WELCOME TO AK LIVER DISEASE ECHO

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

NPAIHB
Indian Leadership for Indian Health

AK Liver Disease ECHO aims to increase Tribal health care providers' knowledge about diagnosis, treatment, management, and prevention of liver disease.

Each session begins with a liver disease didactic presented by a subject matter expert followed by one or more case presentations by a provider(s) to the subject matter experts who can provide holistic, best practices input.

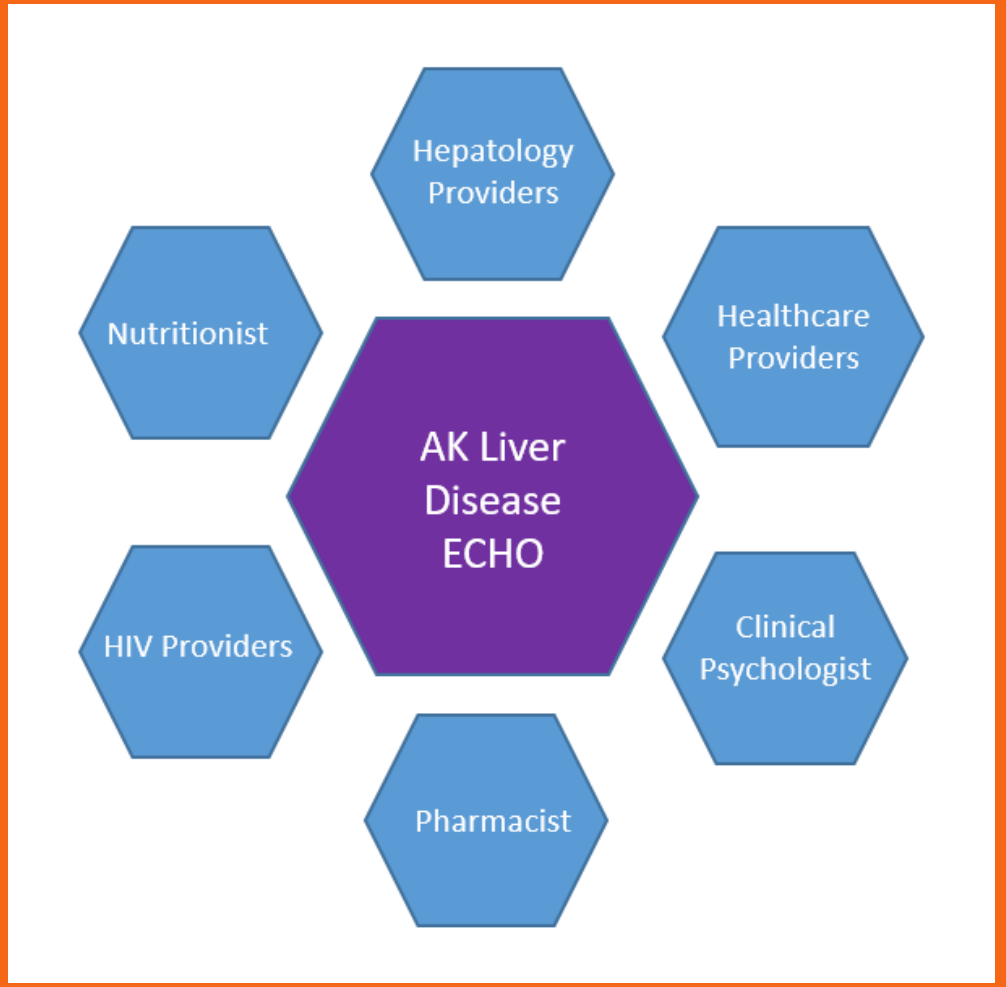
This project is supported by a grant from the Northwest Portland Area Indian Health Board and funding is provided from the HHS Secretary's Minority HIV/AIDS Fund.

