PROSPECTIVE MANAGEMENT OF DM & MAFLD

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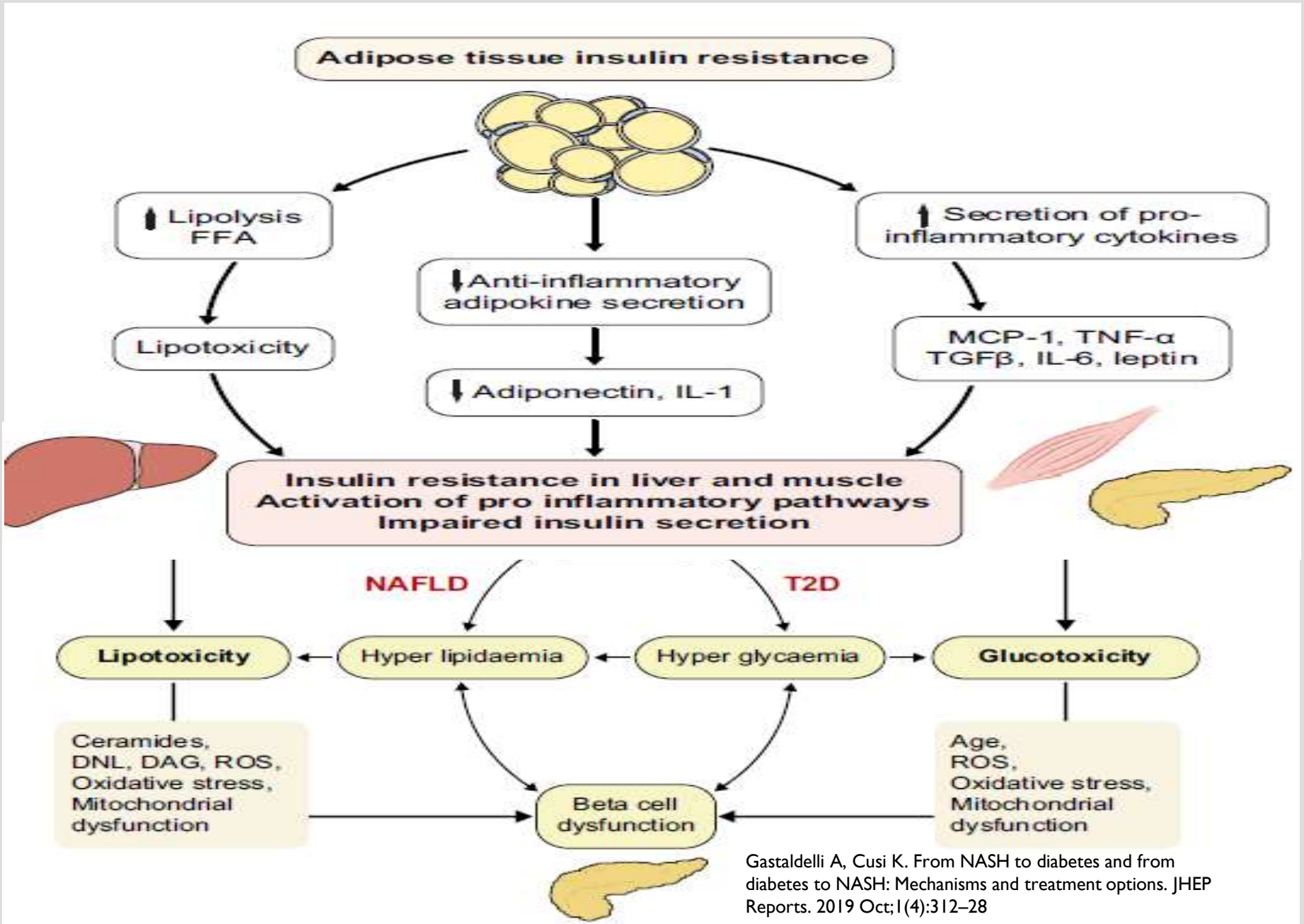
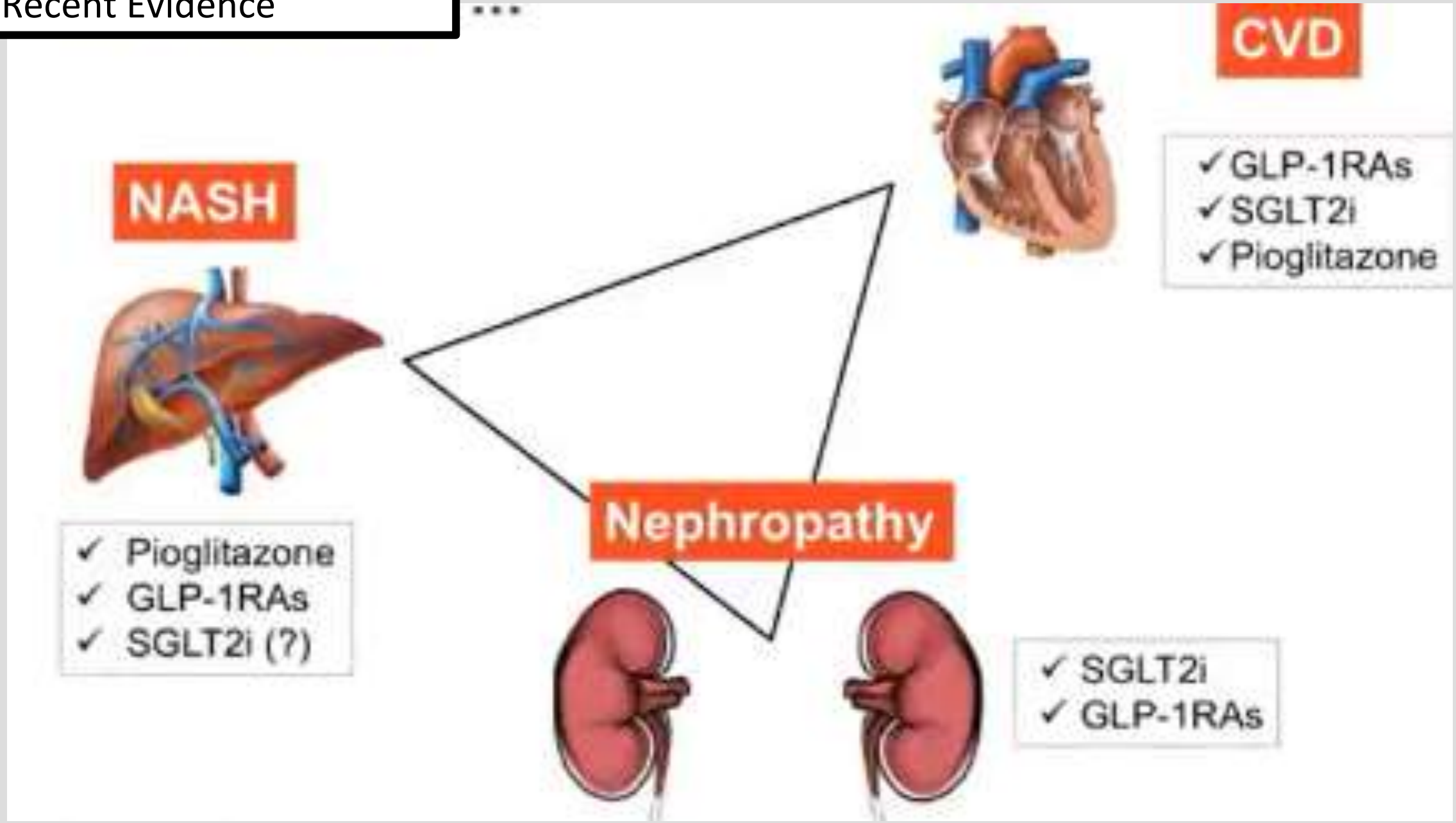
MAFLD / NAFLD



Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: Mechanisms and treatment options. JHEP Reports. 2019 Oct;1(4):312–28

Recent Evidence



Lifestyle interventions and bariatric surgery
Recommended to treat:
- Obesity
- Diabetes
- Cardiovascular disease

GLP-1 receptor agonists
Approved to treat:
- Obesity:
  Liraglutide 3·0 mg/day
  Semaglutide 2·4 mg/week
- Type 2 diabetes:
  Liraglutide 1·8 mg/day
  Semaglutide 1·0 mg/week

Pioglitazone
Approved to treat:
- Type 2 diabetes (15–45 mg/day)

Healthy liver

Non-alcoholic fatty liver
(SGLT2 inhibitors and insulin reduce hepatic steatosis)

Non-alcoholic steatohepatitis and fibrosis (F1–F3)

Cirrhosis

Metformin

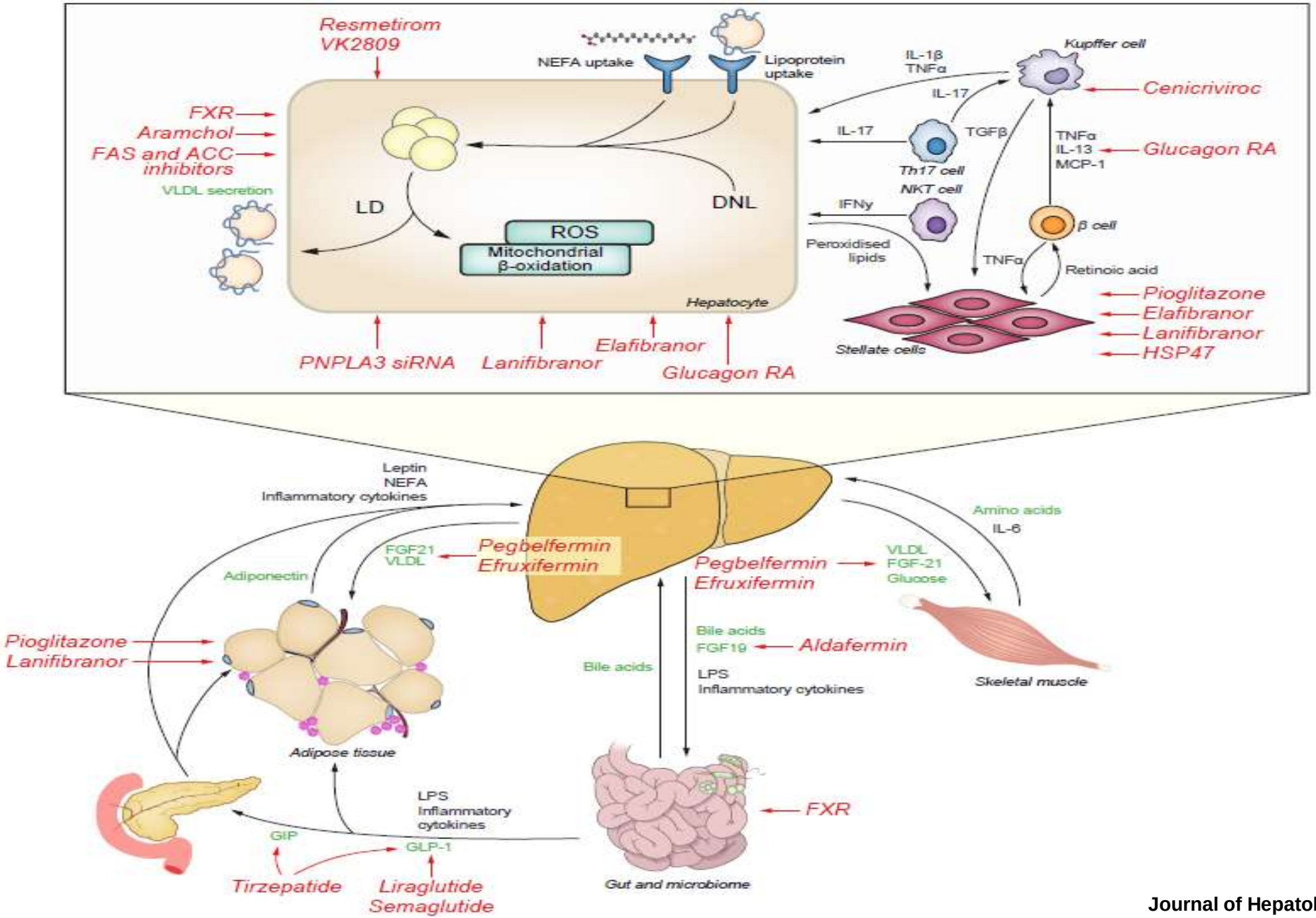
Small, open-label, or non-randomized published trials in both diabetic and non-diabetic patients with biopsy-proven NAFLD

