments?	Not initially, but yes today	Not initially, but yes today	**Pioglitazone** GLP-1RA? vitamin E? Others in 2020

Prevalence of NAFLD using different diagnostic tools



Bril & Cusi, Diabetes Care 2017 40:419-430

The Prevalence of NAFLD* in T2DM: 55.5%



- NASH prevalence: 37.3% (10 studies)
- Fibrosis prevalence: 17% (7 studies)

*80 studies: 74 used liver ultrasound, 6 used magnetic resonance imaging

Younossi et al, J Hepatology 2019

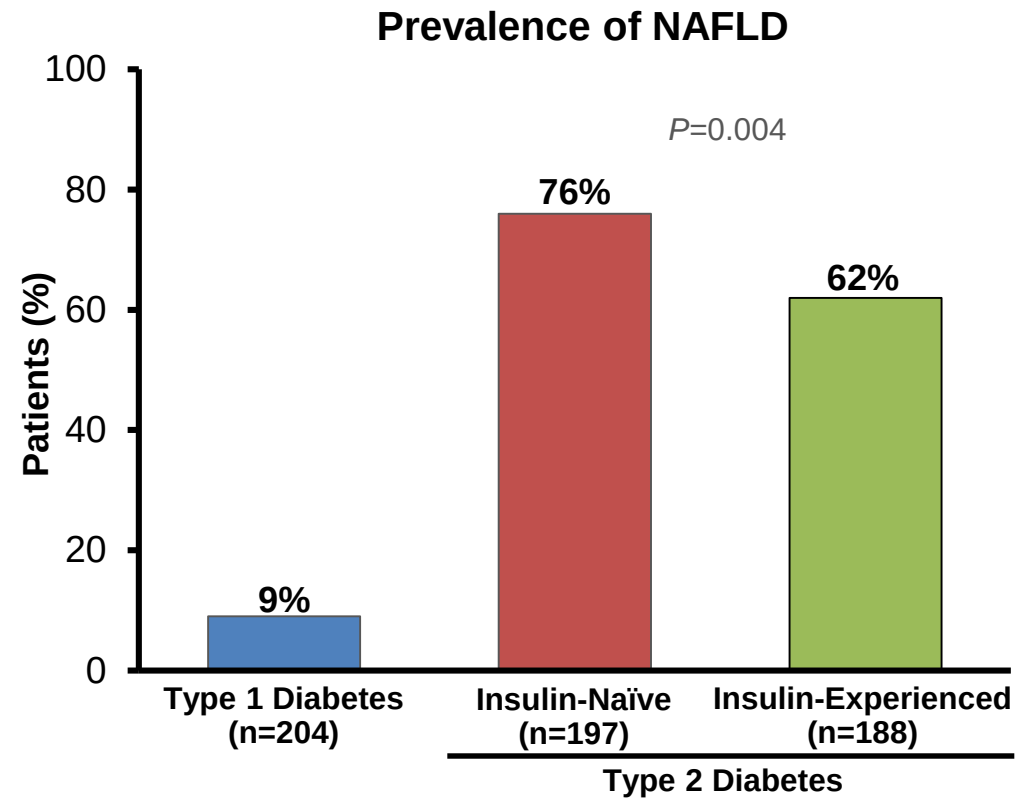
Type 1 and 2 Diabetes: NAFLD Prevalence and Metabolic Associations

Post-hoc analysis of baseline data from 4 phase 3 trials (n=589):

Type 1 diabetes (IMAGINE 1 and 3); insulin-naïve type 2 diabetes (IMAGINE 2); insulin-experienced type 2 diabetes (IMAGINE 5)

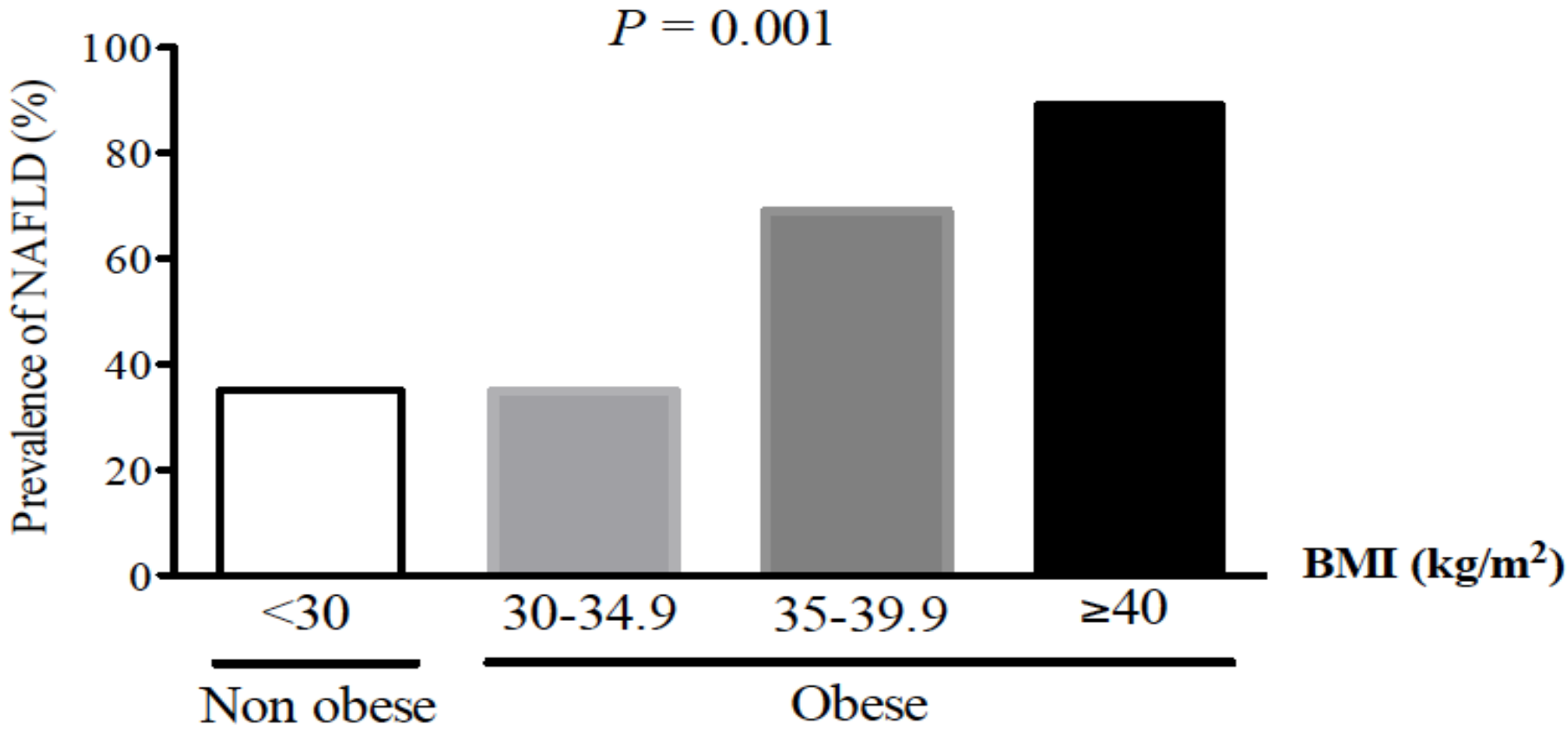
Mean hepatic fat fraction: 3.2% versus 13.0% versus 10.2%, respectively

- **NAFLD: hepatic fat fraction ≥6% by MRI**



Cusi K, et al. *Diabetes Obes Metab.* 2017;19:1630-1634.

The Prevalence of NAFLD* Increases with BMI in T2DM even when AST/ALT ≤40 IU/L



*Screened by magnetic resonance and spectroscopy

Portillo-Lopez et al, JCEM 2015

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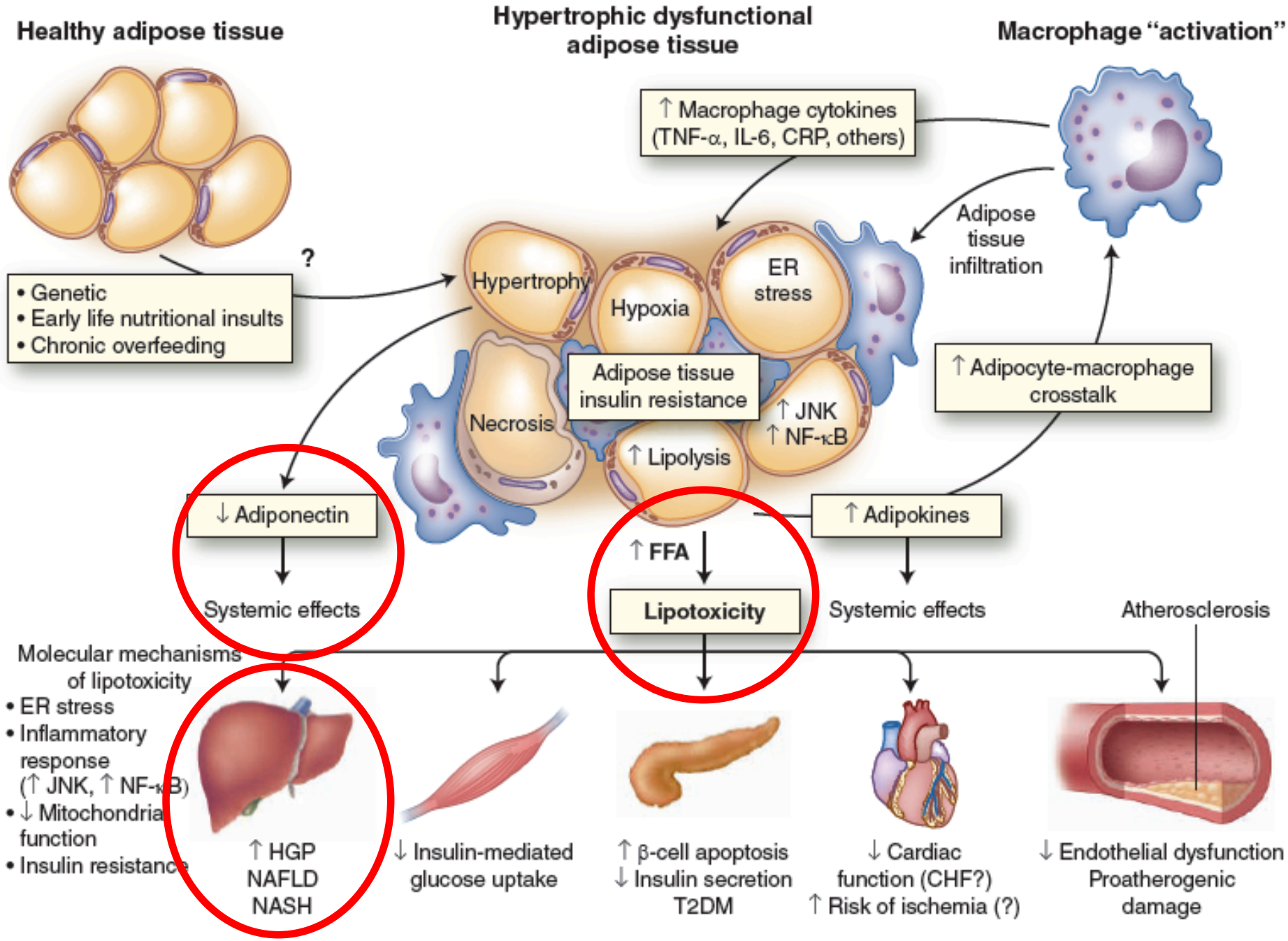

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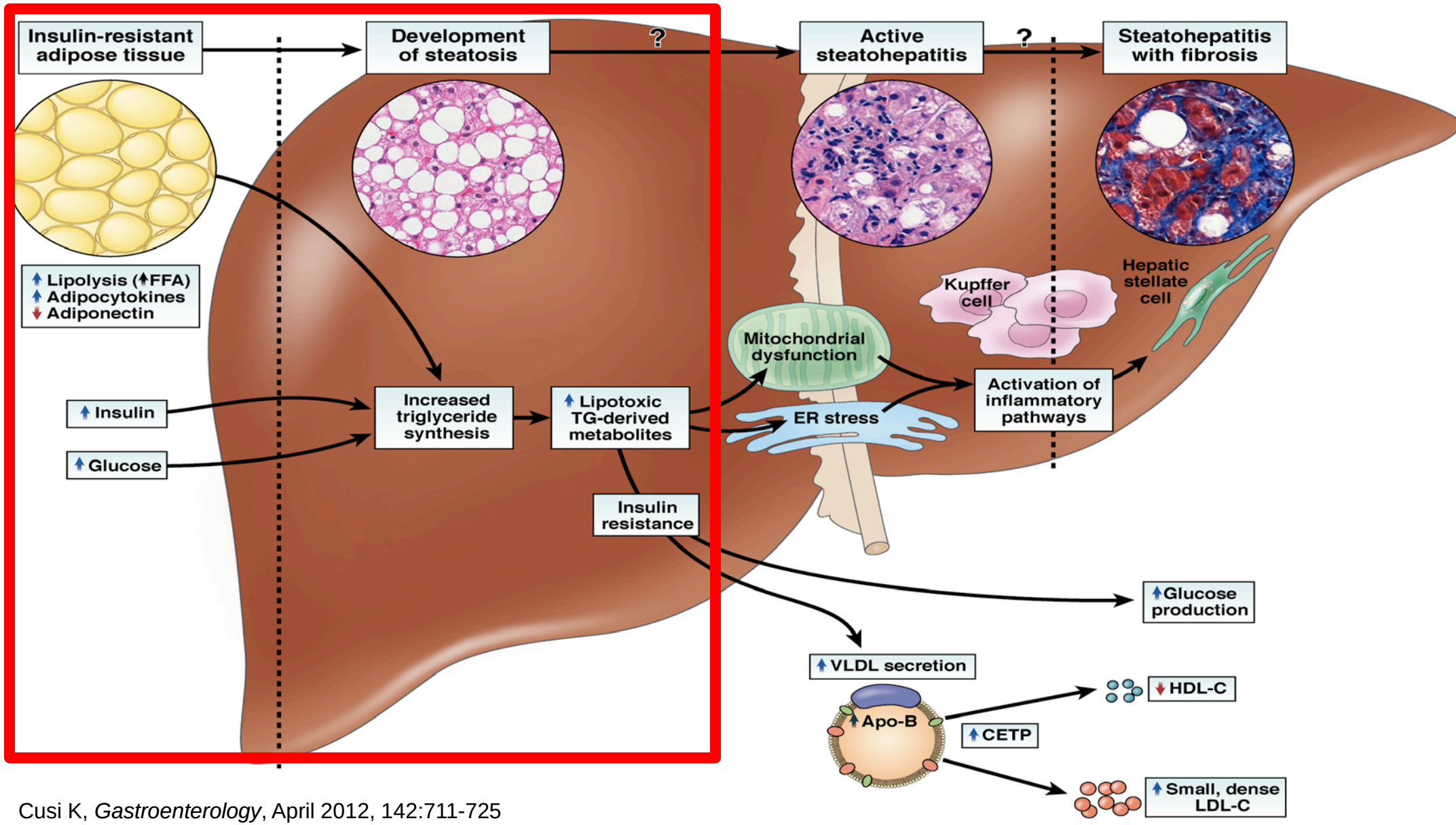
K Cusi. Current Diabetes Reports. 2010 10:306-315

From Obesity to Dyslipidemia, Lipotoxicity (NASH) and Cirrhosis



Cusi K, *Gastroenterology*, April 2012, 142:711-725

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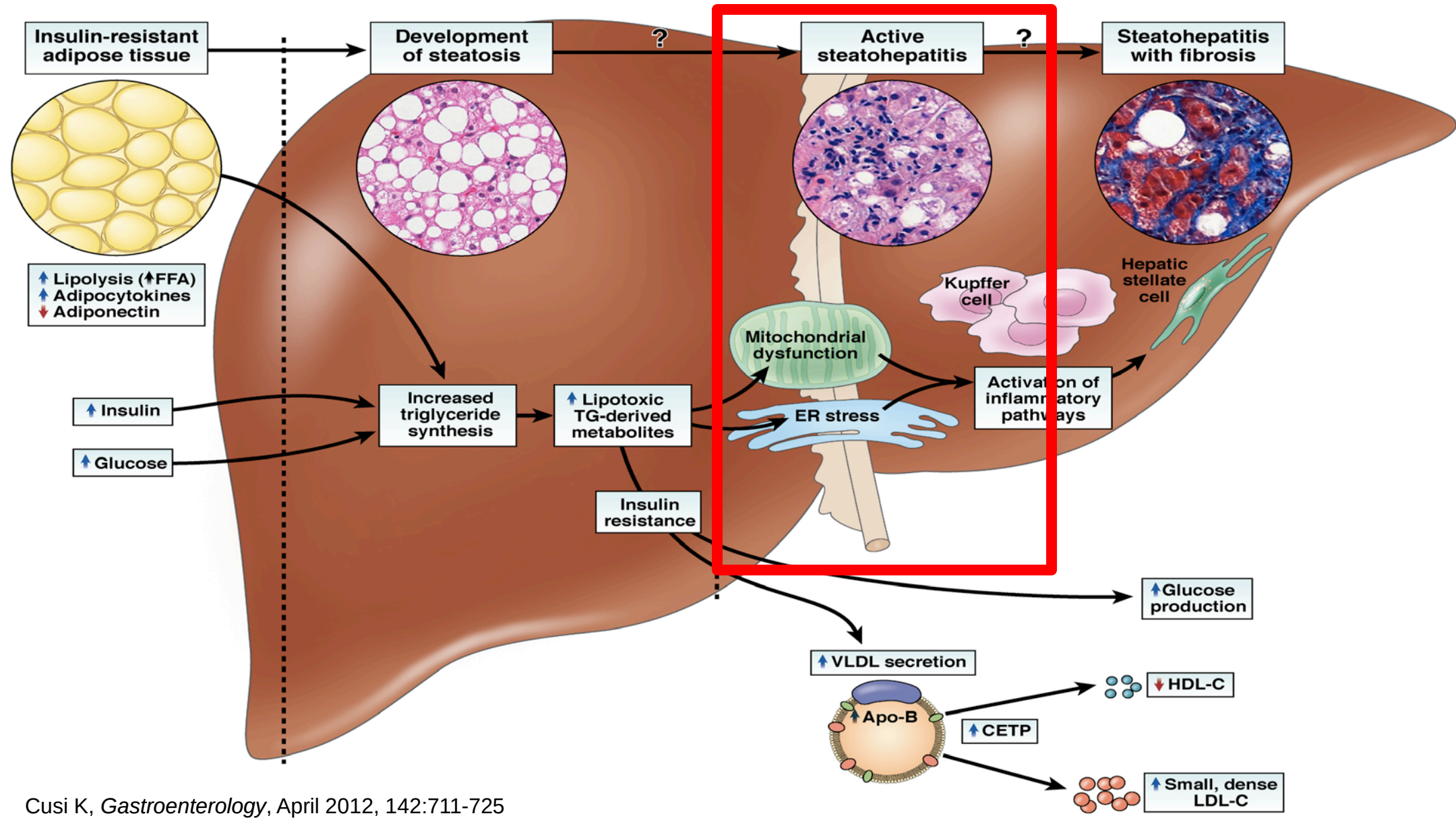