WHAT WE DO

- Didactic Presentations pertaining to ECHO topics
- We're accepting **case presentations and questions pertaining to:**
  - Elevated Liver Function Tests
  - Cirrhosis
  - Managing Complications of Decompensated Cirrhosis – Ascites, encephalopathy, esophageal varices
  - Alcohol-related liver disease, including Alcohol Hepatitis
  - Autoimmune liver disease – Autoimmune Hepatitis, Primary Biliary Cholangitis, Overlap
  - Nonalcoholic fatty liver disease/Nonalcoholic steatohepatitis
  - Hepatocellular carcinoma
- Provide Expert Panelists

CONSULTANT TEAM

- Brian McMahon, MD Hepatologist
- Youssef Barbour, MD Hepatologist
- Lisa Townshend, ANP Hepatology Provider
- Annette Hewitt, ANP Hepatology Provider
- Leah Besh, PA-C HIV/Hepatology Provider
- Anne Fleetwood, MS, RDN, NDN
- Brittany Keener, PharmD, MPH, BCPS



Welcome to Alaska Liver Disease ECHO

Approved Provider Statements:

In support of improving patient care, Alaska Native Medical Center (ANMC) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Conta

ANMC designates this activity for a maximum of 12 contact hours, including 3 total pharmacotherapeutics contact hours, commensurate with participation.

Financial Disclosures:

Youssef Barbour, MD & Lisa Townshend-Bulson, APRN / faculty for this educational event, are primary investigators in an ANTHC sponsored hepatitis C study funded in part by Gilead Sciences. All of the relevant financial relationships listed have been mitigated.

Requirements for Successful Completion:

To receive CE credit please make sure you have actively engaged in the entire activity, your attendance is recorded by the facilitator, and complete the course evaluation form found here: https://forms.gle/R8vibUZgMbRcoScw9.

For more information contact
jlfielder@anthc.org or (907) 729-1387

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

LIVER DISEASE ECHO SCHEDULE AT A GLANCE

- April 21st – Future Drugs for NALFD
- May 19th – Hepatitis B and other Vaccine Updates
- June 16th AIH in AN/AI Population in Alaska
- July 21st – PBC/Overlap
- August 18th – Most Common Liver Toxic Drugs
- September 15th – Trauma Informed Care and Liver Disease
- October 20th – Screening for Alcohol Use Disorder

LAND ACKNOWLEDGEMENT

Out of great respect, we acknowledge the Creator of all living things and the original inhabitants upon whose traditional lands we respectively now gather or reside.

Let us, forever, remember the benefits and bounty of the vast resources that stem from these traditional lands, and thank the original inhabitants for their past and present stewardship of the resources (i.e., waters, plants, animals), and the spiritual practices which they cherish on the lands we now call home.