- Metformin is associated with improvement in insulin resistance, aminotransferase levels, and no effect on liver histology

DPP-4 inhibitors

two open-label trials of **sitagliptin**

- **Reduction in intrahepatic lipid content** in diabetic patients with clinical NAFLD.
- Improvements in hepatic steatosis and ballooning in patients with biopsy-proven NASH irrespective of DM status.



Journal of Hepatology 2022 vol. 76 j 1263–1278

Promising drugs that are already in phase III registrational trials

farnesoid X receptor (FXR)

FXR plays important roles in:

- Bile acid metabolism.
- Metabolic, inflammatory and fibrogenic pathways.

Obeticholic acid (OCA) is a first-in-class, potent and selective FXR agonist which initially demonstrated an insulin-sensitizing effect in patients with type 2 diabetes.

Since OCA induces side effects such as ***pruritus and increases in LDL***, many second generation FXR agonists have been developed on the premise that a non-bile acid pharmacological structure may alleviate some of these effects.

Tropifexor is another FXR agonist that ***failed to elicit histological improvement*** on conventional histology. Other than the obvious explanation of different lengths of therapy (12 vs. 18 months) or statistical power, the reason for these discordant results is unknown.

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Promising drugs that are already in phase III registrational trials

Thyromimetics

In the liver, an imbalance of deiodinase activity favors the synthesis of inactive thyroid hormone T3 thus leading to a state of ***cellular hypothyroidism.***

Thyroid hormones have many beneficial functions, such as inducing ***lipophagy and mitochondrial biogenesis*** which contributes to the removal of liver fat.

However, a NASH drug would need to be highly selective for the β-isoform of the thyroid hormone receptor in order to avoid ***unwanted extrahepatic side effects.***

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Promising drugs that are already in phase III registrational trials

Thyromimetics

Resmetirom is the first such oral, *liver-directed THR-b1-selective agonist* demonstrating marked effects on lipid parameters. In a phase II trial, **resmetirom** had a potent anti-steatogenic effect and improved atherogenic dyslipidemia in patients with NASH, while weight and glycemic parameters were unaffected.

Another compound with liver-specific thyromimetic properties, **VK2809**, is currently under investigation (NCT04173065).

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Promising drugs that are already in phase III registrational trials

Incretins and other metabolic hormones

Two trials in NASH have already been completed and **semaglutide,** the leading compound in this class, not only leads to metabolic improvement, but also improves features of steatohepatitis.

Several dual or even triple agonists are in development, associating GLP-1 with GIP agonism (**tirzepatide**) or GLP-1 with glucagon agonism (**cotadutide**), or even triple agonists. Combinations of GLP-1 receptor agonists and long-acting amylin analogues are being tested as well.

Trials of these compounds in NASH are underway and combinations of incretins seem to ***induce weight loss*** of an even higher magnitude than GLP-1 receptor agonists alone.

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Promising drugs that are already in phase III registrational trials

PPAR agonists – α, β/δ and γ –

PPARs have pleiotropic actions as critical regulators of fatty acid metabolism, glucose metabolism, inflammation and fibrogenesis.

Mono PPAR-α ***agonists*** are ineffective in NASH and selective PPAR-δ agonists, such as **seladelpar**, are currently being developed for primary biliary cholangitis and tested in NASH.

Pioglitazone, a **PPAR- γ agonist** is associated with a broad spectrum of metabolic effects resulting from the restoration of adipose tissue biology and a decrease in chronic systemic inflammation. In patients with NASH, these changes are associated with improvements in liver histology.

Possibly a more efficient attempt to mitigate the side effects of thiazolidinediones would be the induction of ***combined PPAR agonism using dual or triple agonists***. The most successful story so far has been with **lanifibranor**, a pan-PPAR agonist with a higher potency

Promising drugs that are already in phase III registrational trials

Lipogenesis inhibitors

De novo lipogenesis is an important source of liver fat in patients with NAFLD especially under dietary stress from high-fructose intake.

Aramchol, already in a phase III trial (NCT04104321).
is a fatty acid / bile acid conjugate which is a partial ***inhibitor of hepatic steroyl-CoA desaturase - a rate-limiting enzyme in the biosynthesis of monounsaturated fatty acids*** which regulates body adiposity, energy expenditure, fatty acid β-oxidation in liver and insulin sensitivity.

In experimental models, aramchol improved inflammation, oxidative stress and fibrosis. Phase II studies in humans have confirmed the reduction in liver fat and indicated histological improvements in steatohepatitis and fibrosis.