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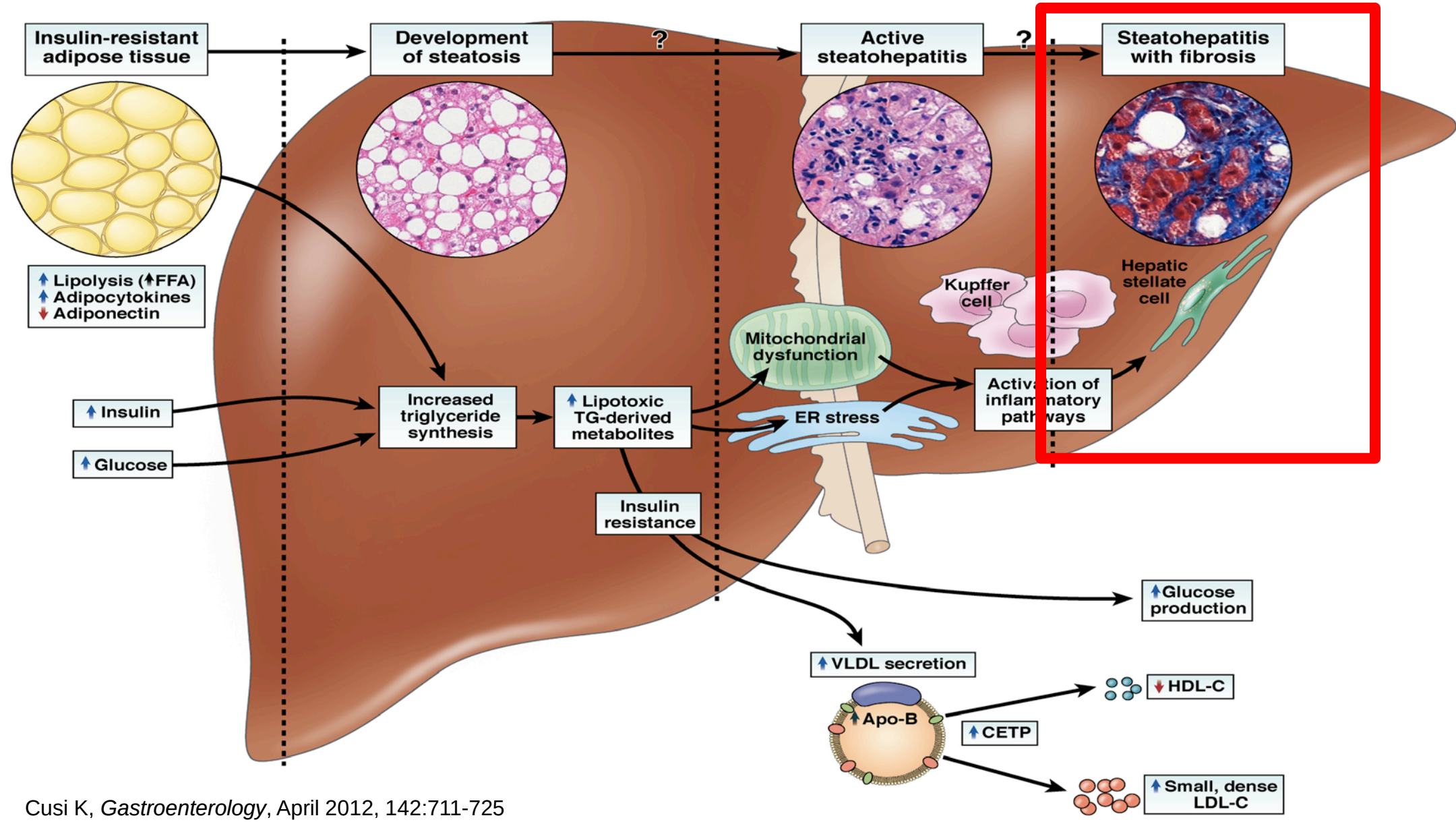

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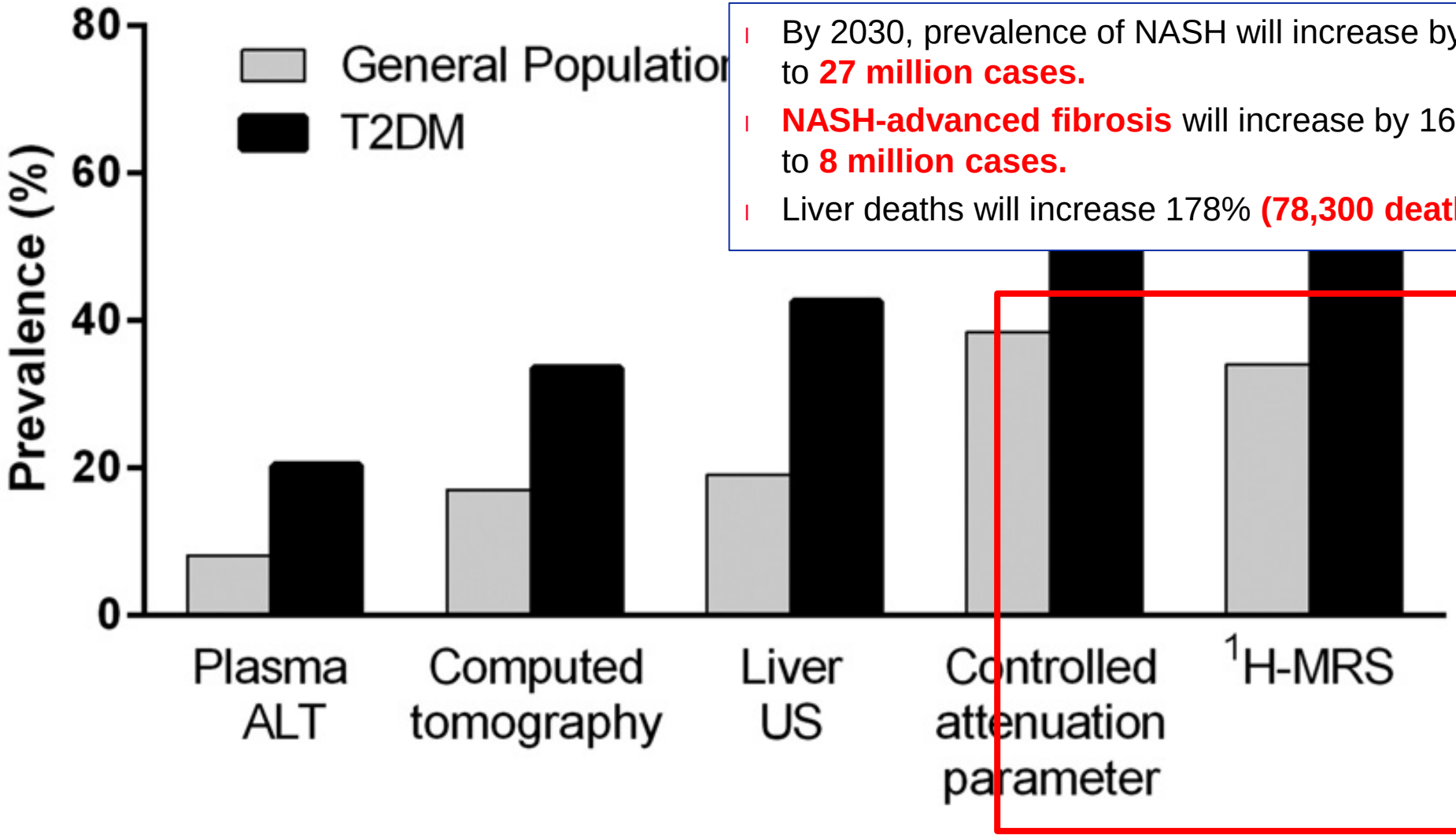
- Liver: risk of fibrosis/cirrhosis and hepatocellular carcinoma

A Prevalence of NAFLD using different diagnostic tools



- By 2030, prevalence of NASH will increase by 63% to **27 million cases.**
- **NASH-advanced fibrosis** will increase by 160% to **8 million cases.**
- Liver deaths will increase 178% **(78,300 deaths).**

Bril & Cusi, Diabetes Care 2017 40:419-430

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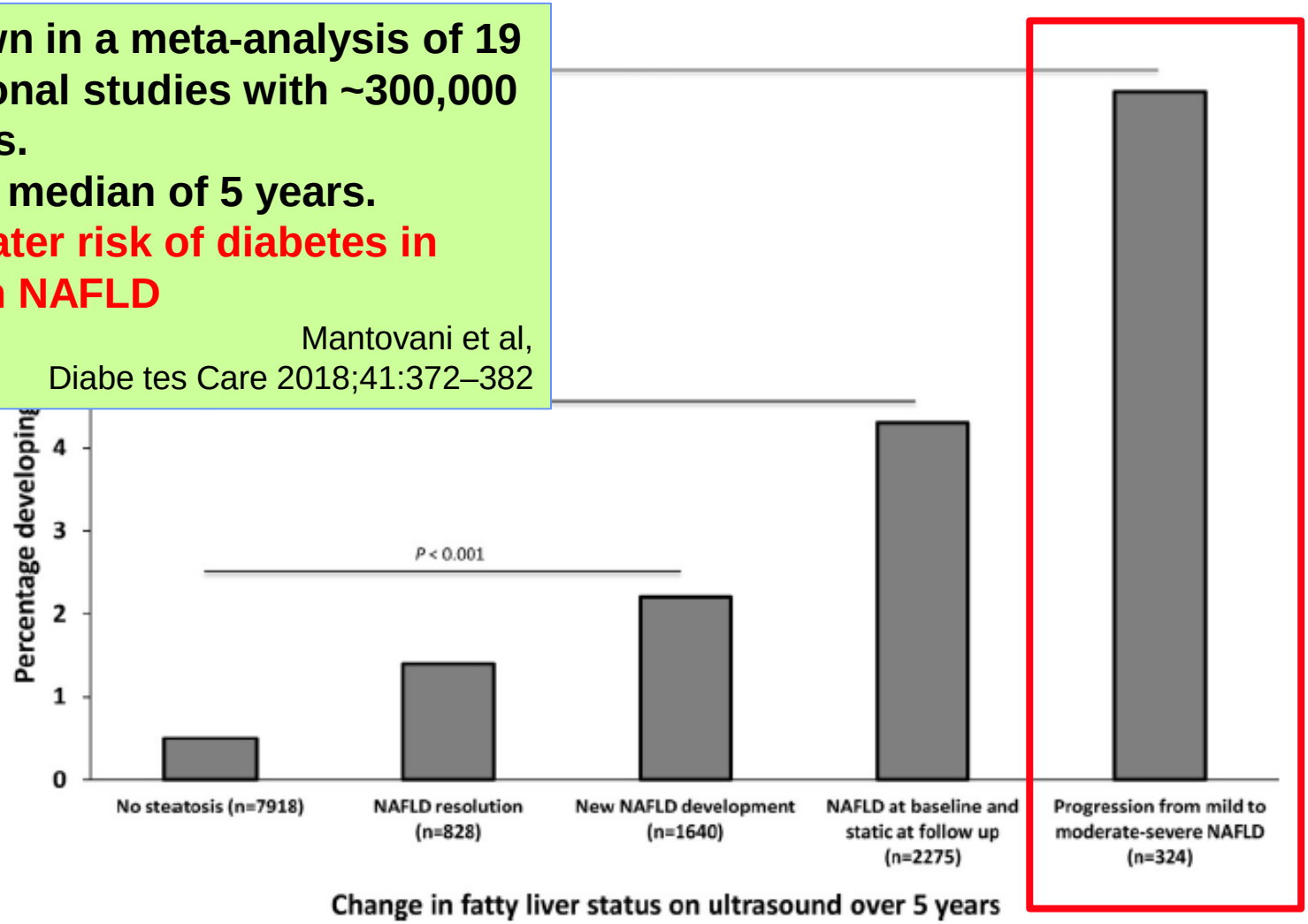
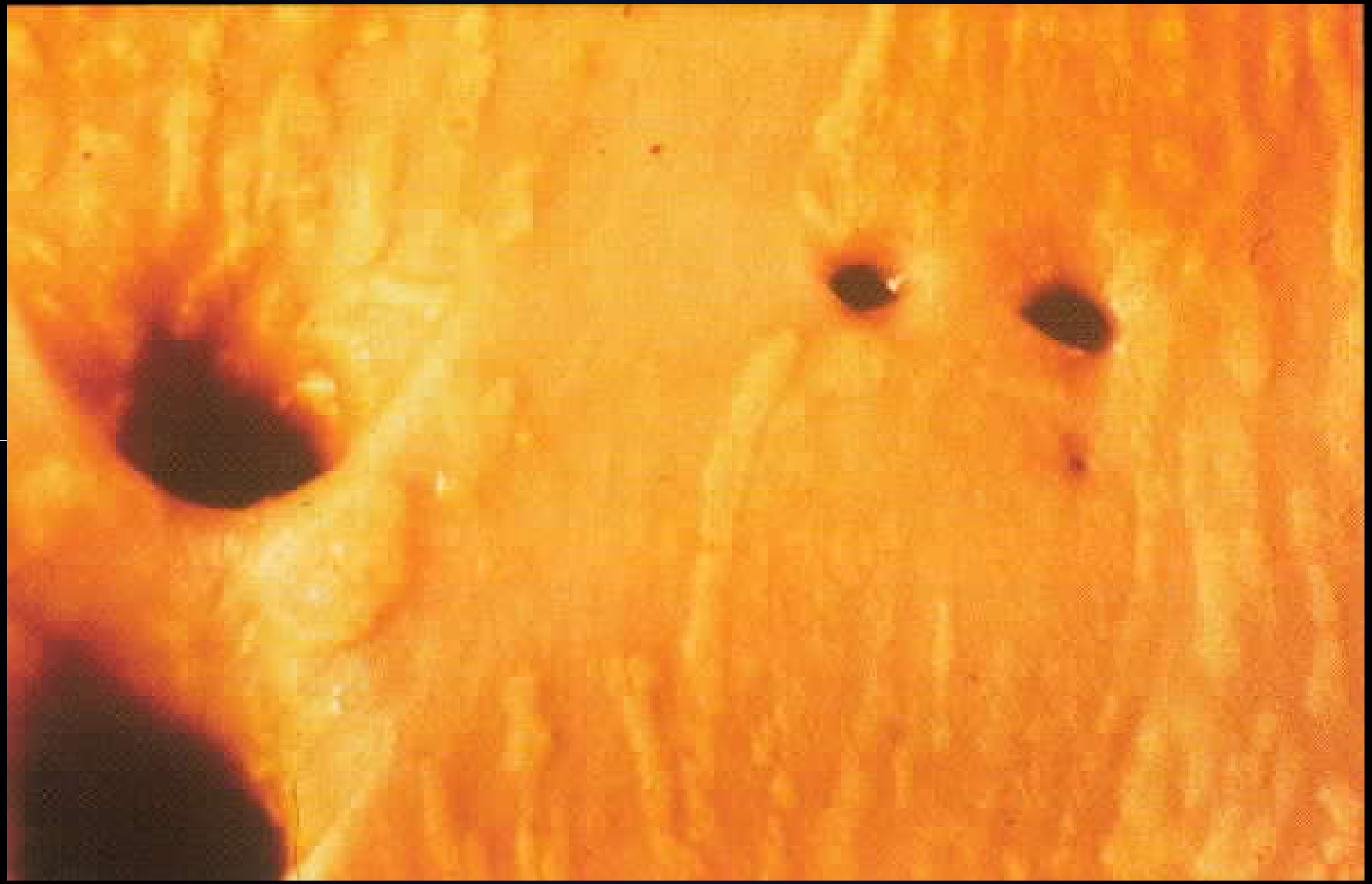
Relationship between Change in Liver Fat and Development of T2DM

- **Also shown in a meta-analysis of 19 observational studies with ~300,000 individuals.**
- **Follow-up median of 5 years.**
- **2-fold greater risk of diabetes in patients in NAFLD**

Mantovani et al,
Diabe tes Care 2018;41:372–382



Sung et al, JCEM 2013;98:3637-43.

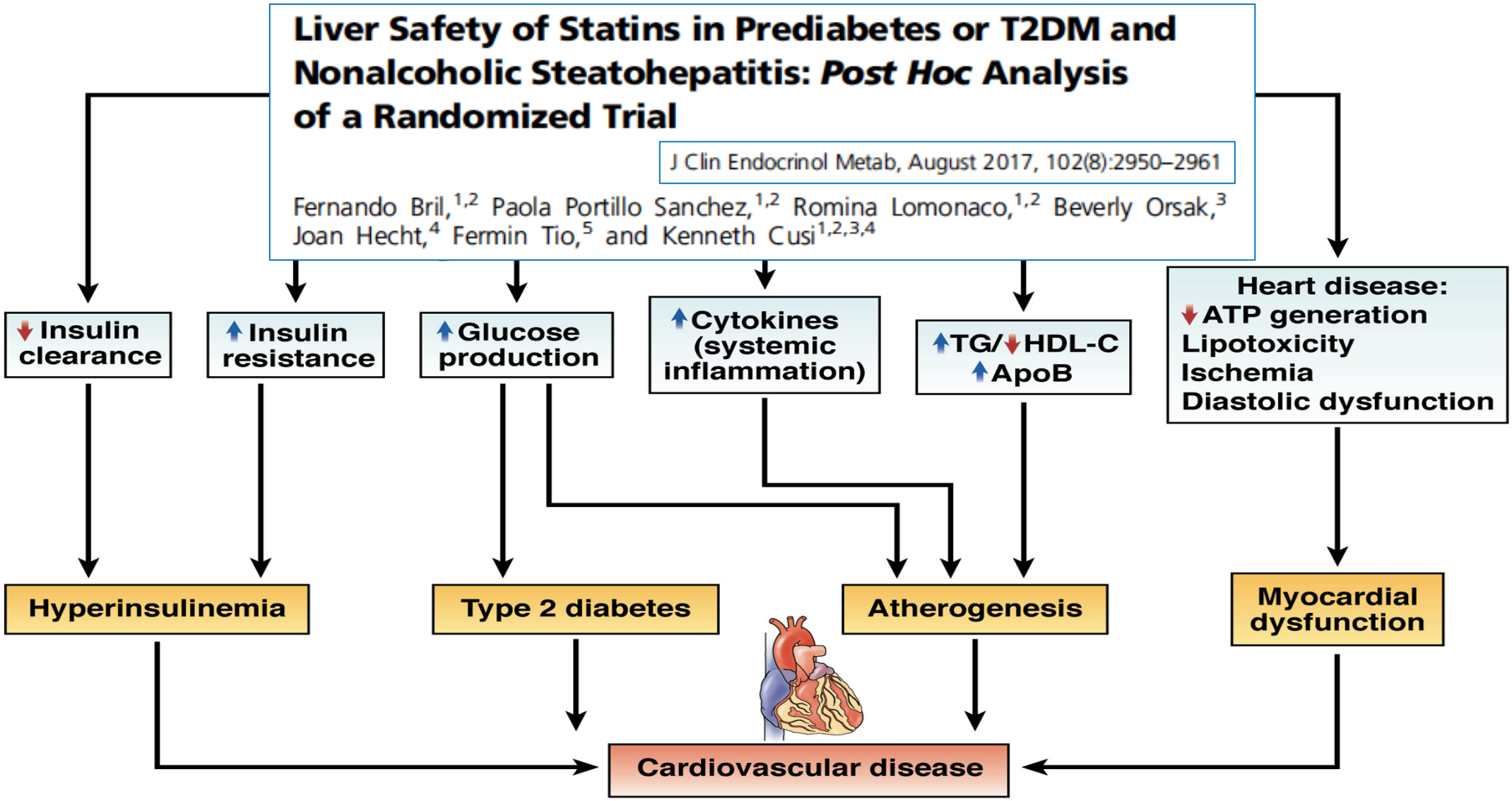


Cardiovascular Consequences of NAFLD

Liver Safety of Statins in Prediabetes or T2DM and Nonalcoholic Steatohepatitis: *Post Hoc* Analysis of a Randomized Trial