Type 2 Diabetes, NAFLD, and Medications They Share

Christy Pierce, APRN, MSN, ACNP-BC-FNP-C, BC-ADM

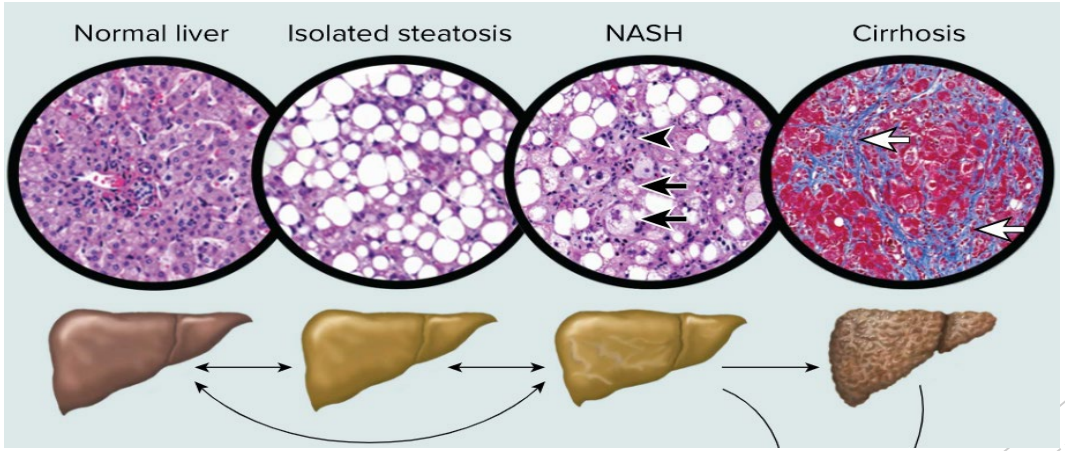
ANTHC DM Team

March 2022

Objectives

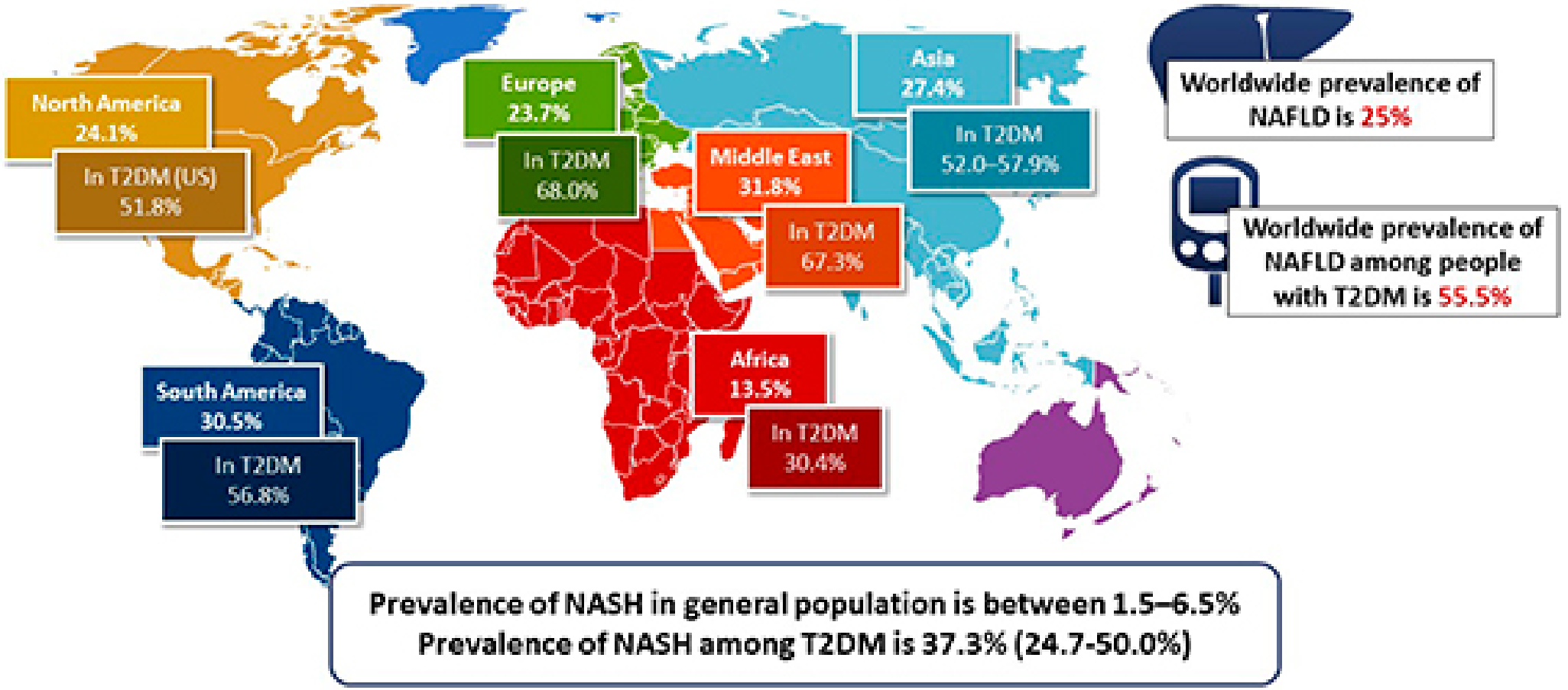
- Explain relationship among type 2 diabetes, obesity and NAFLD
- Describe lifestyle management and goals of NAFLD and type 2 DM
- Describe pharmacological management and goals of NAFLD and type 2 DM