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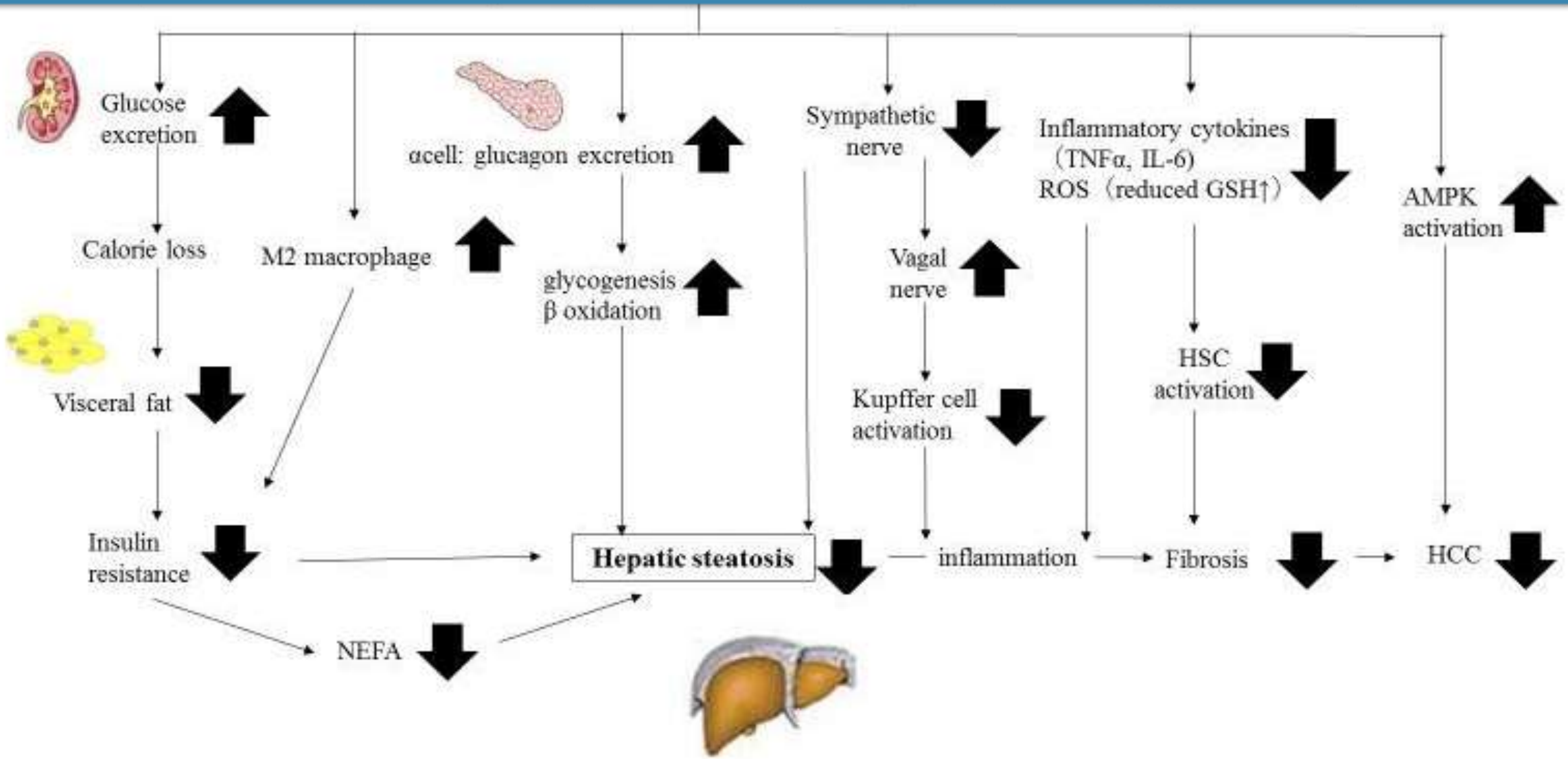
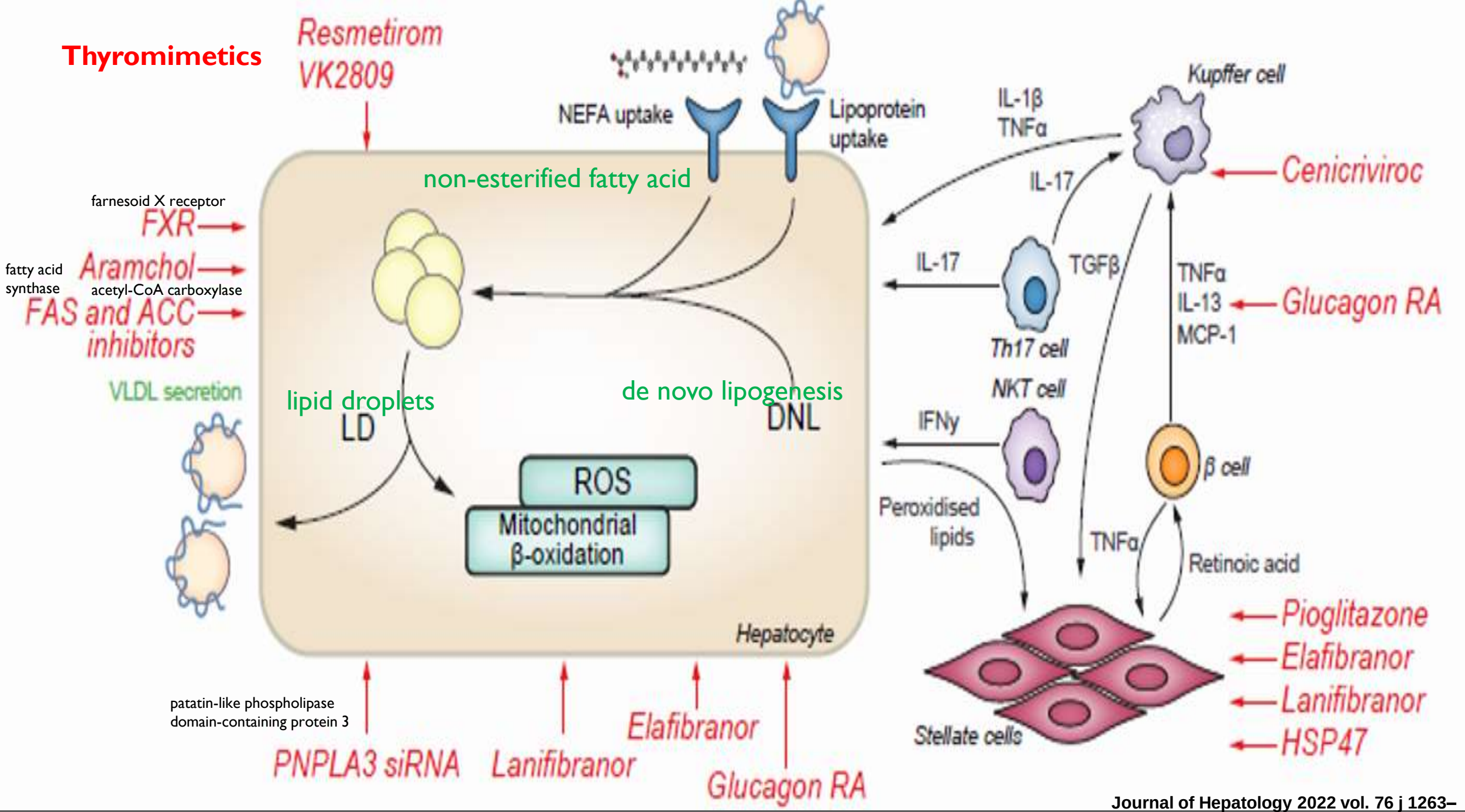
Promising drugs that are already in phase III registrational