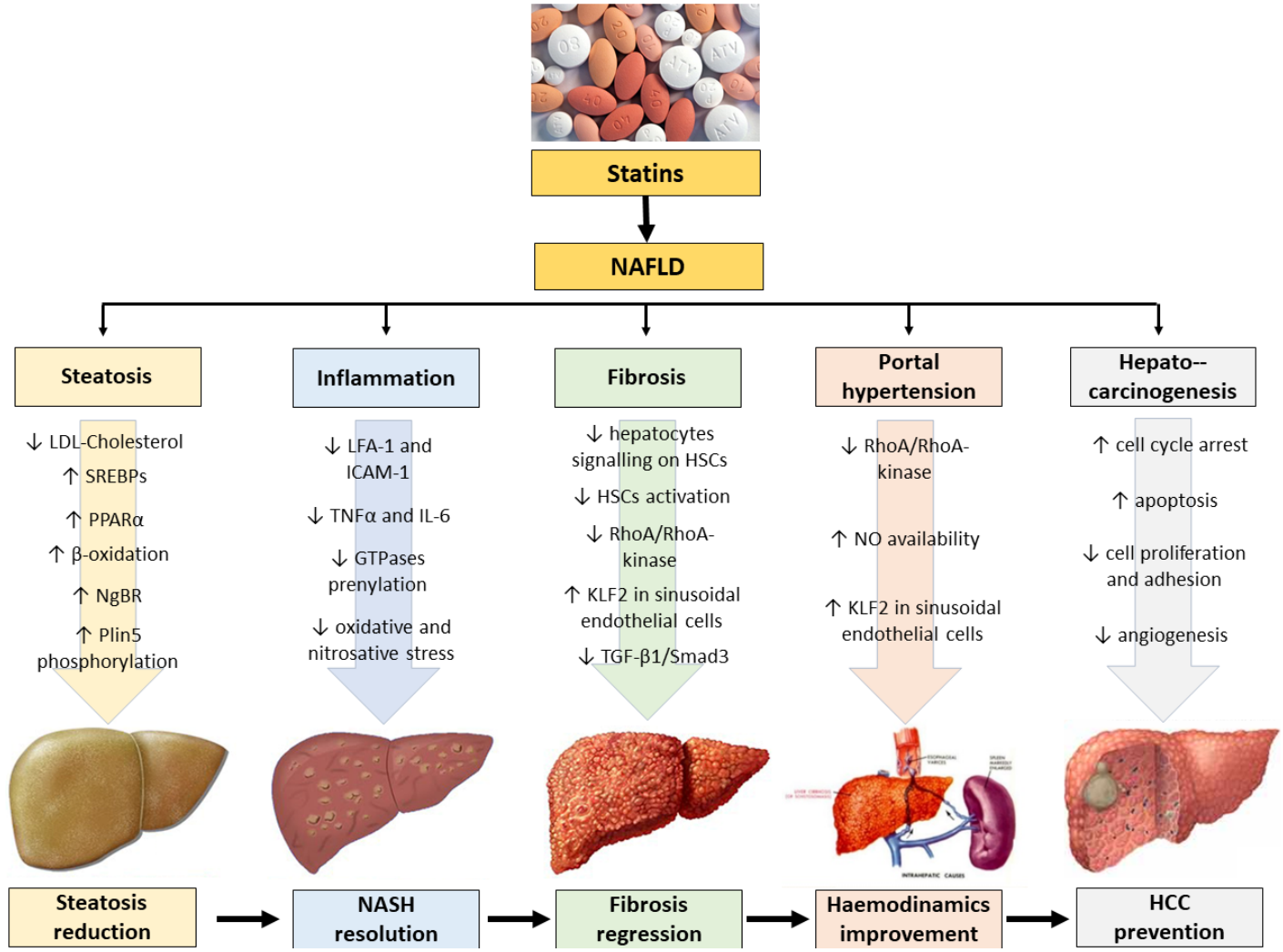
J Clin Endocrinol Metab, August 2017, 102(8):2950–2961

Fernando Bril,[1,2] Paola Portillo Sanchez,[1,2] Romina Lomonaco,[1,2] Beverly Orsak,[3] Joan Hecht,[4] Fermin Tio,[5] and Kenneth Cusi[1,2,3,4]



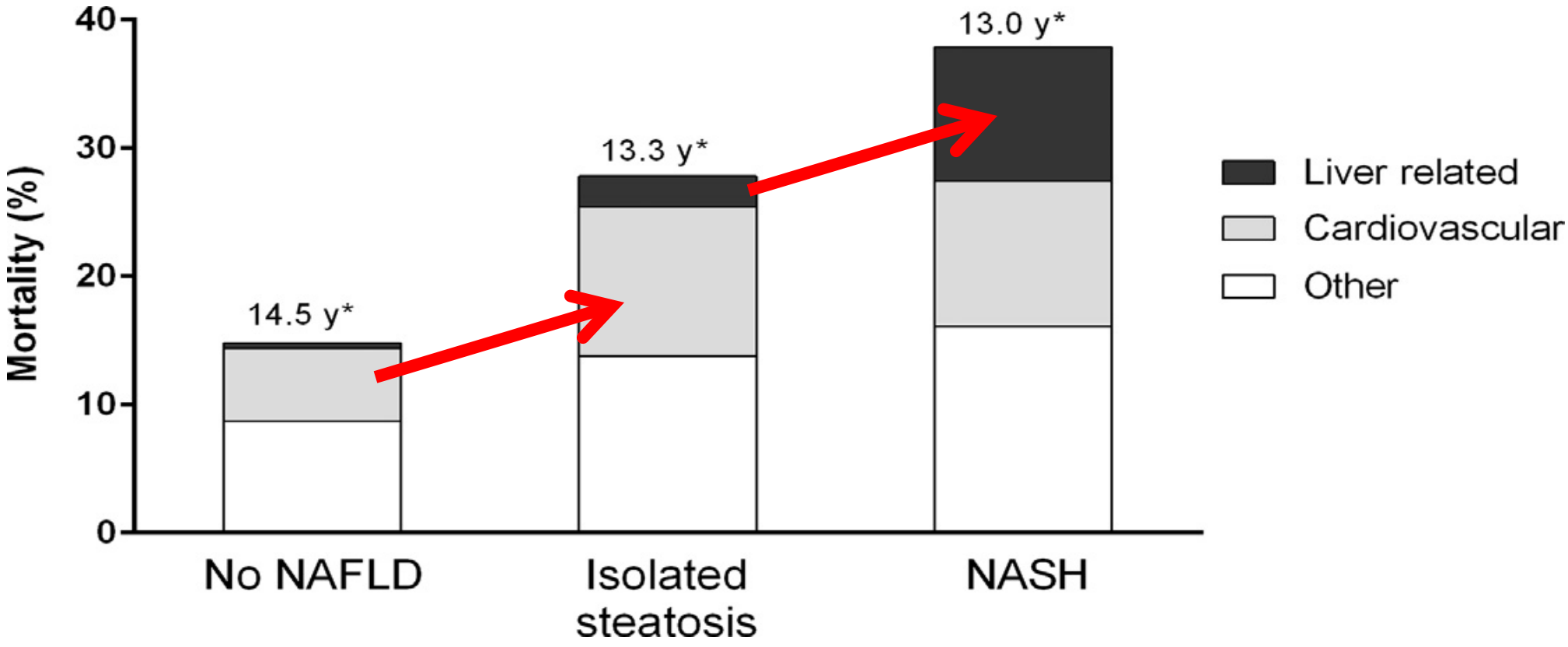
Cusi K, *Gastroenterology*, April 2012, 142:711-725

Potential mechanisms by which statins may favorably affect liver histology and hepatic complications in NAFLD



Nascimbeni F et al. *Atherosclerosis* 2019.

Mortality in Isolated Steatosis versus NASH



Bril & Cusi, Metabolic Clinics North America 2016

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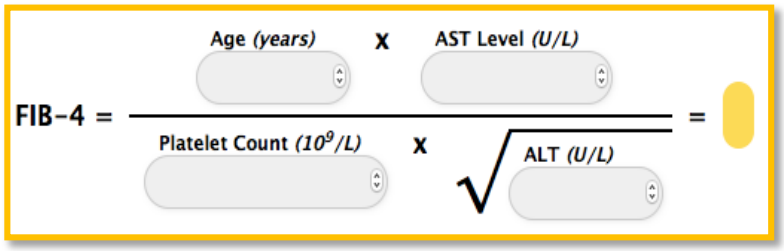
- Diagnosis

Interpretation of FIB-4 and NFS for the Diagnosis of Advanced Fibrosis (stages 3-4)

FIB-4

Risk of advanced fibrosis (stages 3-4)

- Low: <1.3 (F0-F1)
- Indeterminate: 1.3 – 2.67 (F1-F2)
- High: >2.67 (F3-F4)



Parameters
Age
AST
ALT
Platelets
BMI
Serum Glucose (IGT or DM?)
Albumin

NFS

Risk of advanced fibrosis (stages 3-4)

- Low: < -1.455
- Indeterminate: 1.455 – 0.676
- High: >0.676

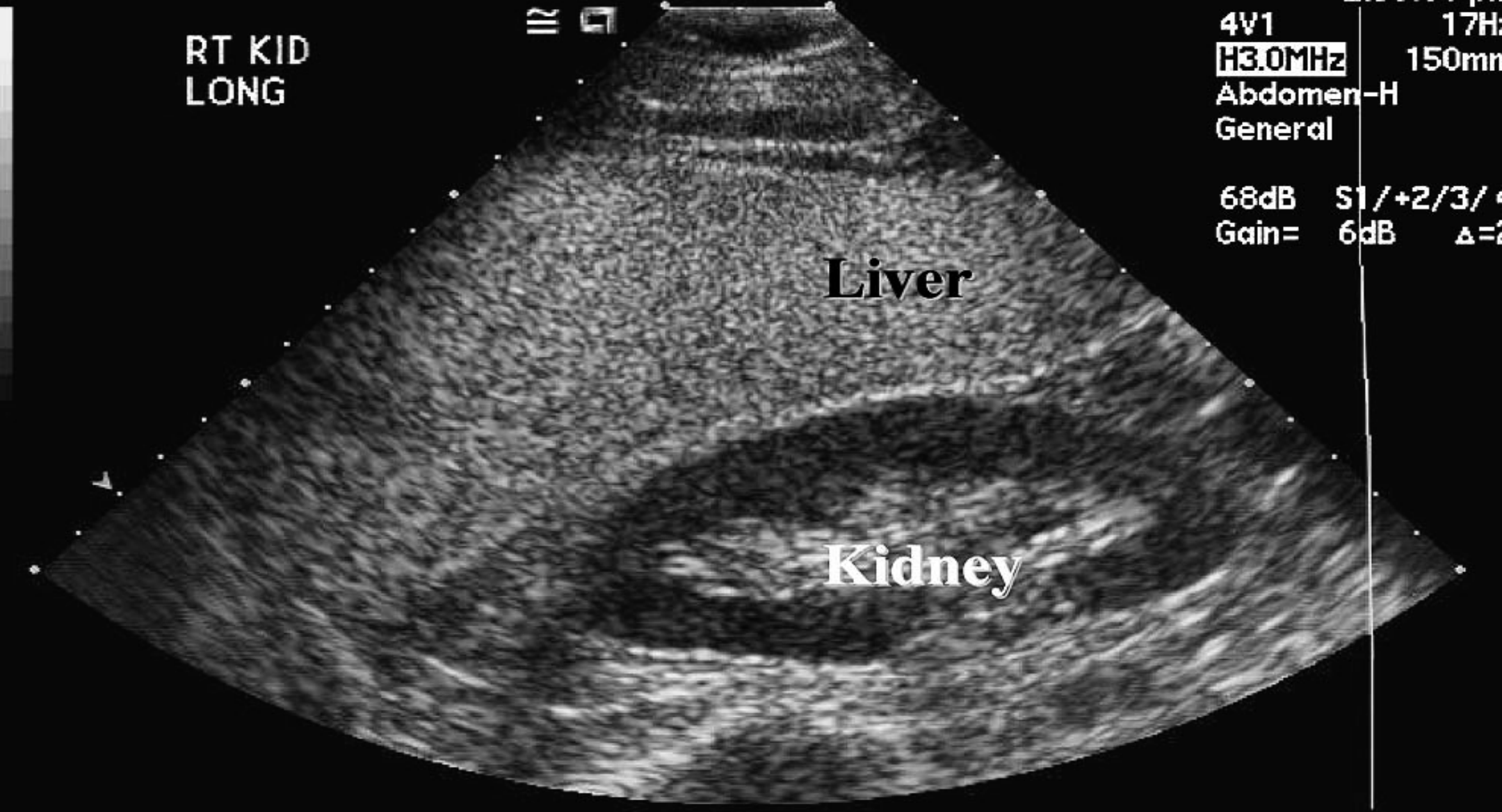
FIB-4: Fibrosis-4 score; NFS: NAFLD fibrosis score.

Budd & Cusi, American Journal of Medicine, 2020 *(in press)*

Diagnosing Advanced Liver Fibrosis with Biomarker Panels

	Parameters and biomarkers	Cutoffs for advanced fibrosis*
Non-invasive biomarker detection methods		
NAFLD fibrosis score[50]	Age, BMI, IFG and diabetes, AST-to-ALT ratio, platelets, and albumin	≤−1·455 >0·676
FIB-4 index[51]	Age, AST, ALT, and platelet	<1·3 >2·67
Enhanced liver fibrosis test[54]	Age, hyaluronic acid, aminoterminal propeptide of type III collagen, and tissue inhibitor of matrix metalloproteinase 1	≥9·8
FibroTest (FibroSure)[55]	Total bilirubin, γ-glutamyltransferase, α2-macroglobulin, apolipoprotein A1, and haptoglobin, corrected for age and sex	>0·30 >0·70

Stefan & Cusi, The Lancet Diabetes Endocrinol, 2019;7:313-324.


RT KID
LONG
4V1
H3.0MHz
Abdomen-H
General
68dB
Gain= 6dB
Liver
Kidney

Imaging Techniques Used to Assess Fibrosis in NAFLD

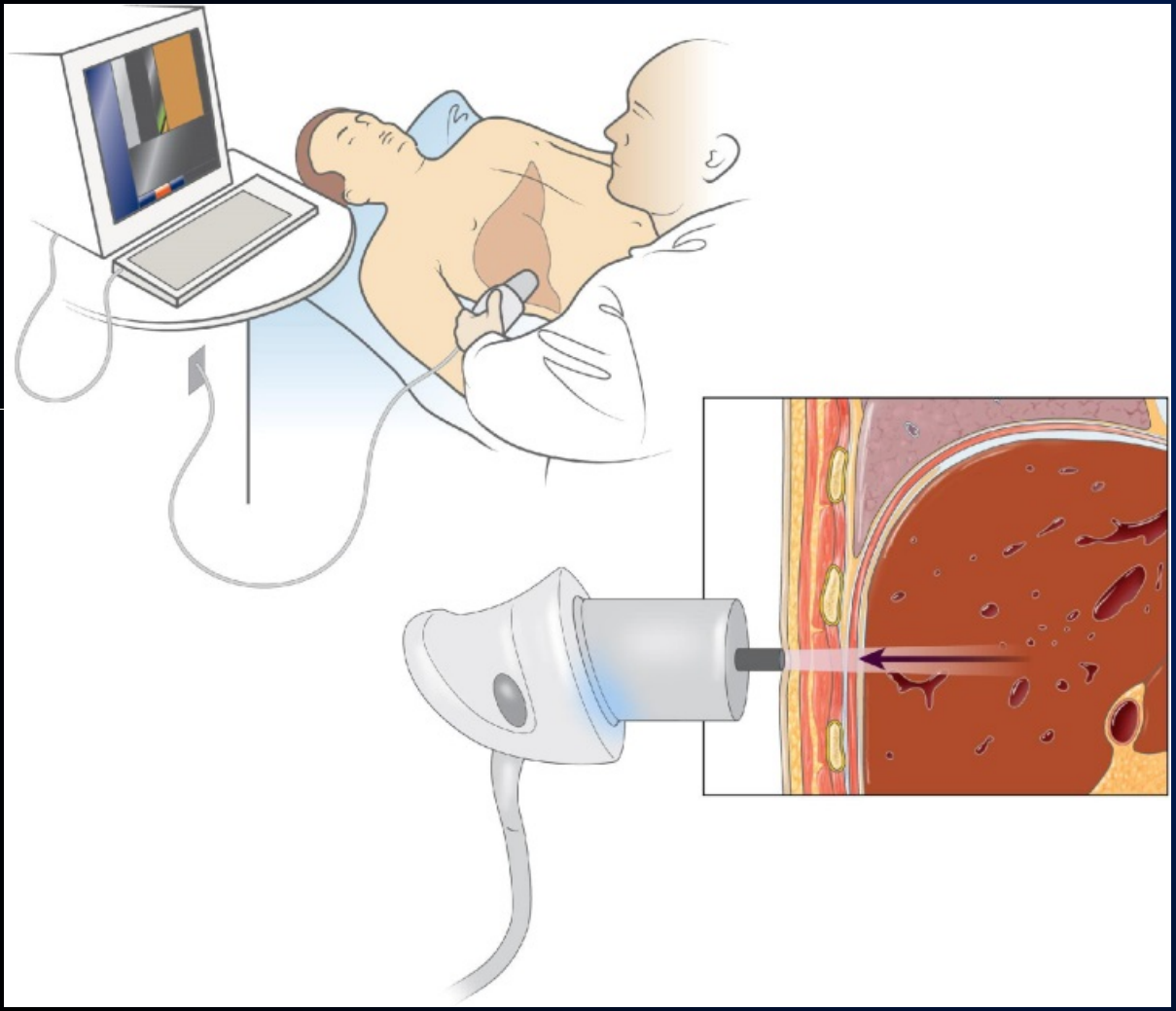
Elastography

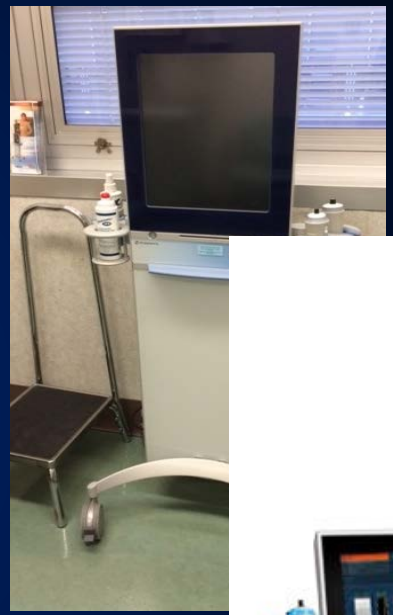
- **Vibration-controlled transient elastography (*FibroScan*®)[1,2]**
  - Accurate in detecting advanced fibrosis
  - Estimates hepatic fat
  - Predicts risk of decompensation and complications
  - Correlates well with portal pressure
  - Most reliable in ruling out advanced disease
  - Most widely used
- **Shear wave elastography (SWE)[2]**
  - Uses acoustic radiation force impulse (ARFI) technology
  - Point quantification: SWE or 2-D supersonic shear imaging (SSI) SWE
- **MR elastography[3]**
  - Most accurate of the imaging modalities
  - Costly, no point-of-care access

Soft liver: no fibrosis **Stiff liver: severe fibrosis**

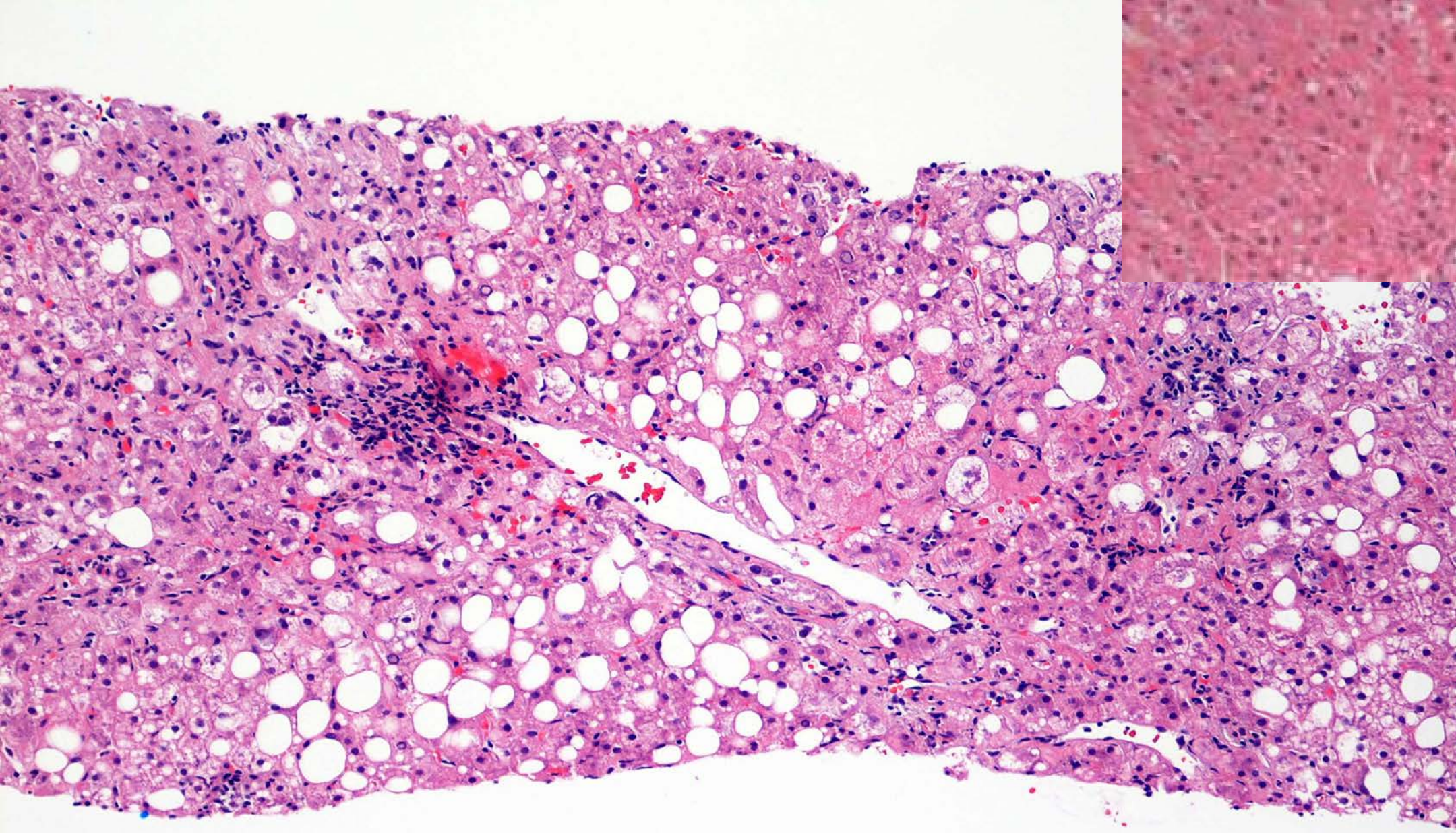
1. Yoneda M, et al. *Dig Liver Dis.* 2008;40(5):371-378.
2. 2. Frulio N, Trillaud H. *Diagn Interv Imaging*. 2013;94(5):515-534.
3. 3. Loomba R, et al. *Hepatology.* 2014;60(6):1920-1928.