SGLT2 inhibitors



Thyromimetics



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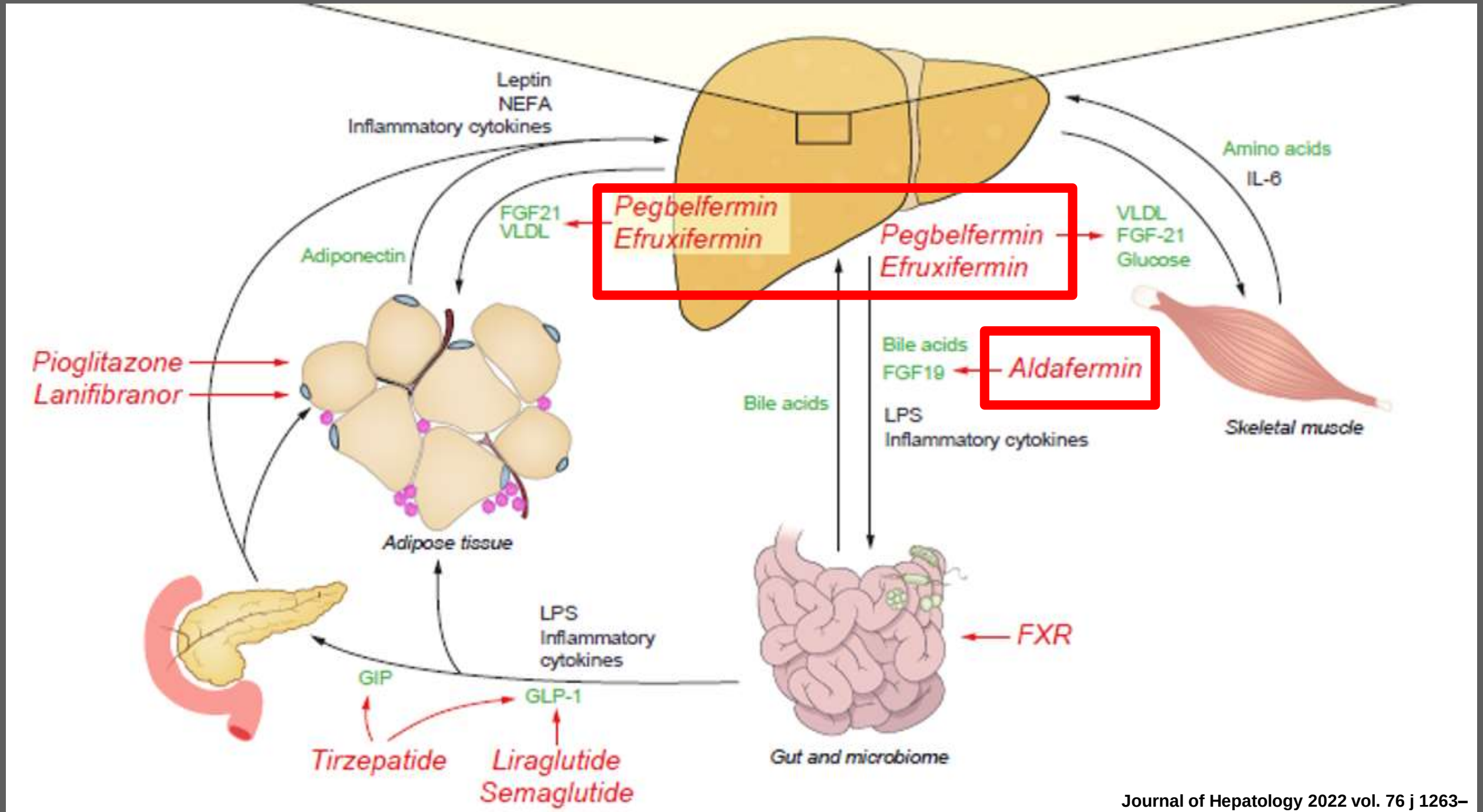

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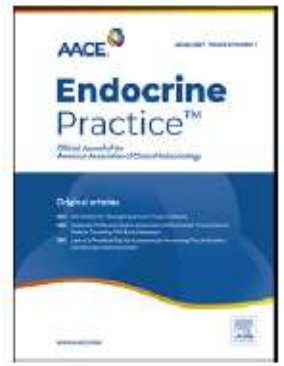