Diagnosis of Fibrosis in NASH with Elastography*

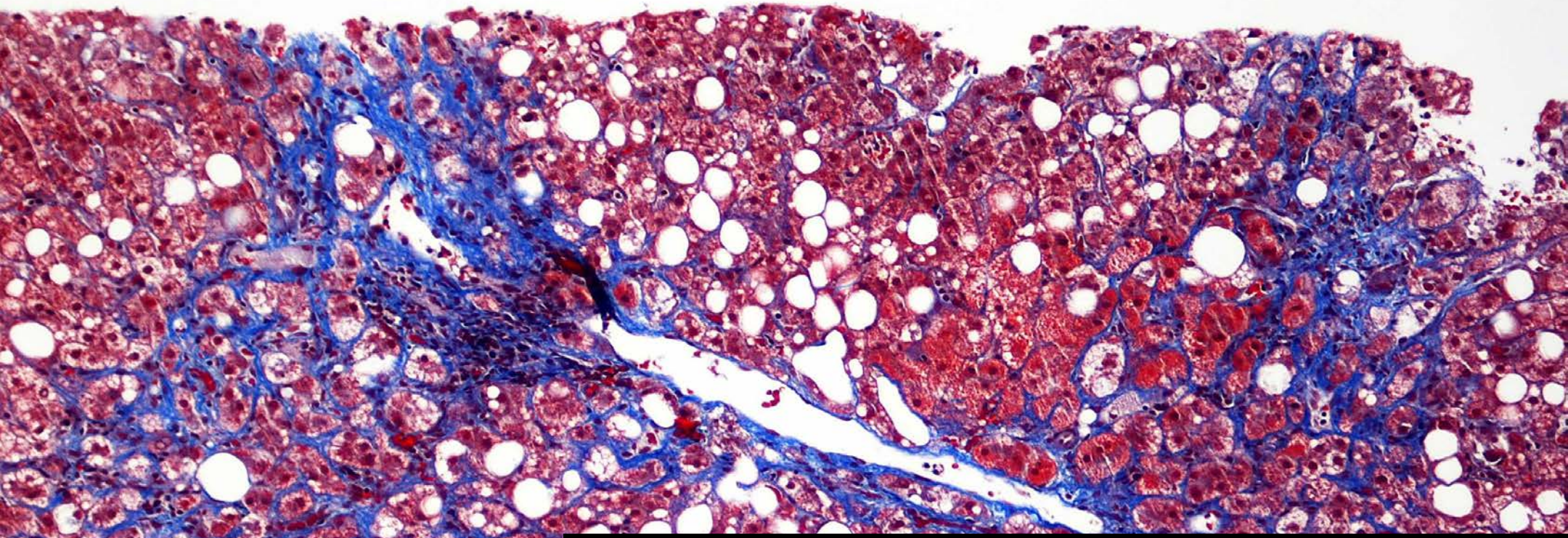




* Vibration controlled transient elastography (VCTE by Fibroscan® - Echosens)



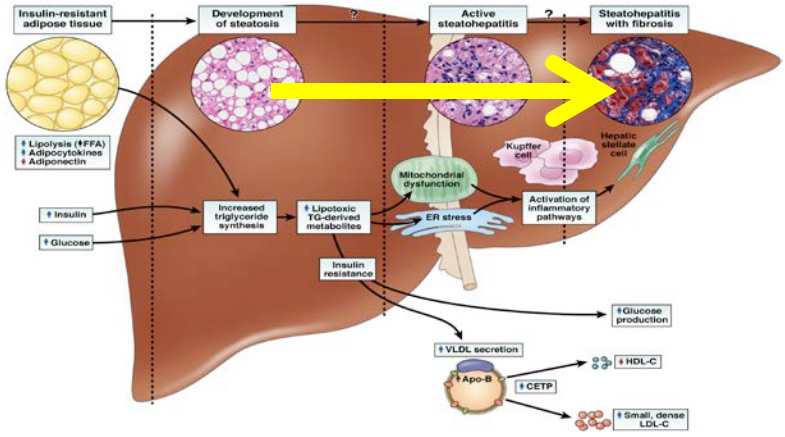
NASH = risk of cirrhosis and hepatocellular carcinoma

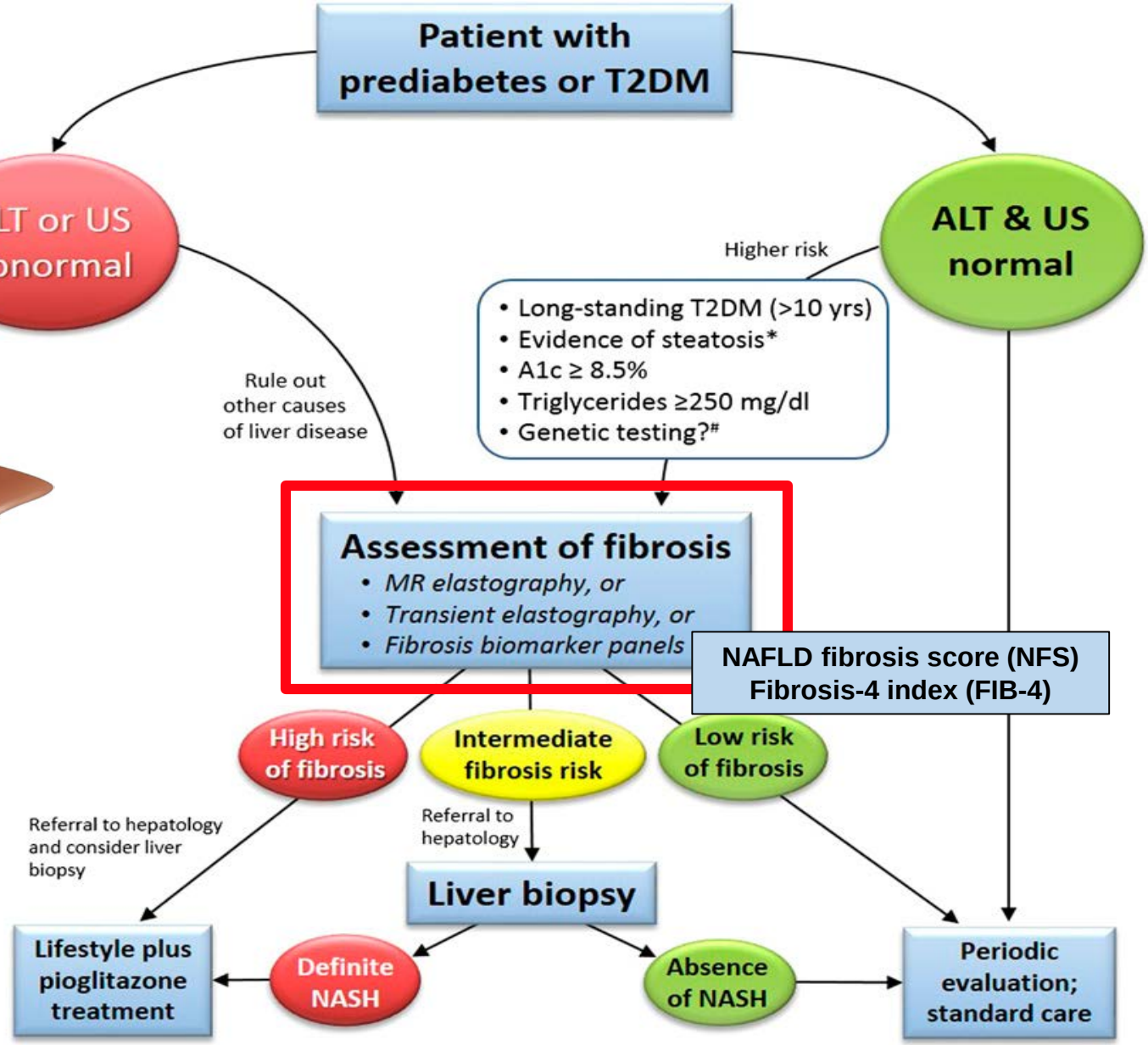


Liver biopsy remains the "suboptimal" gold standard to characterize liver histology in NAFLD/NASH

- Confirms the diagnosis and staging of disease
- Determines prognosis by severity of liver injury and fibrosis
- Limitations: high cost, potential complications, sampling/reader error

Diagnostic Algorithm for NASH in the Primary Care Setting





Bril & Cusi

Diabetes Care, March 2017 40:419-430

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- Mechanisms

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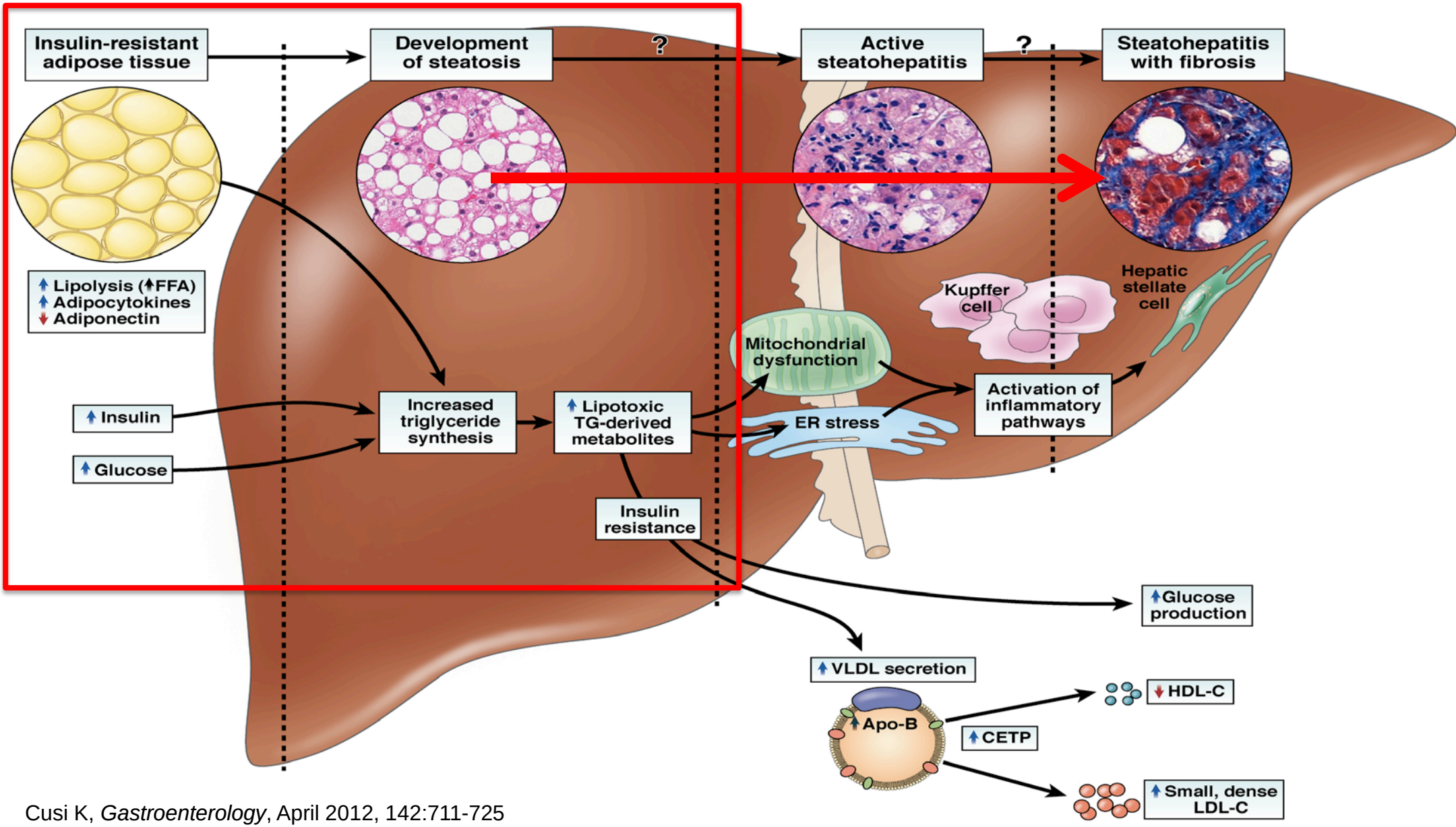
- Liver: risk of cirrhosis, hepatocellular carcinoma
- Extra-hepatic: development of T2DM and of CVD

3. Management

- Diagnosis
- Treatment of NASH, prevention of fibrosis and cirrhosis

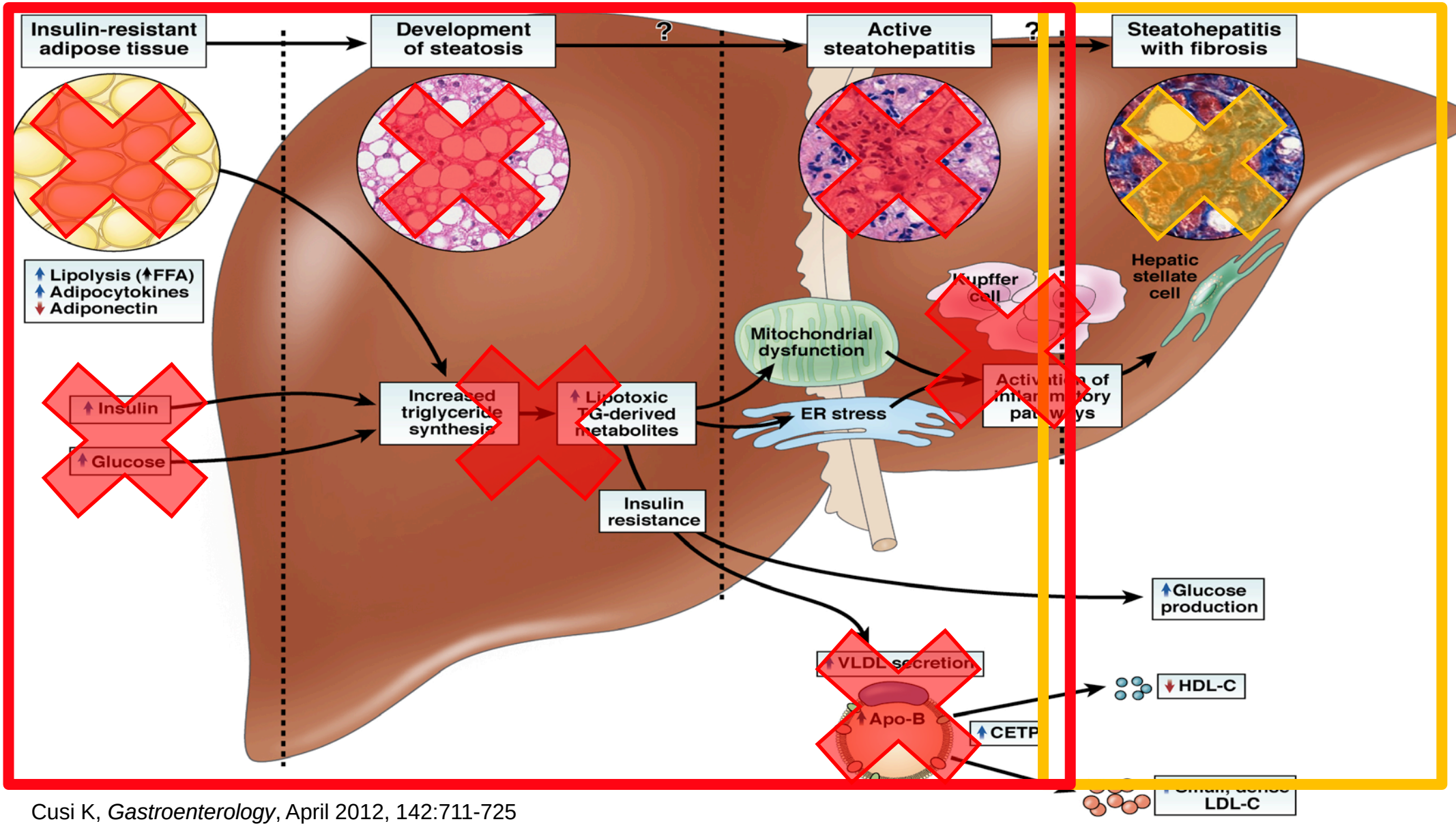

I ♥ DOUBLE STUFFED BURGERS!
"GOOD ON SO MANY LEVELS!"
AVAILABLE NOW, FOR A LIMITED TIME ONLY!