Clinical Practice Guidelines

American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

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Management Algorithm for Persons with NAFLD in Primary Care and Endocrinology Clinical Settings

 https://doi.org/10.1016/j.eprac.2022.03.010

Management Algorithm for Persons with NAFLD

in Primary Care and Endocrinology Clinical Settings

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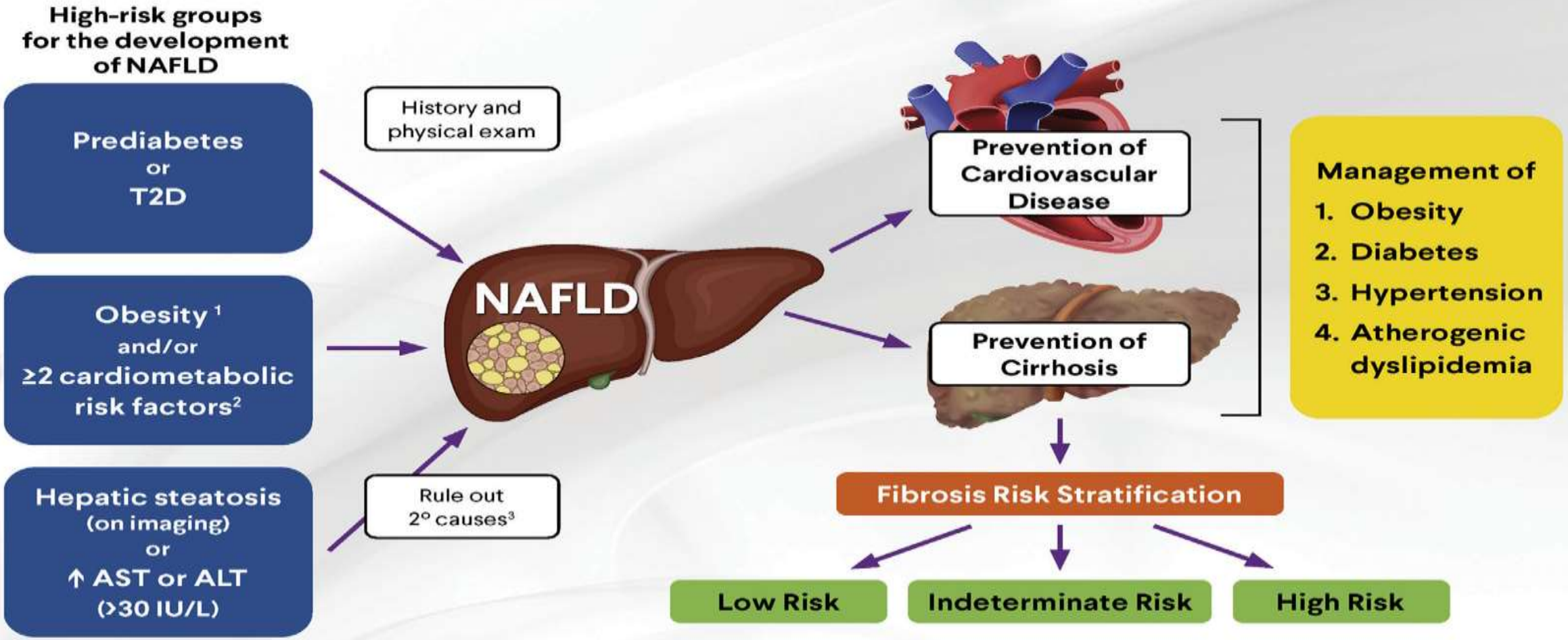
AACE.

Management Algorithm for NAFLD – Overview



Abbreviations: ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, T2D = Type 2 diabetes mellitus

1. Adiposity-based chronic disease (ABCD) is a diagnostic term proposed by AACE to better describe the disease of obesity in a complication-centric manner of abnormal adipose tissue mass, distribution, function and resulting morbidity that can be ameliorated with weight loss.
2. Cardiometabolic risk factors of the metabolic syndrome are waist circumference >40 inches men >35 inches women, triglycerides ≥150 mg/dL, HDL-C <40 mg/dL men, <50 mg/dL women, BP ≥130/≥85 mm Hg, fasting plasma glucose ≥100 mg/dL (NCEP ATP III)
3. Secondary causes of liver steatosis or elevated transaminases (AST or ALT) are excessive alcohol consumption (≥14 drinks/week for women or ≥21 drinks/week for men), hepatitis B, hepatitis C (genotype 3), Wilson's disease, alpha 1 antitrypsin deficiency, lipodystrophy, starvation, parenteral nutrition, abetalipoproteinemia, hemochromatosis, mass lesions, medications and other causes.

 https://doi.org/10.1016/j.eprac.2022.03.010
Algorithm Figure 1

AACE.

Cirrhosis Prevention in NAFLD

High-risk groups for NAFLD

- Prediabetes or T2D
- Obesity and/or ≥2 cardiometabolic risk factors
- Steatosis (on imaging) or ↑ AST or ALT

Fibrosis Risk Stratification

FIB-4 Index

- **Low Risk** — FIB-4: <1.3
- **High Risk** — FIB-4: >2.67
- **Indeterminate Risk** — FIB-4: 1.3 - 2.67

Order second test

Liver Stiffness Measurement (LSM) by Elastography
or
ELF Blood Test

Cirrhosis risk higher if:

- T2D (or prediabetes)
- Age >50
- Higher BMI (40 kg/m²)
- More metabolic risk factors
- Genetic factors (i.e., PNLPA3)

Low Risk

FIB-4 <1.3 or LSM <8 kPa or ELF <7.7
(or if a liver biopsy was performed fibrosis stage is F0-F1)

- Managed by primary care team, endocrinologist, other
- Focus care on obesity management & CVD prevention

Indeterminate Risk

FIB-4 1.3 - 2.67 or LSM 8 - 12 kPa
or ELF 7.7 - 9.8
(liver specialist to consider need for biopsy)

- Referral to liver specialist for additional proprietary biomarkers or imaging (MRE, cT1, other)
- Multidisciplinary team to prevent cirrhosis and CVD

High Risk

FIB-4 >2.67 or LSM >12 kPa or ELF >9.8
(or if a liver biopsy was performed fibrosis stage is F2-F4)

Abbreviations: ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, cT1 = Liver multiscan, CVD = Cardiovascular disease, ELF = Enhanced liver fibrosis test™, FIB-4 = Fibrosis-4 index, kPa = Kilopascals, LSM = Liver stiffness measurement, MRE= Magnetic resonance elastography, T2D = Type 2 diabetes mellitus

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Algorithm Figure 2

AACE.