From Obesity to Dyslipidemia, Lipotoxicity (NASH) and Cirrhosis



Cusi K, *Gastroenterology*, April 2012, 142:711-725

The Future: "Combination Therapy" to Prevent Disease Progression



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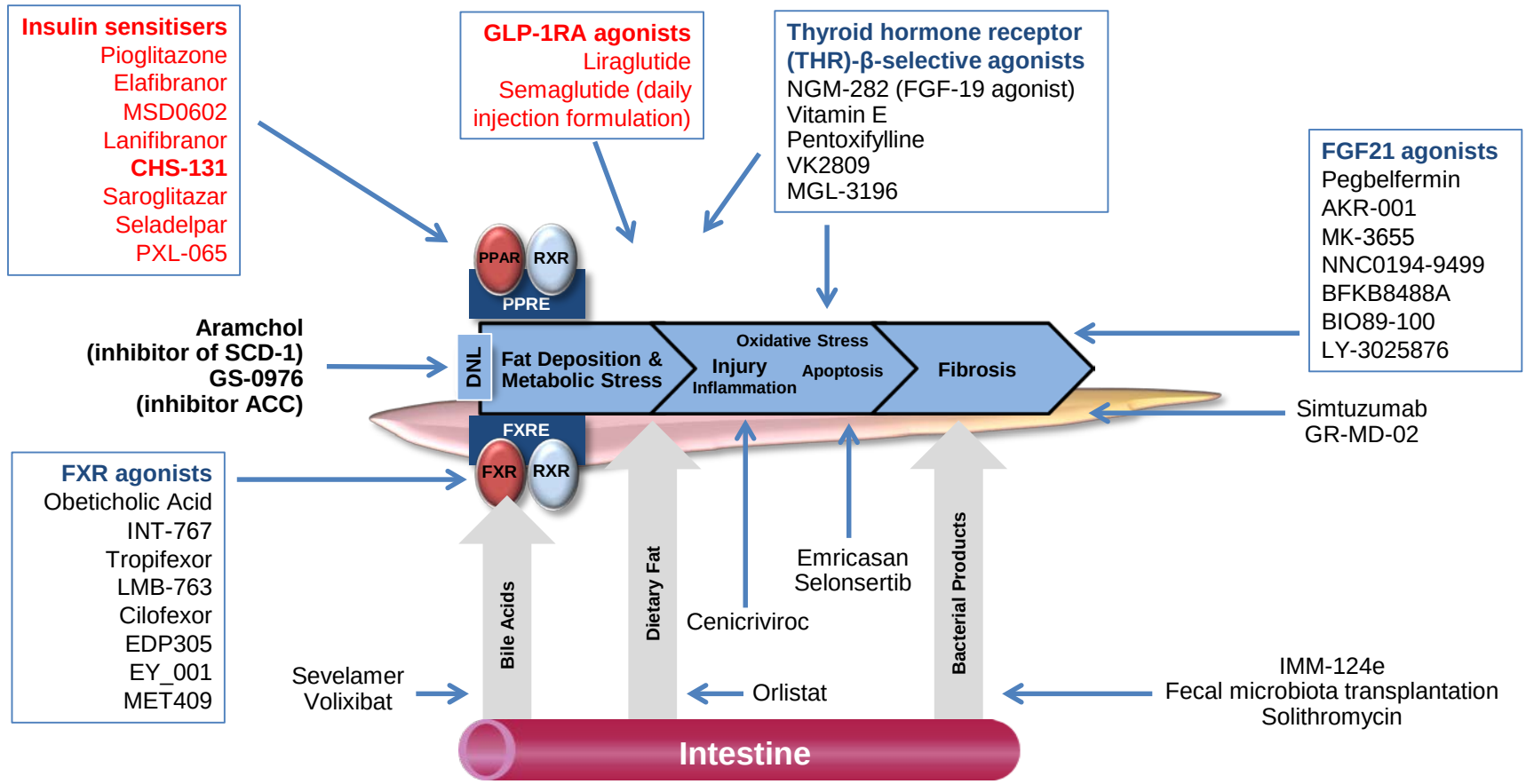
Potential Therapeutic Targets in NASH



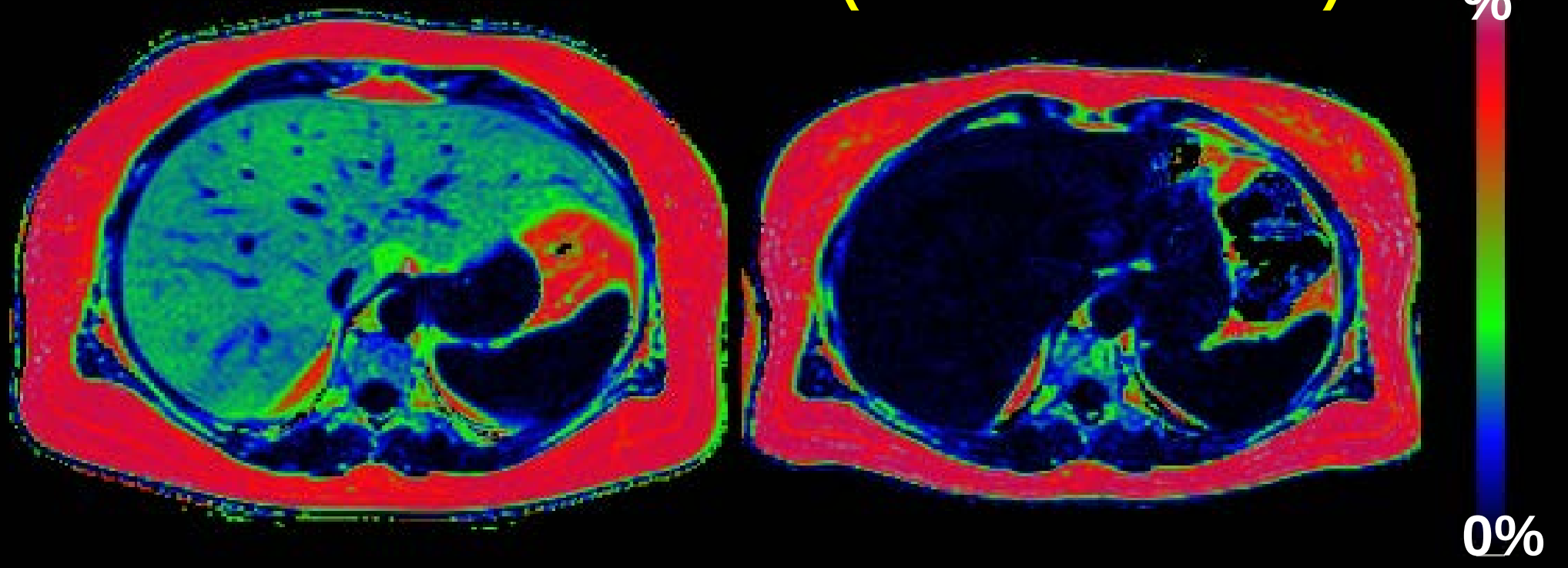
ACC, acetyl-CoA carboxylase; DNL, *de novo* lipogenesis; FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; ; GLP-1RA, glucagon-like peptide-1 receptor agonist; MPC' mitochondrial pyruvate carrier; NASH, non-alcoholic steatohepatitis; PPAR' peroxisome proliferator-activated receptor; RXR, retinoid X receptor.

Adapted from Rotman et al. *Gut.* 2017;66:180–90

Physicians ask:

“Why diagnose NASH if there are no treatments…?”

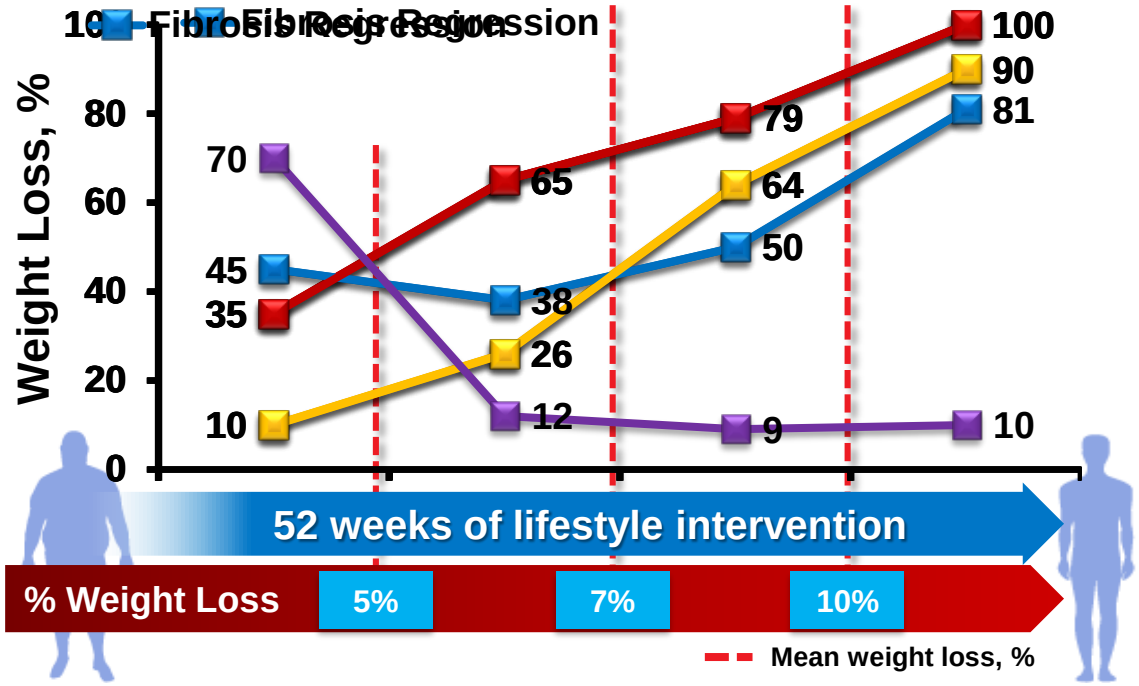
Changes in Liver Fat with a VLCD (600 kcal/day)*

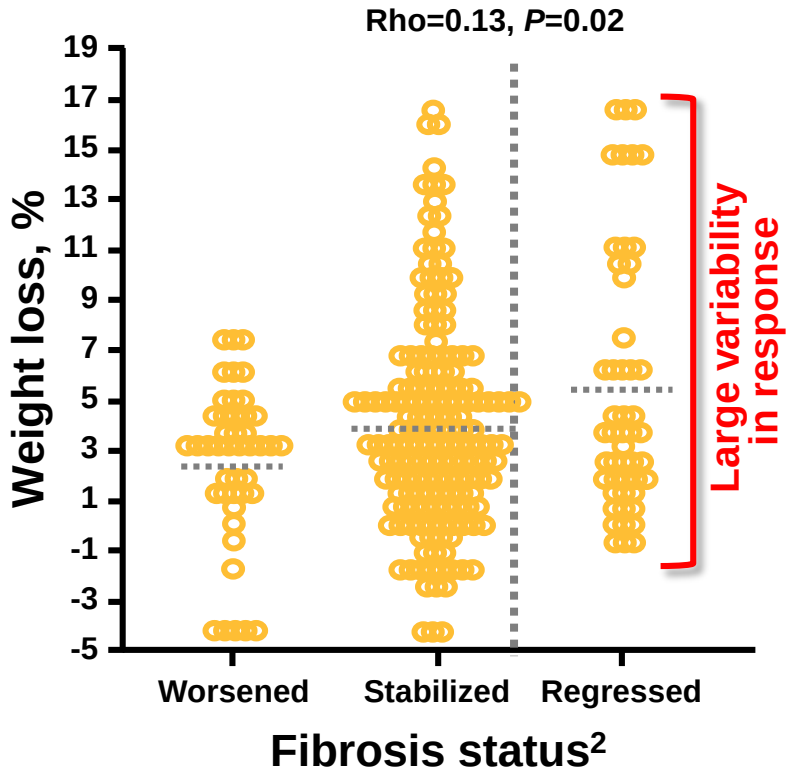


(Courtesy of Dr. R. Taylor)

Increasing Benefit of Weight Loss on Fibrosis

Probability of Improving NASH Components According to Weight Loss[1,2]





[a]At least one stage.

N=293 patients with NASH were encouraged to adopt lifestyle changes for weight loss over 52 weeks.

1. Romero-Gómez M, et al. *J Hepatol*. 2017;67(4):829-846; 2. Vilar-Gomez E, et al. *Gastroenterology*. 2015;149(2):367-378.

The Diagnosis and Management of NAFLD:

Practice Guidance From the American Association for the Study of Liver Diseases (AASLD) 2018

Guidance statements – Weight Loss and Exercise

- **Weight loss (#21):** 3%-5% needed to improve steatosis, but 7%-10% minimal need to improve the majority of the histopathological features of NASH, including fibrosis.

- **Exercise (#22):** Exercise alone may prevent or reduce steatosis, but its ability to improve other aspects of liver histology remains unknown

- **Bariatric surgery (#29-31):**
  - 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.

Chalasani et al, Hepatology 2018

The Diagnosis and Management of NAFLD:

Practice Guidance From the AASLD 2018

Guidance statements – Pharmacological Agents

- **Metformin (#23):** Not recommended for treating NASH in adult patients.

- **Pioglitazone (#24-25):**
  - Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH.
  - Risks and benefits should be discussed with each patient.

- **GLP-1RAs (#26):** It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH.

- **Vitamin E (#27-28) for non-diabetics:**
  - At 800 IU/day improves liver histology in nondiabetic adults with NASH.
  - Risks and benefits should be discussed with each patient.
  - Not recommended for NASH in diabetic patients, NAFLD without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis

Chalasani et al, Hepatology 2018

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The NEW ENGLAND JOURNAL of MEDICINE
NEJM 2006, 355, 2297-2307

ORIGINAL ARTICLE

A Placebo-Controlled Tr
in Subjects with Nonalcol

Renata Belfort, M.D., Stephen A. Harriso
Celia Darland, R.D., Joan Finch, R.N., Jean H
Amalia Gastaldelli, Ph.D., Fermin Tio,
Rachele Berria, M.D., Jennie Z. Ma, F
Russell Havranek, M.D., Chris Fincke, I
George A. Bannayan, M.D., Steven Schenk

GASTROENTEROLOGY 2008;135:1176–1184

Randomized, Placebo-
Subjects With Nonalco

The NEW ENGLAND JOURNAL of MEDICINE
NEJM 2010;362:1675–1685

ORIGINAL ARTICLE

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D., David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D., and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

Annals of Internal Medicine

ORIGINAL RESEARCH

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus

A Randomized, Controlled Trial

Kenneth Cusi, MD; Beverly Orsak, RN; Fernando Bril, MD; Romina Lomonaco, MD; Joan Hecht, RN; Carolina Ortiz-Lopez, MD; Fermin Tio, MD; Jean Hardies, PhD; Celia Darland, RD; Nicolas Musi, MD; Amy Webb, MD; and Paola Portillo-Sanchez, MD

Background: The metabolic defects of nonalcoholic steatohepatitis (NASH) and prediabetes or type 2 diabetes mellitus (T2DM) seem to be specifically targeted by pioglitazone. However, information about its long-term use in this population is limited.

Objective: To determine the efficacy and safety of long-term pioglitazone treatment in patients with NASH and prediabetes or T2DM.

Design: Randomized, double-blind, placebo-controlled trial. (ClinicalTrials.gov: NCT00994682)

Setting: University hospital.

Participants: Patients (n = 101) with prediabetes or T2DM and biopsy-proven NASH were recruited from the general population and outpatient clinics.

Intervention: All patients were prescribed a hypocaloric diet (500-kcal/d deficit from weight-maintaining caloric intake) and then randomly assigned to pioglitazone, 45 mg/d, or placebo for 18 months, followed by an 18-month open-label phase with pioglitazone treatment.

Measurements: The primary outcome was a reduction of at least 2 points in the nonalcoholic fatty liver disease activity score (NAS) (in 2 histologic categories) without worsening of fibrosis. Secondary outcomes included other histologic outcomes, hepatic triglyceride content measured by magnetic resonance and proton spectroscopy, and metabolic parameters.

Results: Among patients randomly assigned to pioglitazone, 58% achieved the primary outcome (treatment difference, 41 percentage points [95% CI, 23 to 59 percentage points]) and 51% had resolution of NASH (treatment difference, 32 percentage points [CI, 13 to 51 percentage points]) (P < 0.001 for each). Pioglitazone treatment also was associated with improvement in individual histologic scores, including the fibrosis score (treatment difference, −0.5 [CI, −0.9 to 0.0]; P = 0.039); reduced hepatic triglyceride content from 19% to 7% (treatment difference, −7 percentage points [CI, −10 to −4 percentage points]; P < 0.001); and improved adipose tissue, hepatic, and muscle insulin sensitivity (P < 0.001 vs. placebo for all). All 18-month metabolic and histologic improvements persisted over 36 months of therapy. The overall rate of adverse ev
groups, although weight gain was g
kg vs. placebo).

Limitation: Single-center study.

Conclusion: Long-term pioglitazon
tive in patients with prediabetes or

Primary Funding Source: Burro
American Diabetes Association.

Annals of Intern Med, 2

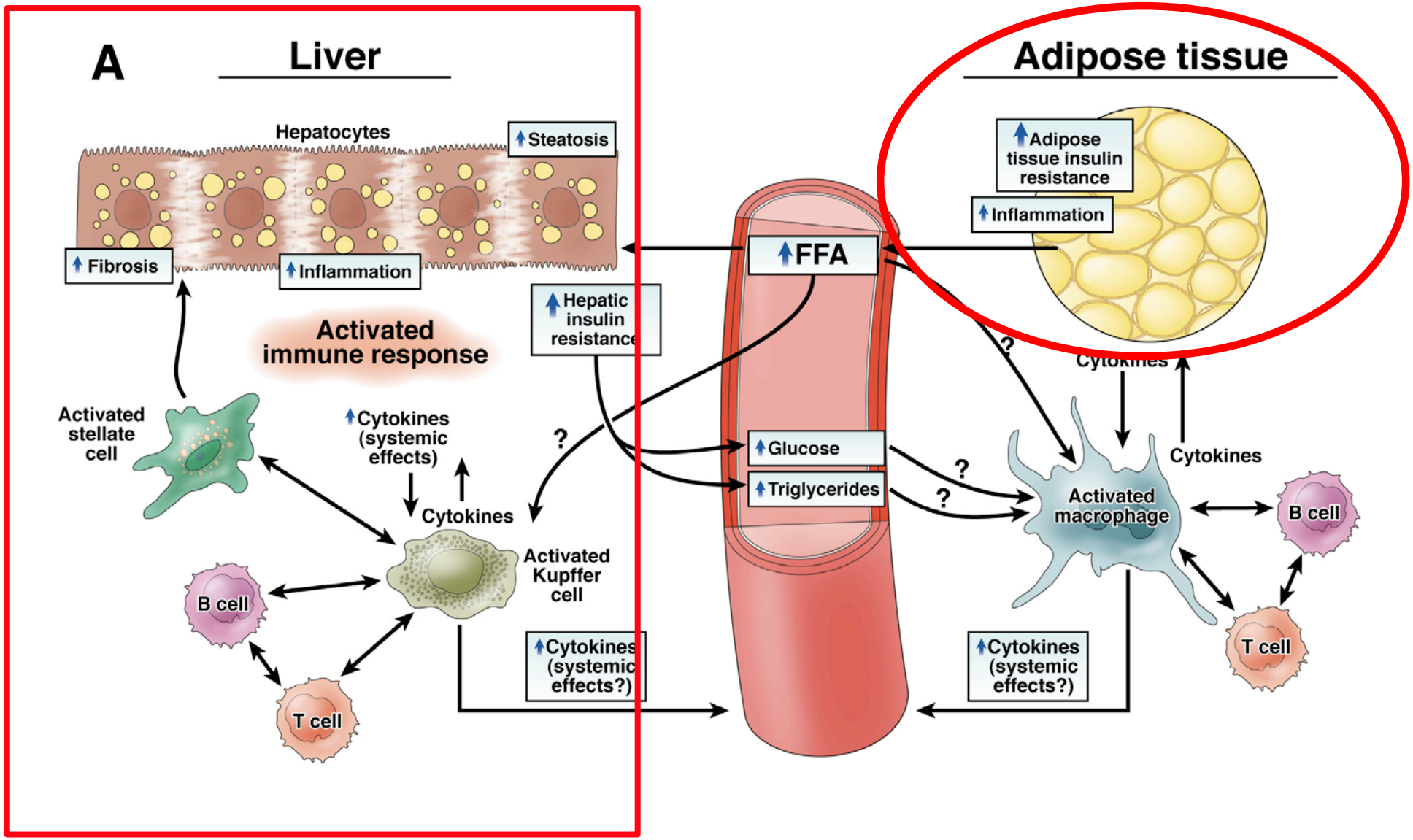
Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes: A Randomized Controlled Trial

Fernando Bril,[1] Diane M. Biernacki,[1] Srilaxmi Kalavalapalli,[1] Romina Lomonaco,[1] Sreevidya K. Subbarayan,[1] Jinping Lai,[2] Fermin Tio,[3] Amitabh Suman,[4] Beverly K. Orsak,[5] Joan Hecht,[6] and Kenneth Cusi[1,7]