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, & 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/week) + resistance training 20-30 min (2-3 times/week).		
Alcohol intake	Minimize	Minimize	Avoid if F3 or cirrhosis (F4)[1]
Weight loss goal to treat NAFLD (if overweight or obesity)[2]	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, anti-obesity medications, bariatric surgery.
Medical therapy to treat obesity	Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liragluitde 3 mg/d, semaglutide 2.4 mg/wk	GLP-1 RA preferred for NASH.[3,4]	GLP-1 RA preferred for NASH.[3,4]
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.

Abbreviations: GLP-1 RA = Glucagon-like peptide-1 receptor agonists, HCC = Hepatocellular carcinoma, NASH = Nonalcoholic steatohepatitis

1. Persons with confirmed cirrhosis based on biopsy or high likelihood based on LSM >13.6kPa from vibration controlled transient elastography (FibroScan®), ELF ≥9.8 or >5.0 kPa on MRE) should undergo HCC surveillance. Varices screening is recommended if LSM >20 kPa or platelet count of <150,000/mm^3.
2. These goals should only be taken as a broad guidance. NAFLD/NASH may also improve by changes in macronutrient content, exercise and other factors beyond magnitude of weight loss. All high-quality studies available limited to a maximum of 12 month duration.
3. No high-quality evidence for pharmacotherapy in persons with NASH cirrhosis. Treatment should be individualized and used with caution only by liver specialists.
4. Among GLP-1 RAs, semaglutide has the best evidence of benefit in persons with steatohepatitis and fibrosis.

 https://doi.org/10.1016/j.eprac.2022.03.010

Algorithm Figure 3

AACE.

Diabetes 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[1]** 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[1], caution with risk of hypoglycemia and avoid oral agents[2]
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[3]. No evidence that SGLT2i improve steatohepatitis.	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. 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

Abbreviations: CKD = Chronic kidney disease, CVD = Cardiovascular disease, DPP-4i = Dipeptidyl peptidase 4, GLP-1 RA = Glucagon-like peptide-1 receptor agonists, HF = Heart failure, NASH = Nonalcoholic steatohepatitis, SGLT2i = Sodium-glucose cotransporter-2 inhibitors.

1. Advanced cirrhosis is defined as persons with cirrhosis based on biopsy and Child class B or C with clinical evidence of comorbidities (varices, portal hypertension, ascites, etc.).
2. Limited data on oral diabetes medications and GLP-1 RA in persons with cirrhosis. Avoid metformin, GLP-1 RA appear safe, insulin preferred. Avoid oral agents in advanced cirrhosis.
3. Among GLP-1 RAs, semaglutide has the best evidence of benefit in persons with steatohepatitis and fibrosis.

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Algorithm Figure 4

AACE.

Hypertension 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[1]** 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 months and intensify therapy until goal achieved.		
Goal (individualize) [2,3,4]	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 if decompensated cirrhosis
Dietary recommendations	In addition to general dietary recommendations, reduce sodium & increase high potassium foods (e.g., DASH diet).		
Pharmacotherapy for hypertension[5]	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[6] 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.

Abbreviations: ACEIs = Angiotensin-converting enzyme inhibitors, ARBs = angiotensin II receptor blockers, BB = beta blockers, CCB = calcium channel blockers.

1. Advanced cirrhosis defined as persons with cirrhosis based on biopsy and Child class B or C and clinical evidence of comorbidities (varices, portal hypertension, ascitis, etc.).
2. AACE recommends that BP control be individualized, but that a target of <130/80 mm Hg is appropriate for most persons.
3. Less-stringent goals may be considered for frail persons with complicated comorbidities or those who have adverse medication effects.
4. A more intensive goal (e.g., <120/80 mm Hg) should be considered for some persons if this target can be reached safely without adverse effects from medication.
5. If initial BP > 150/100 mm Hg start with dual therapy. (ACEI or ARB + CCB, BB or thiazide diuretic).
6. Prefer weight neutral beta-blockers: carvedilol, nebivolol.

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Algorithm Figure 5

AACE.

Atherogenic Dyslipidemia Management in NAFLD

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/d), prioritize vegetables, fruits whole grains, nuts, reduce saturated fat & added sugars (e.g., Mediterranean diet).		
Lipid risk levels	**High CV Risk**[1] ≥2 risk factors and 10-year risk 10-20% Diabetes or CKD ≥3 with no other risk factors	**Very high CV Risk**[1] Established CVD or 10-year risk >20% Diabetes with >1 risk factor, CKD ≥3, HeFH	**Extreme CV Risk**[1] Progressive CVD CVD + diabetes or CKD ≥3 or HeFH FHx premature CVD (<55 yrs male <65 yrs 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
Apo B goal (mg/dL)	<90	<80	<70
First line pharmacotherapy: Statins	Use a moderate-to-high intensity statin[2], unless contraindicated. Statins are safe in NAFLD or NASH but do not use in decompensated cirrhosis (Child C).		
If LDL-C not at goal[3]: Intensify statin therapy	Use higher dose or higher potency statin.		
If LDL-C not at goal (or statin intolerant)[4]: add 2nd agent, then add 3rd agent	Ezetemibe, 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).[5]		
If TG 135-499 mg/dL on max statin dose	Emphasize diet (as above).	Add icosapent ethyl.[6]	Add icosapent ethyl.[6]

Adapted from Handelsman Y, et al. Endocr Pract. 2020;26:1196-1224.

Abbreviations: CKD = Chronic kidney disease, CVD = cardiovascular disease, FA = Fatty acids, HeFH = Heterozygous familial hypercholesterolemia, HTN = Hypertension, Rx = Prescription

1. Major risk factors: age >40, DM, HTN, FHx of early CVD, low HDL C, elevated LDL, Smoking, CKD 3,4
2. High intensity statin therapy: rosuvastatin 20, 40 mg/d, atorvastatin 40, 80 mg/d.
3. Other lipid modifying agents should be used in combination with maximally tolerated statins if goals not reached: ezetimibe, PCSK9 inhibitor, bempedoic acid, colesevelam, or inclisiran.
4. Assess adequacy and tolerance of therapy with focused laboratory evaluations and patient follow up.
5. Niacin may lower triglycerides but does not reduce CVD and worsens insulin resistance. It may promote hyperglycemia in a population at high-risk of diabetes.
6. Icosapent ethyl 4g/d is recommended as an adjunct to maximally tolerated statin therapy to reduce risk of cardiovascular disease in high-risk persons.

Algorithm Figure 6

AACE.

Medication Recommendation:

- **Pioglitazone and GLP-1 RAs are recommended for persons with T2D and biopsy-proven NASH.** *(A)*
- Clinicians must consider treating diabetes with **pioglitazone and/or GLP-1 RAs** when there is an elevated probability of **having NASH based on elevated plasma aminotransferase** levels and noninvasive tests. (*A*)
- To offer **cardiometabolic benefit in persons with T2D and NAFLD**, clinicians must consider treatment with **GLP-1 RAs, pioglitazone, or SGLT2 inhibitors**; however, there is no evidence of benefit for treatment of steatohepatitis with SGLT2 inhibitors. *(A)*

Medications to Treat Diabetes and Their Efficacy for the Treatment of Nonalcoholic Fatty Liver Disease

Medication	Liver fat	Disease activity (steatohepatitis/NAS)	Studies
Metformin	Unchanged	Neutral	(298-302)
Pioglitazone	Decreased	Improved*	(97, 98, 280-282)
Insulin	Decreased	Effect unknown	(177, 178, 306)
GLP-1 RAs (semaglutide and liraglutide)	Decreased	Improved*	(99, 286-288)
SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin)	Decreased	Effect unknown	(28, 294-297)
DPP-IV inhibitors (sitagliptin and vildagliptin)	Unchanged (in RCTs)	Effect unknown	(286, 303-305)

Abbreviations: DPP-IV = dipeptidyl peptidase IV; GLP-1 RAs = glucagon-like peptide11 receptor agonists; NAS = nonalcoholic fatty liver disease activity score; RCTs = randomized controlled trials; SGLT2 = sodium-glucose cotransporter 2.

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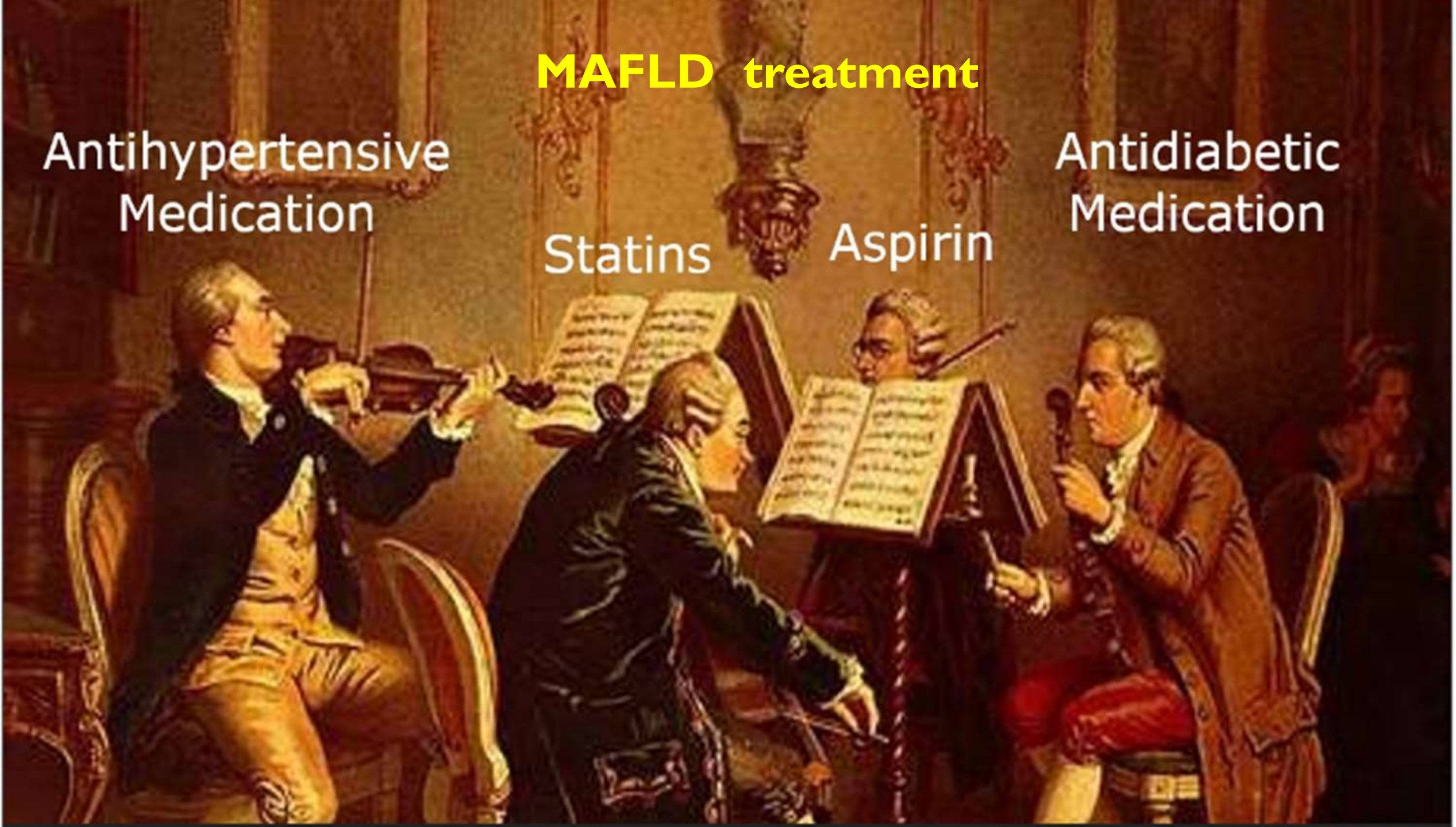
MAFLD treatment
Antihypertensive Medication
Statins
Aspirin
Antidiabetic Medication


Thank You