Diabetes Care 2019;42:1481–1488 | https://doi.org/10.2337/dc19-0167

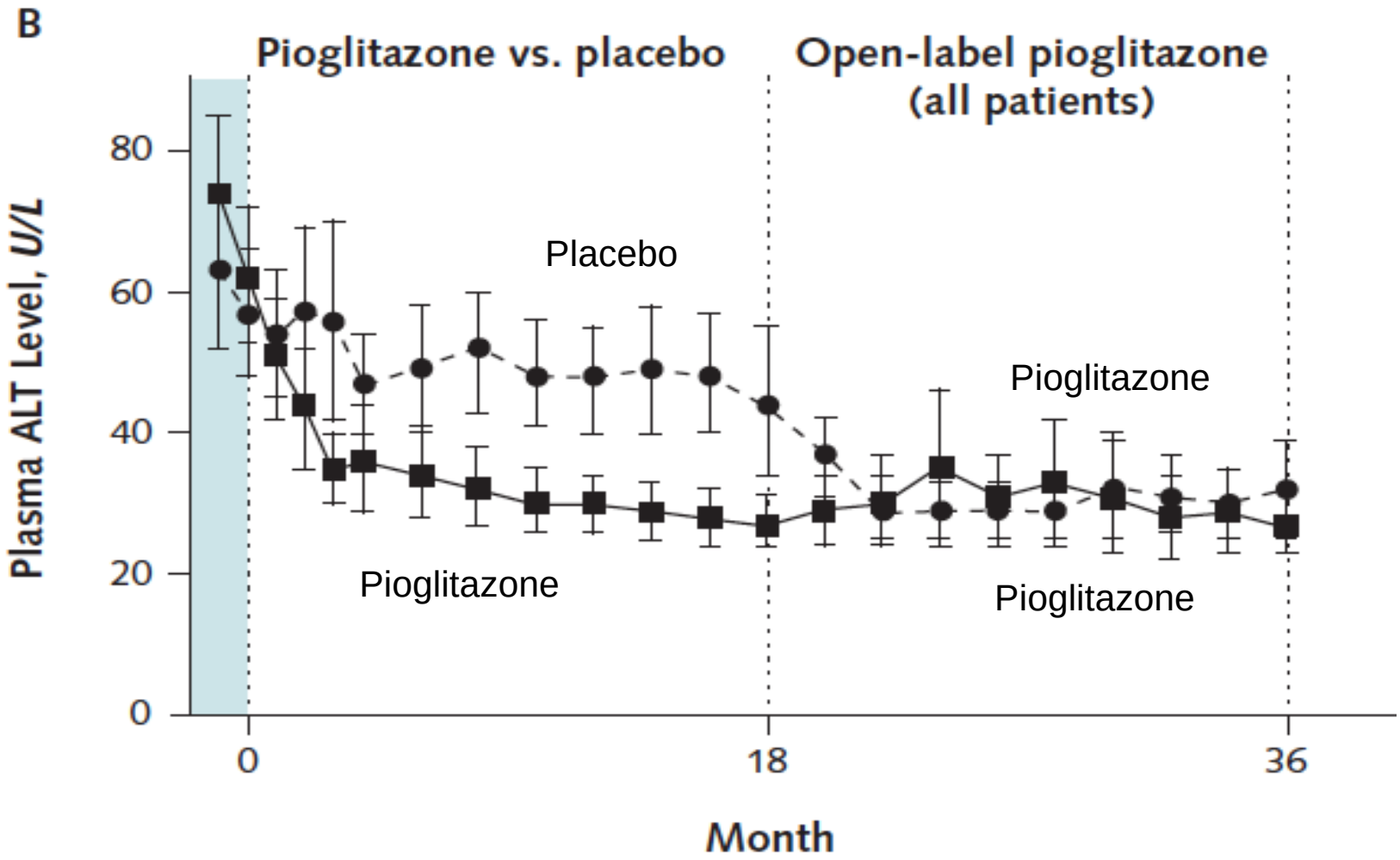
Pioglitazone is not approved for treatment of NAFLD or NASH.

Rationale for Pioglitazone in NASH



Cusi K. Gastroenterology 2012, 142:711-25

Plasma ALT Concentration after 18 months of Pioglitazone or Placebo, and after 18 or 36 Months of Pioglitazone



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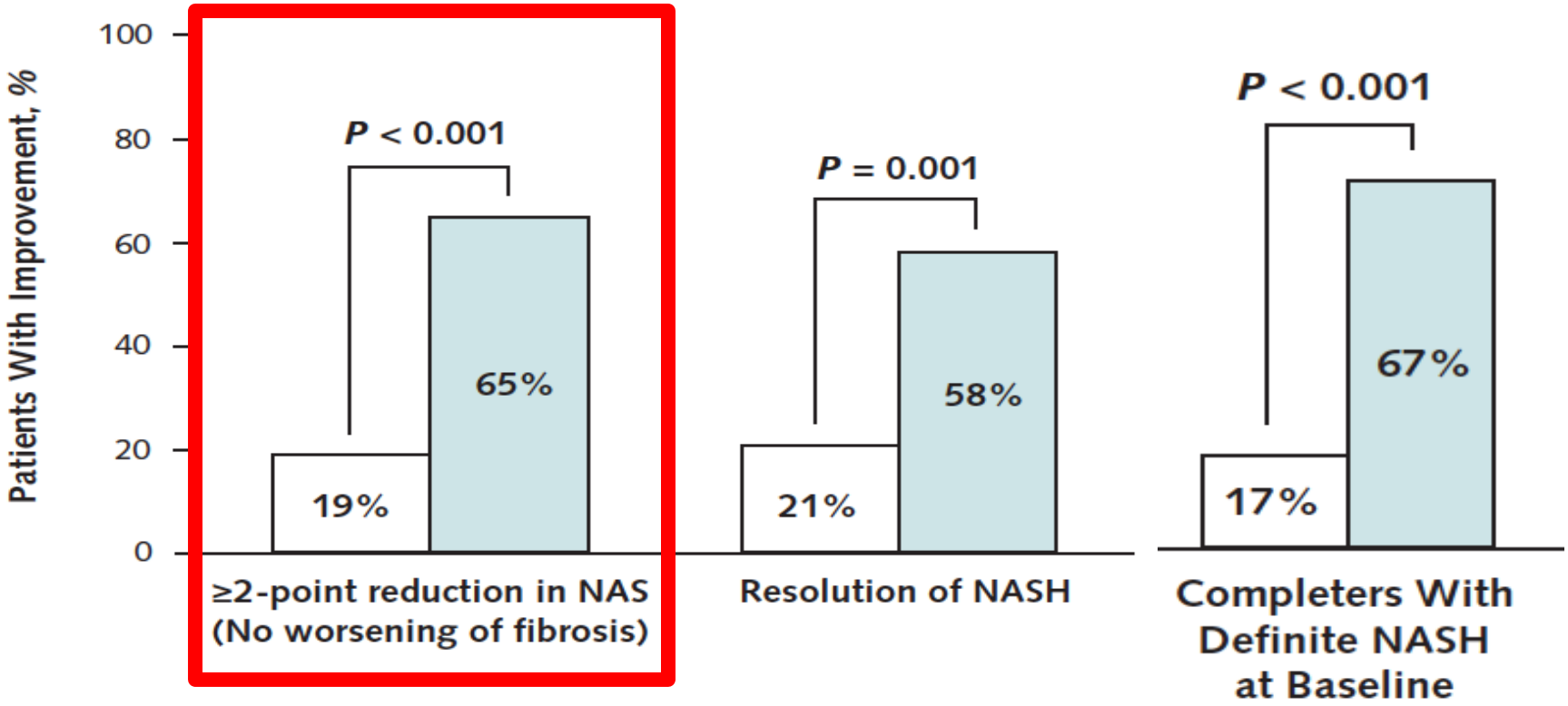
Cusi et al, Annals of Intern Med, 2016;165:305-15.

Long-term Effect of Pioglitazone in NASH

Primary endpoint



~50% response rate vs. placebo

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College of Medicine
College of Medicine

Cusi et al, Annals of Intern Med, 2016;165:305-15.

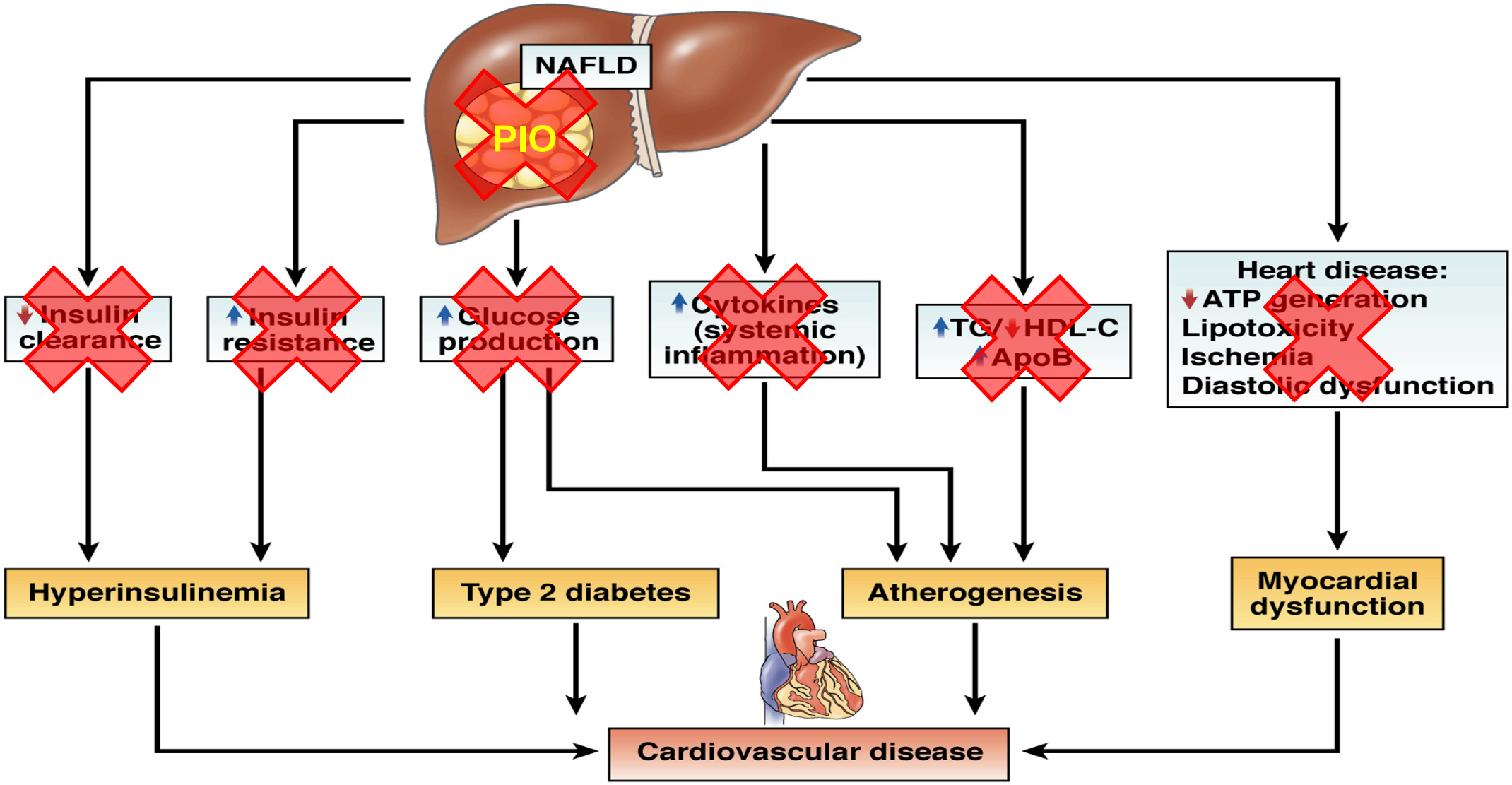
Pioglitazone profile: pros and cons in diabetes

The "good"

- **Liver:**
  - Resolution of NASH in ~ 30 to 40% (placebo-subtracted)
  - Prevention of fibrosis progression
- **Extra-hepatic**
  - Reversal of IR, systemic inflammation, ectopic fat deposition and lipotoxicity
  - Improved lipid panel (lower TG; higher HDL-C)
  - Reduction of cardiovascular disease
  - Prevention of type 2 DM and durable metabolic effects in diabetes

Khan, Bril, Cusi and Newsome, Hepatology 2019

Cardiovascular Consequences of NAFLD



Cusi K, *Gastroenterology*, April 2012, 142:711-725

Pioglitazone Reduces CVD, Prevents Progression of Atherosclerosis and Improves LV Function

- PROACTIVE (Lancet 2006)
- CHICAGO (JAMA 2007)
- PERISCOPE (JAMA 2008)
- IRIS Study (NEJM 2016; Circulation 2017; JAMA 2019)

Pioglitazone Improves Left Ventricular Diastolic Function in Subjects With Diabetes

Diabetes Care 2017;40:1530–1536 | https://doi.org/10.2337/dc17-0078

Geoffrey D. Clarke,[1,2] Carolina Solis-Herrera,[1] Marjorie Molina-Wilkins,[1] Sandra Martinez,[1] Aurora Merovci,[1] Eugenio Cersosimo,[1] Robert J. Chilton,[3] Patricia Iozzo,[5] Amalia Gastaldelli,[1,5] Muhammad Abdul-Ghani,[1] and Ralph A. DeFronzo[1,4,6]

JAMA Neurology | Original Investigation

Pioglitazone Therapy in Patients With Stroke and Prediabetes
A Post Hoc Analysis of the IRIS Randomized Clinical Trial

J. David Spence, MD; Catherine M. Viscoli, PhD; Silvio E. Inzucchi, MD; Jennifer Dearborn-Tomazos, MD; Gary A. Ford, MB, Bchir; Mark Gorman, MD; Karen L. Furie, MD; Anne M. Lovejoy, PA-C; Lawrence H. Young, MD; Walter N. Kernan, MD; for the IRIS Investigators

JAMA Neurology, February 2019

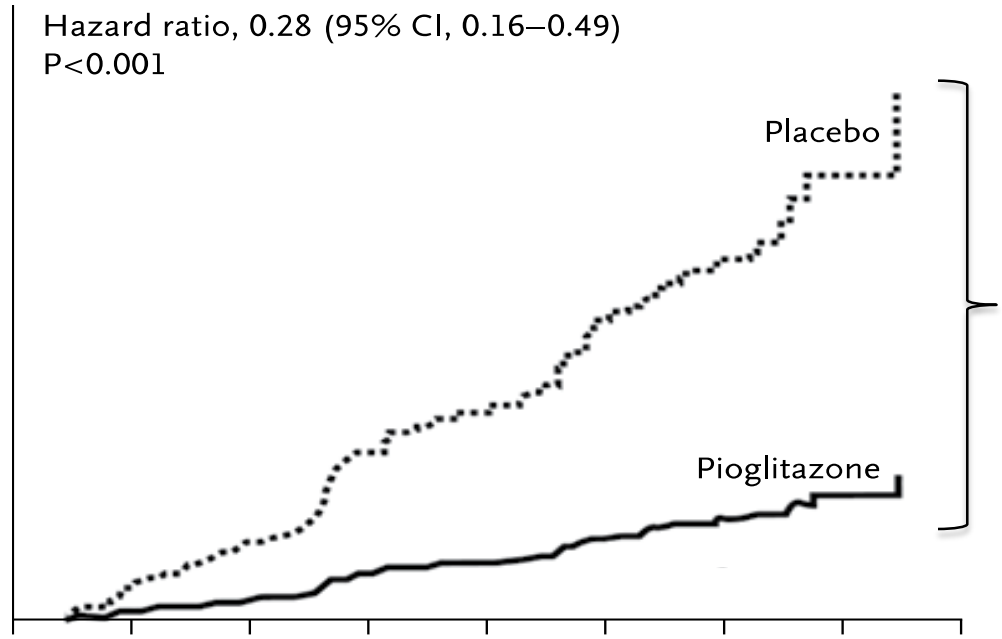
n = 1454

Table 2. Hazard Ratios in Cox Regression for On-Treatment and Intention-to-Treat Analyses

Variable	Hazard Ratio (95% CI)	*P* Value	NNT
Adherence ≥80%			
Stroke/MI	0.57 (0.39-0.84)	.004	24
Stroke	0.64 (0.42-0.99)	.04	39
Acute coronary syndrome	0.47 (0.26-0.85)	.01	40
Stroke/MI/HF hospitalization	0.61 (0.42-0.88)	.008	26
New-onset diabetes	0.18 (0.10-0.33)	<.001	12
Intention to treat			
Stroke/MI	0.70 (0.56-0.88)	.002	28
Stroke	0.72 (0.56-0.93)	.01	39
Acute coronary syndrome	0.72 (0.52-1.00)	.052	62
Stroke/MI/HF hospitalization	0.78 (0.63-0.96)	.02	34
New-onset diabetes	0.46 (0.35-0.61)	<.001	19

CONCLUSIONS AND RELEVANCE Pioglitazone may be effective for secondary prevention in patients with stroke/transient ischemic attack and with prediabetes, particularly in those with good adherence.

ACT NOW study: Pioglitazone prevents Type 2 Diabetes



72% reduction in new onset diabetes

DeFronzo et al, NEJM 364, 1104-11, 2011

Pioglitazone profile: pros and cons in diabetes

The "good"

- **Liver:**
  - Resolution of NASH in ~ 30 to 40% (placebo-subtracted)
  - Prevention of fibrosis progression
- **Extra-hepatic**
  - Reversal of IR, systemic inflammation, ectopic fat deposition and lipotoxicity
  - Improved lipid panel (lower TG; higher HDL-C)
  - Reduction of cardiovascular disease
  - Prevention of type 2 DM and durable metabolic effects in diabetes

Watch for

- **Edema:** 5-8% (more if combined with insulin or amlodipine)
- **Risk of bone loss:** should be monitored
- **Bladder cancer?** Unclear, likely very small if so (18 out of 23 studies negative)
- **Weight gain:** 2 to 4 kg (dose-dependent; although less insulin resistance and metabolically healthy fat…)

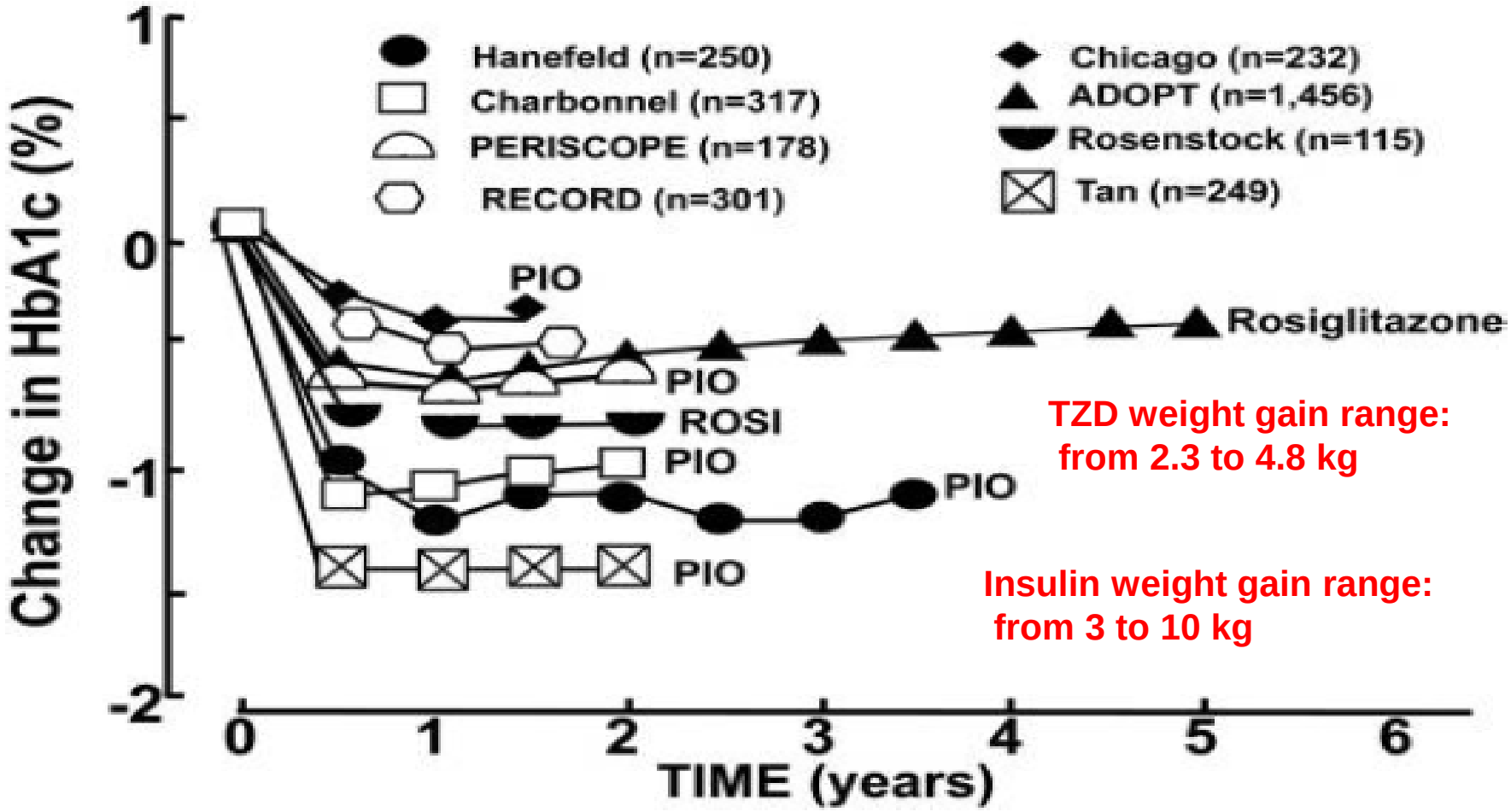
Khan, Bril, Cusi and Newsome, Hepatology 2019

Effect of Low-dose (15 mg/day) Pioglitazone in Patients with T2DM

Author	Dose	Population	n	Duration	diff FPG	diff A1c	diff TG	diff HDL	Weight change
Dose-response studies	(mg/day)			(weeks)	(mg/dL)	%	%	%	%
Aronoff et al, 2000* [24]	15	USA	80	26	-39	–1.0%	-14%	6%	1%
	30		79		-41	–1.0%	-14%	4%	1%
Miyazaki et al, 2002* [25]	15	USA	12	26	-31	–1.3%	-28%	6%	2%
	30		11		-66	–2.0%	-40%	7%	3%
Rosenstock, 2002* [26]	15	USA	188	16	-35	–1.0%	-21%	7%	2%
	30		187		-48	–1.3%	-23%	9%	4%
Rajagopalan, 2015* [27]	15	India	28	26	-40	–0.6%	-18	3%	1%
	30		29		-41	–0.7%	-24	4%	2%

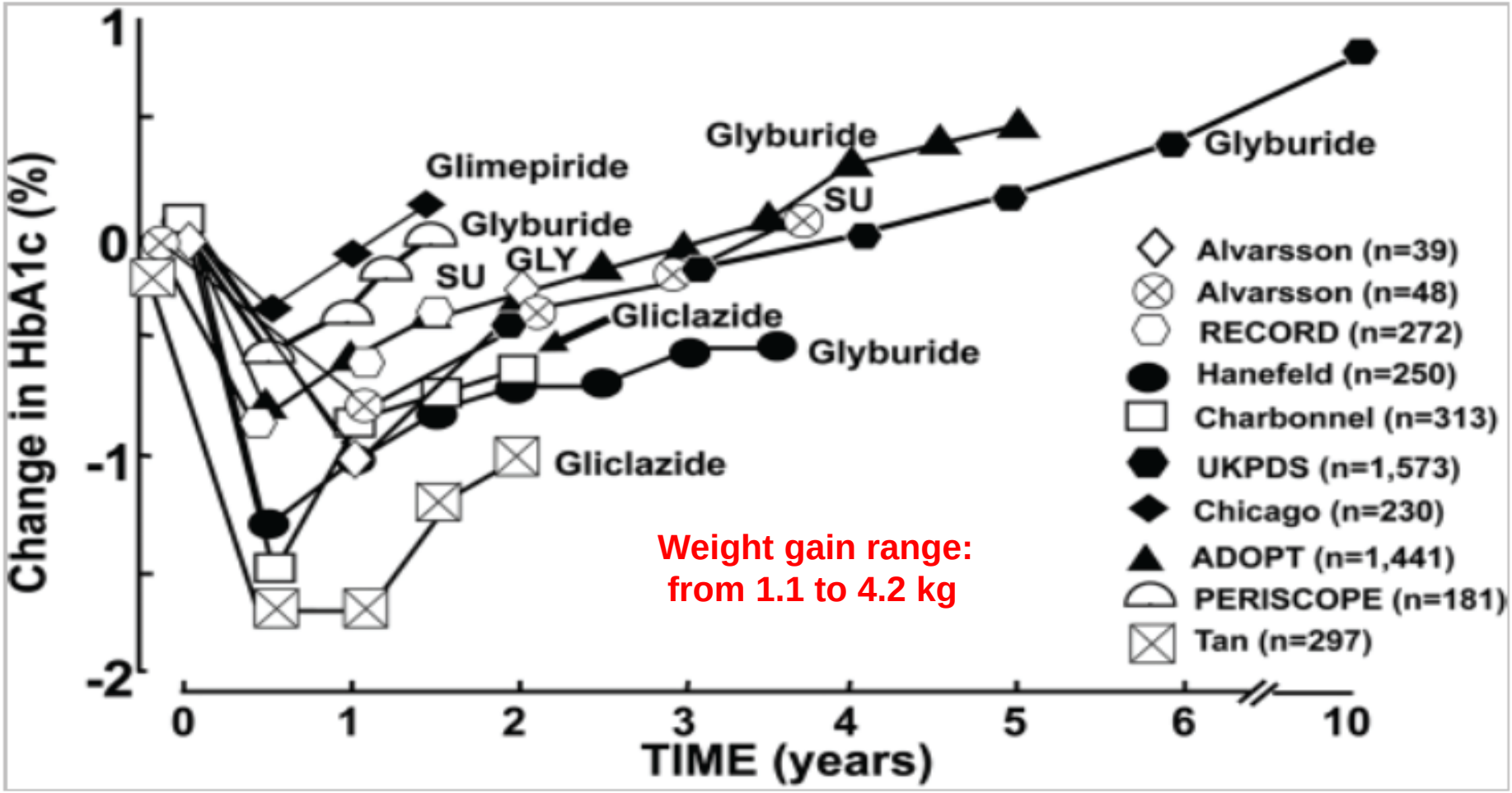
Cusi, 2019 (unpublished)

Prolonged Durability of Glycemic Control with Thiazolidinediones – but Weight Gain



DeFronzo RA, Diabetes. 2009; 58:773–795.

Weight Gain and Poor Durability with Sulfonylurea Treatment in T2DM



DeFronzo RA, Diabetes. 2009; 58:773–795.

Direct and Indirect effects of GLP-1 RA in Humans

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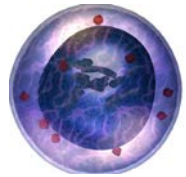
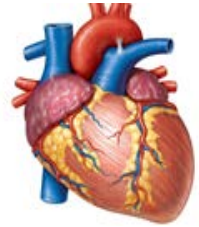
Immune cells
↓ Inflammation

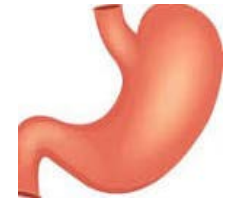


Heart



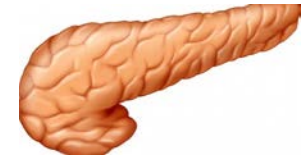
↑Cardiac Function
↑LV Ejection fraction
↑Coronary Flow
↓Infract size

Stomach

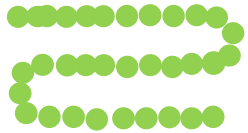


↓ Gastric emptying

Pancreas



↑ Insulin secretion
↓ Glucagon secretion
↑ βcell proliferation
↓ βcell Apoptosis

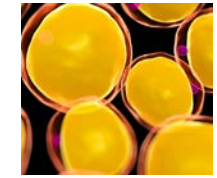


GLP-1R Agonist

Kidneys

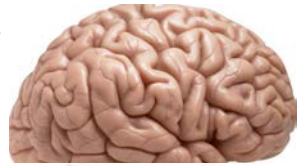
↑ Natriuresis
↓ Blood Volume

Adipocytes



↓White adipocyte
↑Brown adipocyte

Brain



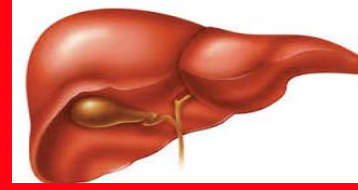
Hypothalamic Nuclei

Early Satiety
Food intake
Neuroprotection

Weight loss

Indirect effect

Liver



↓Steatosis
↓Glucose out put

Dhir G and Cusi K. Journal Invest Med September 2017

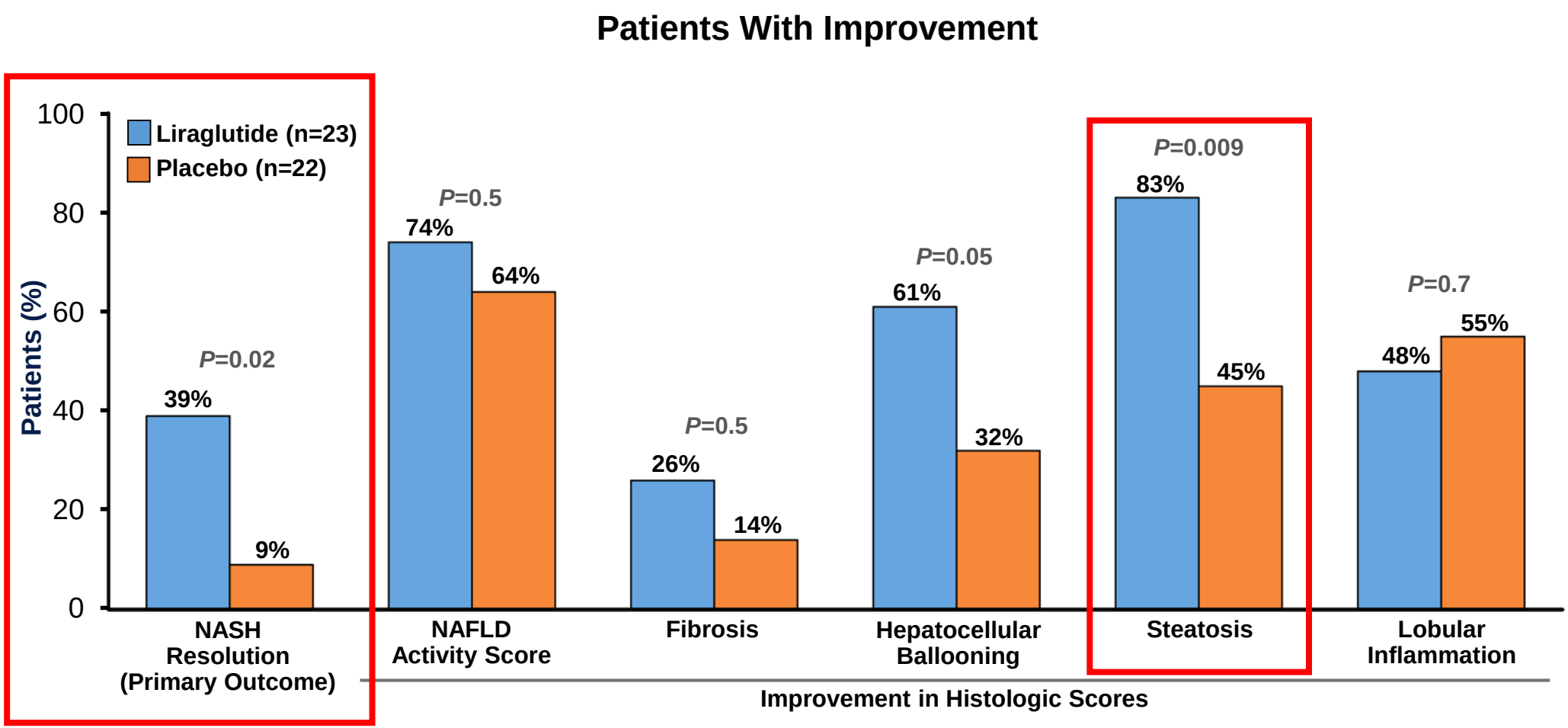
Effect of Liraglutide in Patients with T2DM and NAFLD

Author	N	Duration (Weeks)	Comparator	Main Study Results		
				Weight	ALT	Liver Fat
Open-label studies						
Ohki et al. (2012)	82	74	Sitagliptin, pioglitazone	↓	↓	n/a
Eguchi (2015)	19	24	Lifestyle	↓	↓	↓†
Tang et al. (2015)	35	12	Insulin	↓	Unchanged	Unchanged
Feng et al. (2017)	87	24	Gliclazide, metformin	↓	↓	↓‡
Bouchi et al. (2017)*	17	24	Insulin alone	↓	↓	↓
Petit et al. (2017)	68	24	Insulin alone	↓	↓	↓
Matikainen et al. (2018)	22	16	Lifestyle	↓	Not reported	↓
RCTs						
Smits et al. (2016)	18	12	Sitagliptin or placebo	Unchanged	Unchanged	Unchanged
Armstrong et al. (2016)	52	48	Placebo	↓	↓	↓§
Vanderheiden et al. (2016)*	71	24	Insulin alone	↓	↓	↓
Frossing et al. (2018)	72	26	Placebo	↓	↓	↓

Statistically significant changes vs. comparison(s) indicated by arrows.
*Liraglutide plus insulin vs. insulin alone.
†Ten of 19 had a repeat liver biopsy; NAFLD activity score improved in 6.
‡Reduced more vs. gliclazide (but not metformin).
§Improvement on histology (NAFLD activity score) greater with liraglutide on paired liver biopsies.
Abbreviations: ALT, alanine aminotransferase; n/a, not applicable.

Cusi K. Hepatology Hepatology. 2019 Jun;69:2318-2322.

LEAN Study (Liraglutide Efficacy and Action in NASH): Changes in Liver Histologic Features at Week 48

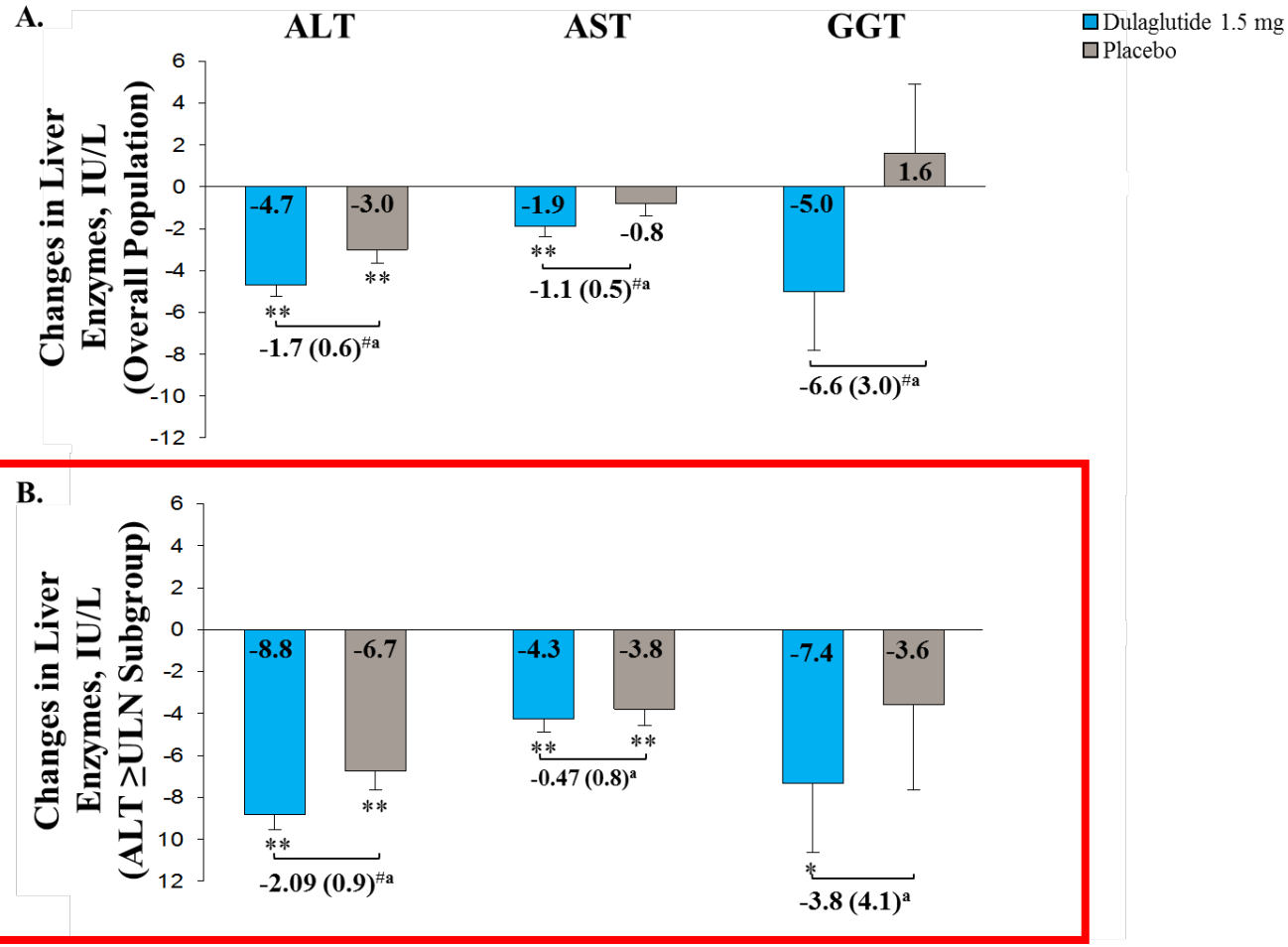


Armstrong MJ, et al. *Lancet.* 2016;387:679-690.

Effect of Dulaglutide in Patients with T2DM: Changes in Plasma ALT, AST and GGT at 24 weeks

All Patients

Patients with NAFLD



*p<0.05 and **p<0.001 vs. baseline; #p<0.05 vs. placebo.
Treatment difference [LSM difference (SE)].
Note: Integrated data from AWARD-1, AWARD-5, AWARD-8 and AWARD-9.

Cusi et al. Diabetic Medicine. 2018; 35:1434-1439.

Effect of Sitagliptin in Patients with T2DM and NAFLD

Author	N	Duration (Weeks)	Comparator	Main Study Results		
				Weight	ALT	Liver Fat (IHTG*)
Open-label studies						
Iwasaki et al. (2011)	30	16	None	Not reported	↓	n/a
Ohki et al. (2012)	82	74	Liraglutide, pioglitazone	Unchanged	↓	n/a
Fukuhara et al. (2014)	44	52	None	Not reported	Unchanged	n/a
Asakawa et al. (2015)	62	57	None	Not reported	Unchanged	n/a
Kato et al. (2015)	20	24	Glimepiride	↓	Not reported	↓
Alam et al. (2018)	40	52	Lifestyle	Unchanged	↓	↓†
Sayari et al. (2018)	138	16	Sitagliptin + synbiotic	↓	↓	n/a
RCTs						
Smits et al. (2016)	18	12	Liraglutide or placebo	Unchanged	Unchanged	No change vs. placebo
Cui et al. (2016)	50	24	Placebo	Unchanged	Unchanged	No change vs. placebo
Joy et al. (2017)	12	24	Placebo	Unchanged	Unchanged	No change vs. placebo‡

Statistically significant changes vs. comparison indicated by arrows.
*Liver fat measured with MRI-based imaging.
†Improvement on histology (NAFLD activity score) greater with sitagliptin on paired liver biopsies.
‡No significant improvement in liver histology on paired liver biopsies.
Abbreviations: ALT, alanine aminotransferase; n/a, not applicable.

Cusi K. Hepatology Hepatology. 2019 Jun;69:2318-2322.

Effect of SGLT2 Inhibitors on Intrahepatic Triglycerides in Patients with T2DM and NAFLD

Author	Agent	n	Duration (weeks)	Comparator	Main study results: Body weight*	Main study results: ALT	Main study results: Liver fat*
Prospective open label studies							
Ito et al, 2017	Ipragliflozin	66	24	Pioglitazone	↓ 3.7%	↓ ¶	↓ ¶
Ohta et al, 2017	Ipragliflozin	20	24	Standard care	↓2.5%	↓	↓39%
Shibuya et al, 2017	Luseogliflozin	32	24	Standard care	↓ 3.2%	unchanged	↓ ¶
Kuchay et al, 2018	Empagliflozin	50	20	Standard care	↓ 1.1%	↓	↓ 26%
Shimizu et al, 2019	Dapagliflozin	57	24	Standard care	↓ 3.1%	↓	↓ †
Inohue et al, 2019	Canagliflozin	20	52	Standard care	↓ 3.4%	↓	↓ 31%
Randomized controlled trials							
Bolinder et al, 2012	Dapagliflozin	67	24	placebo	↓ 2.2%	-	unchanged
Eriksson et al, 2018	Dapagliflozin	84	12	placebo	↓ 2.2%	↓	↓ 10% §
Cusi et al, 2019	Canagliflozin	56	24	placebo	↓ 3.4%	unchanged	↓ 18% §
Latva-Rasku et al, 2019	Dapagliflozin	32	8	placebo	↓ 2.1%	unchanged	↓ 13%
Kahl et al, 2019	Empagliflozin	84	24	placebo	↓ 2.4%	unchanged	↓ 22%

Arrows indicate statistically significant changes vs. comparator

* Comparison-corrected (open-label) or placebo-corrected relative treatment difference in weight and liver fat measured with MRI-based imaging techniques.

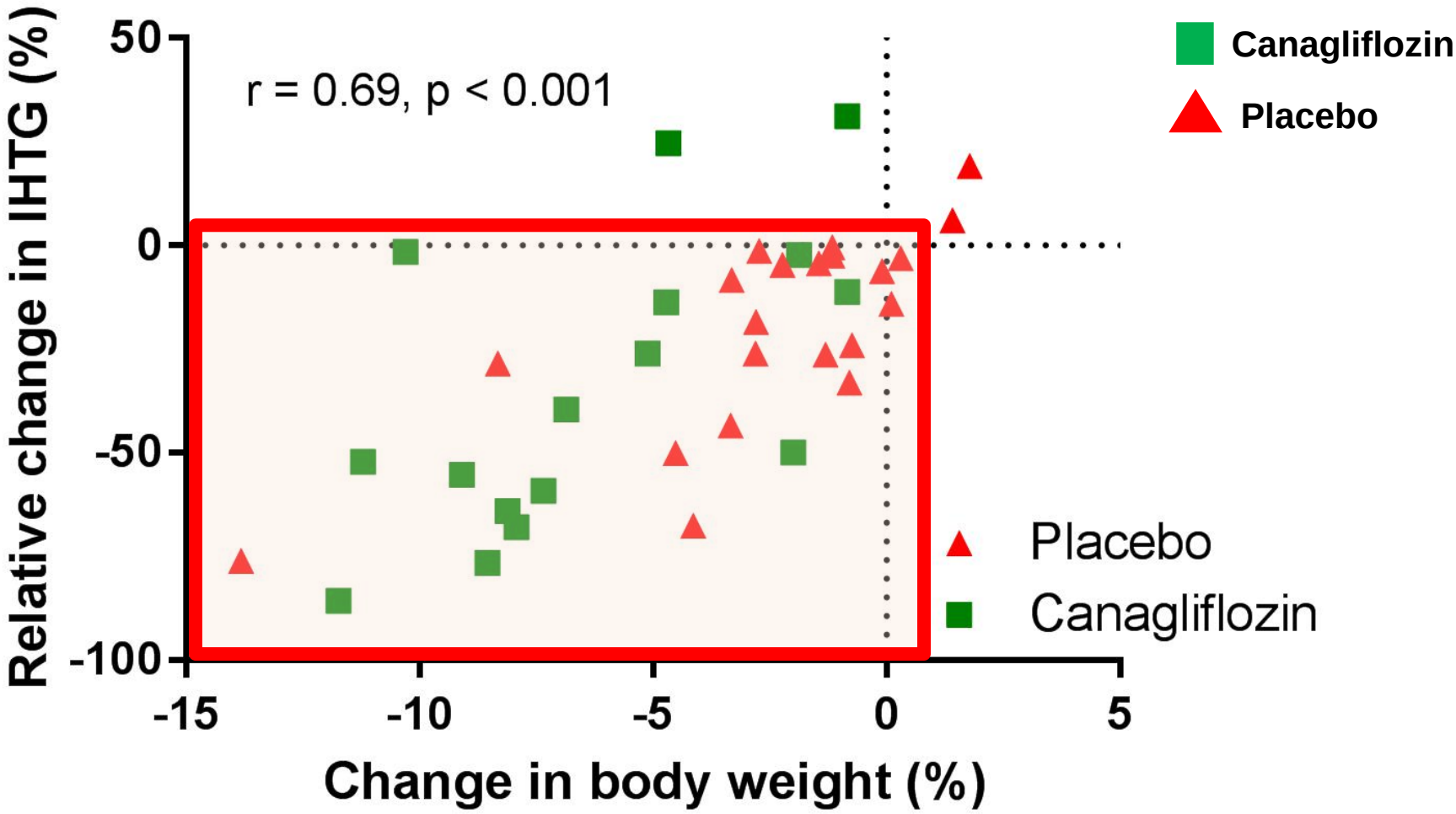
¶ Liver fat measured as liver-to-spleen attenuation ratio on computed tomography. Decrease similar to pioglitazone (comparator) in this trial (also ALT).

† Significant improvement in liver fat by controlled attenuation parameter (CAP; Fibroscan®).

§ Not significant compared to placebo

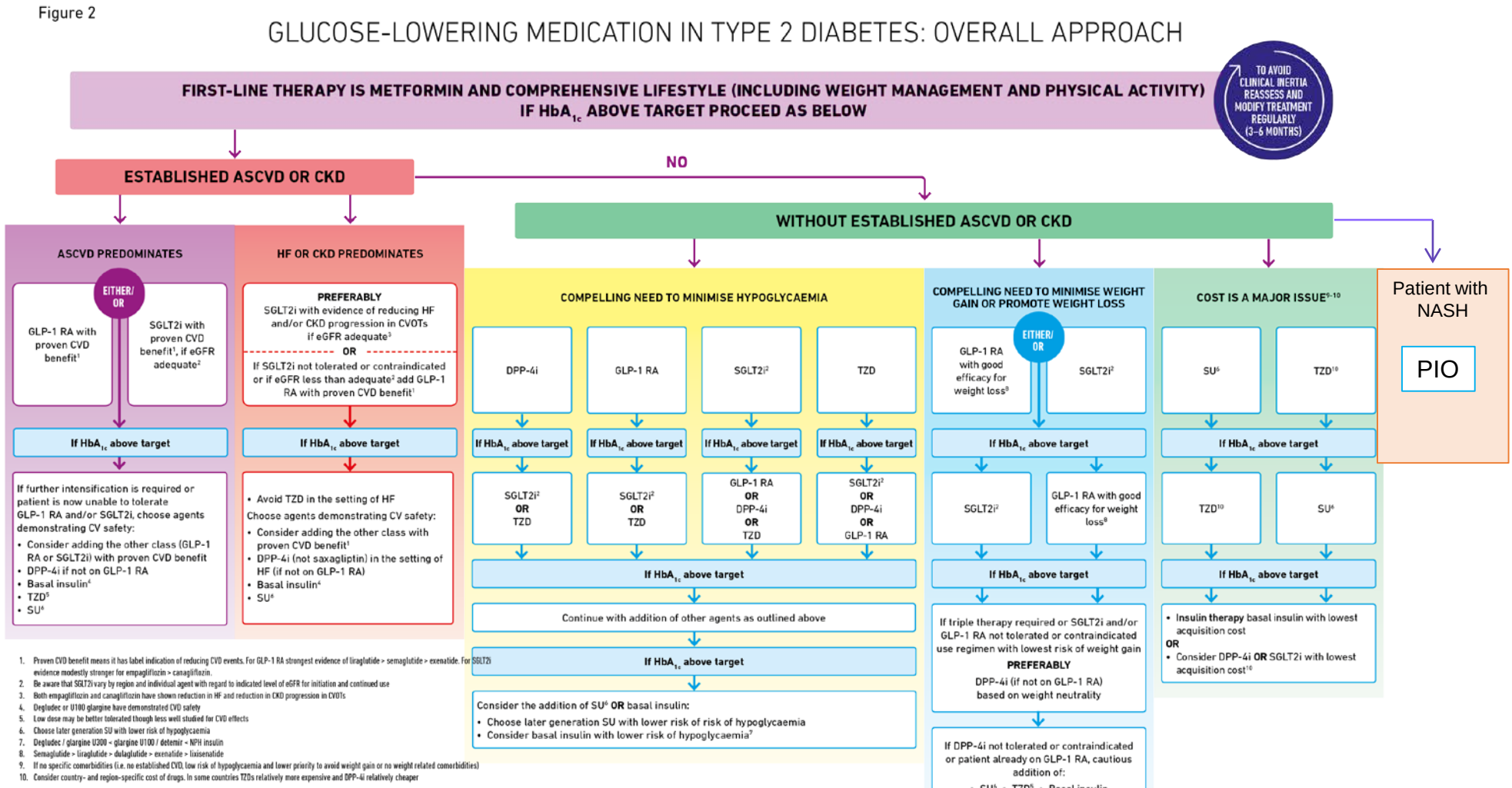
Cusi KI, Diabetes Care 2020 (in press)

Effect of Canagliflozin on Intrahepatic Triglycerides in Patients with Type 2 Diabetes



Cusi K, Bril F, Polidori D et al, Diabetes, Obesity and Metabolism 2019

Figure 2



Davies et al, Diabetes Care 2018;41:2669–2701

NAFLD in Type 2 Diabetes (T2DM)

1. T2DM and risk of NAFLD/NASH

- Prevalence and risk factors
- Mechanisms

2. Complications

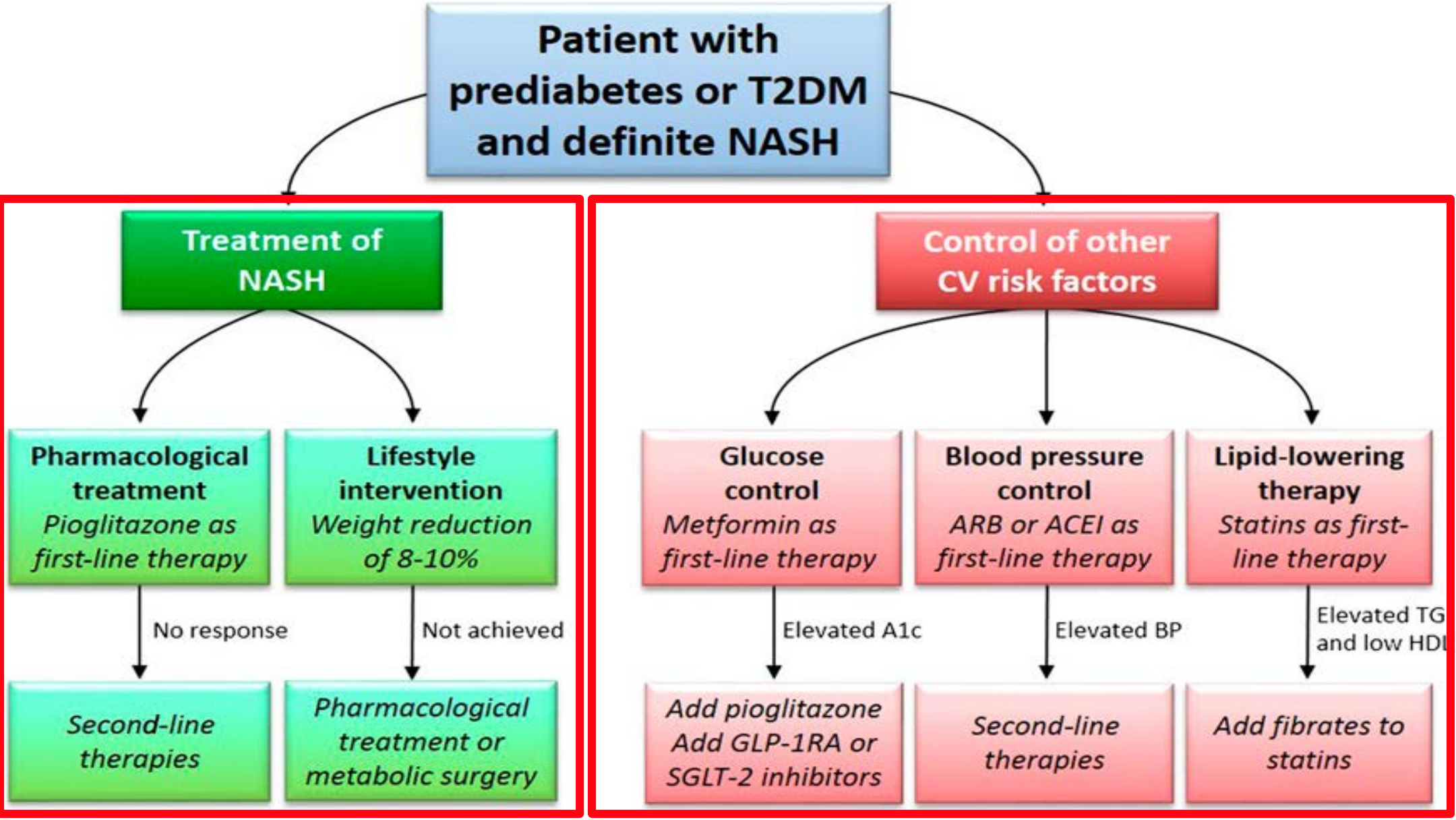
- Liver: risk of cirrhosis, hepatocellular carcinoma
- Extra-hepatic: development of T2DM and of CVD

3. Management

- Diagnosis
- Treatment: a) Liver disease

  b) Extra-hepatic: T2DM prevention and CVD

Treatment of NASH



Bril & Cusi, Diabetes Care 2017 40:419-430

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2019*

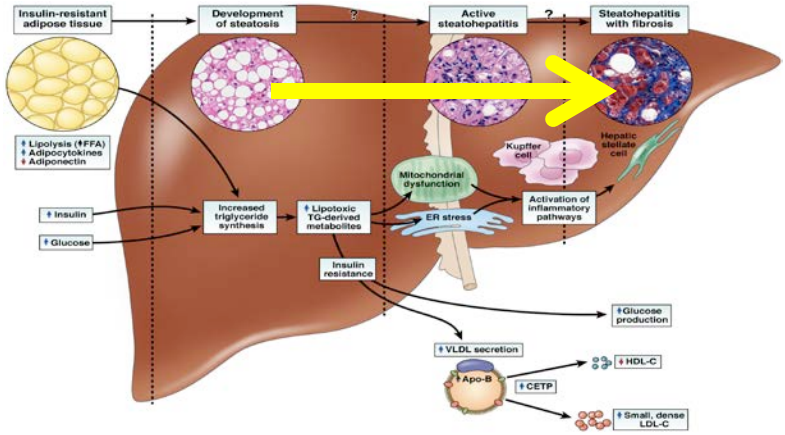
Diabetes Care 2019;42(Suppl. 1):S34–S45 | https://doi.org/10.2337/dc19-S004

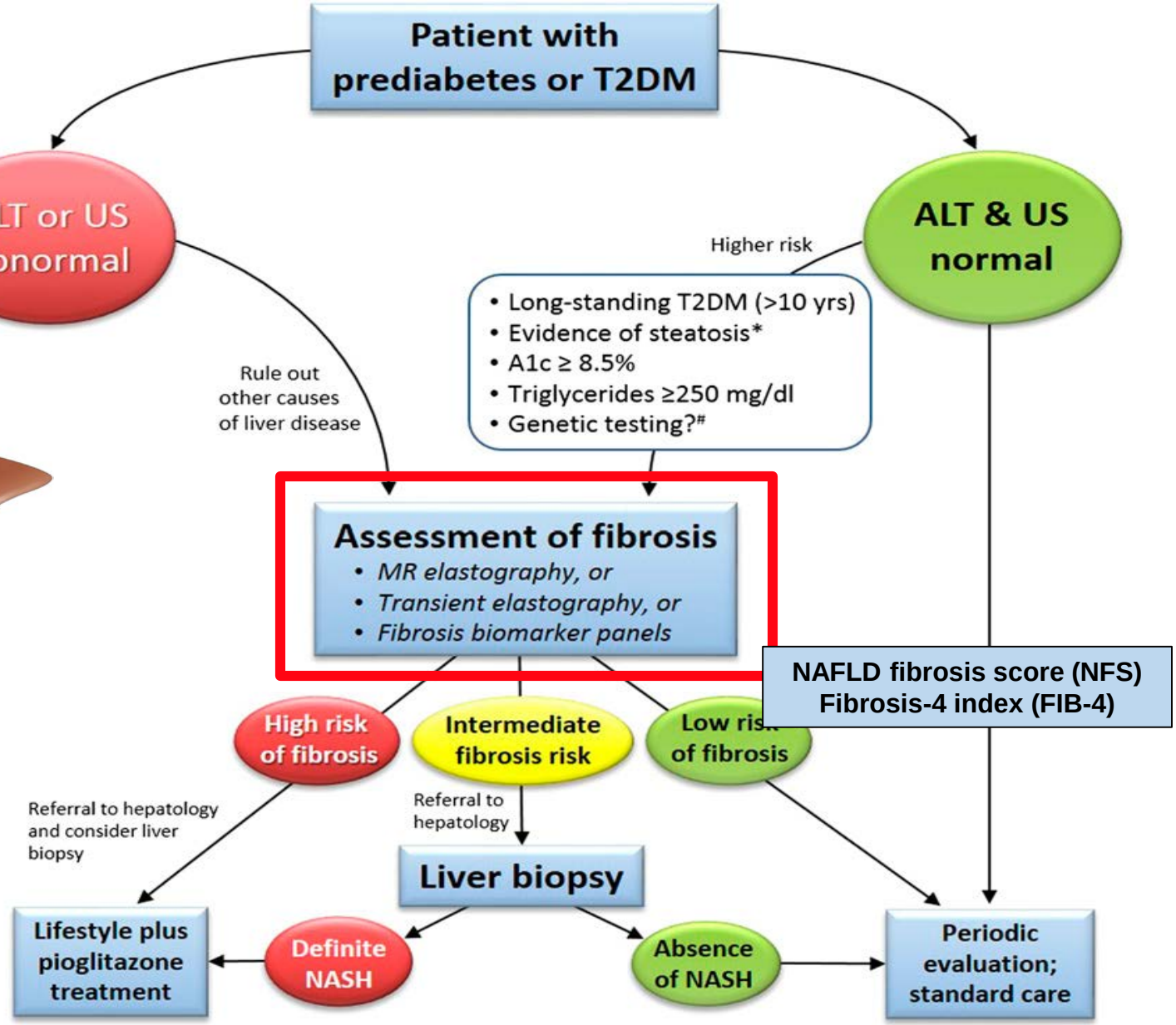
Recommendation

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**

(page S40)

Diagnostic Algorithm for NASH in the Primary Care Setting





Bril & Cusi

Diabetes Care, March 2017 40:419-430

NAFLD in Type 2 Diabetes (T2DM)

1. T2DM and risk of NAFLD/NASH

- SCREEN high risk populations in obese, T2DM, ↑ AST/ALT
- Mechanisms: insulin resistance is key

2. Complications

- Liver: risk of cirrhosis, hepatocellular carcinoma
- High risk of T2DM and of CVD (use of statins overall safe in NASH)

3. Management (ADA: screen and treat fibrosis)

- Elevated ALT or steatosis? Use FIB-4, elastography, biopsy (?)
- Treatment: a) Lifestyle; pioglitazone

  b) Extra-hepatic: aim to prevent CVD