- Non-alcoholic fatty liver: >5% hepatic steatosis without evidence of hepatocellular injury
- Non-alcoholic steatohepatitis (NASH): >5% hepatic steatosis and inflammation with hepatocyte injury (ballooning or fibrosis)
- NASH cirrhosis: cirrhosis with current or previous histological evidence of steatosis or steatohepatitis
- Associated conditions:
  - Obesity, T2DM, Dyslipidemia, Metabolic Syndrome, Polycystic Ovary Syndrome
  - Hypothyroidism, OSA, Hypopituitarism, Hypogonadism, Pancreatoduodenal resection, Psoriasis



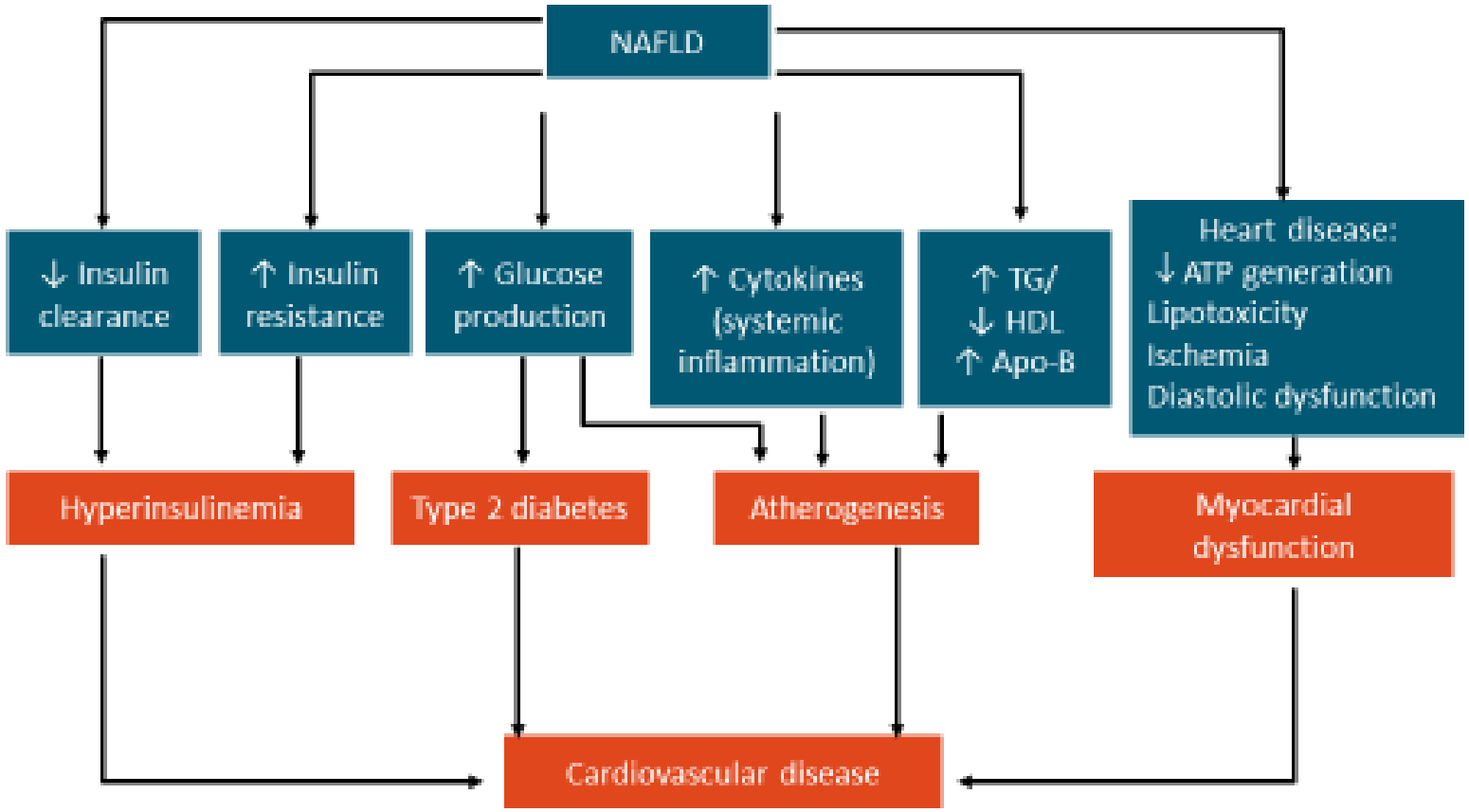
Prevalence of NAFLD in High-Risk Groups

- NAFLD and Metabolic syndrome has a bidirectional association
  - Obesity- from overweight to severely obese (>95% bariatric surgery patients have NAFLD)
  - Type 2 DM- studies suggest 33-66% of patients with T2DM have NAFLD
  - Dyslipidemia- elevated triglycerides and low HDL, estimated 50% of these patients have NAFLD
  - Age, sex, and ethnicity- prevalence of NAFLD and state of liver disease increase with age, Men 2x's more likely, ethnic differences may be explained by genetic variation related to PNPLA-3 gene.



Younossi Z and Henry L, 2019

Metabolic Consequences of NAFLD



Cusi. Gastroenterology. 2012;142:711.

Slide credit: clinicaloptions.com

TREATMENT OF NAFLD/NASH

- Evidence-based guidelines available at AASLD.org

- Goal: normalize liver enzymes or improve liver biopsy findings
- Weight loss diet recommended
- Exercise recommended
- Bariatric surgery
- Management of CVD and dyslipidemia

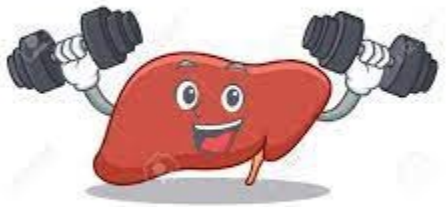
• Medications:

Metformin

Thiazolidinediones: pioglitazone

GLP1's

Exercise and Diet



- Exercise:
  - Daily: 30 – 60 minutes 5 times per week
  - 12,000 steps/day = 400 kcal
  - Helps achieve weight loss
  - Improves insulin sensitivity, may prevent or reduce hepatic steatosis, but improving other aspects of histology is unknown.

- Weight loss:
  - At least 3-5% body weight loss improve hepatosteatosis
  - if >5% weight loss showed stabilized or improved fibrosis in 94% of the cases
  - >10% weight loss associated with improvement in all features of NASH including portal inflammation and fibrosis
- Can use CAP scores to follow diet/exercise progress for liver fat

Metformin

- Randomized-controlled trial 3234 patients with diabetes or pre-diabetes followed for 15 years that compared:
  - Metformin,
  - Intensive life style intervention [ILS]: 6-8 months behavioral modification plus 150 minutes moderate intensity exercise/week (mostly walking)
  - Or placebo
- Results:
  - Proportion who lost > 5lbs at year:
    - ILS 62.6%
    - Metformin (28.5%)
    - Placebo (13.4%)
  - Between years 6 and 15 mean weight loss relative to baseline
    - Metformin 6.2% (95% CI, 5.2%-7.2%)
    - ILS 3.7% (95% CI, 3.1%-4.4%)
    - Placebo 2.8% (95% CI, 1.3%-4.4%)

Apolzan JW et al. Annals Int. Med 2019;170:682-690

Metformin

- Although Metformin can assist with weight loss and maintaining some of that weight loss:
  - Metformin is not recommended for treating NASH as it does not significantly improve liver histology
    - It is however safe to use for treatment of preDM and T2DM and studies have shown you may even have improvement in serum aminotransferases

http://aasldv2019stg.aasld.org/sites/default/files/2019-06/NAFLD%20Guidance%202018.pdf

18months of pioglitazone

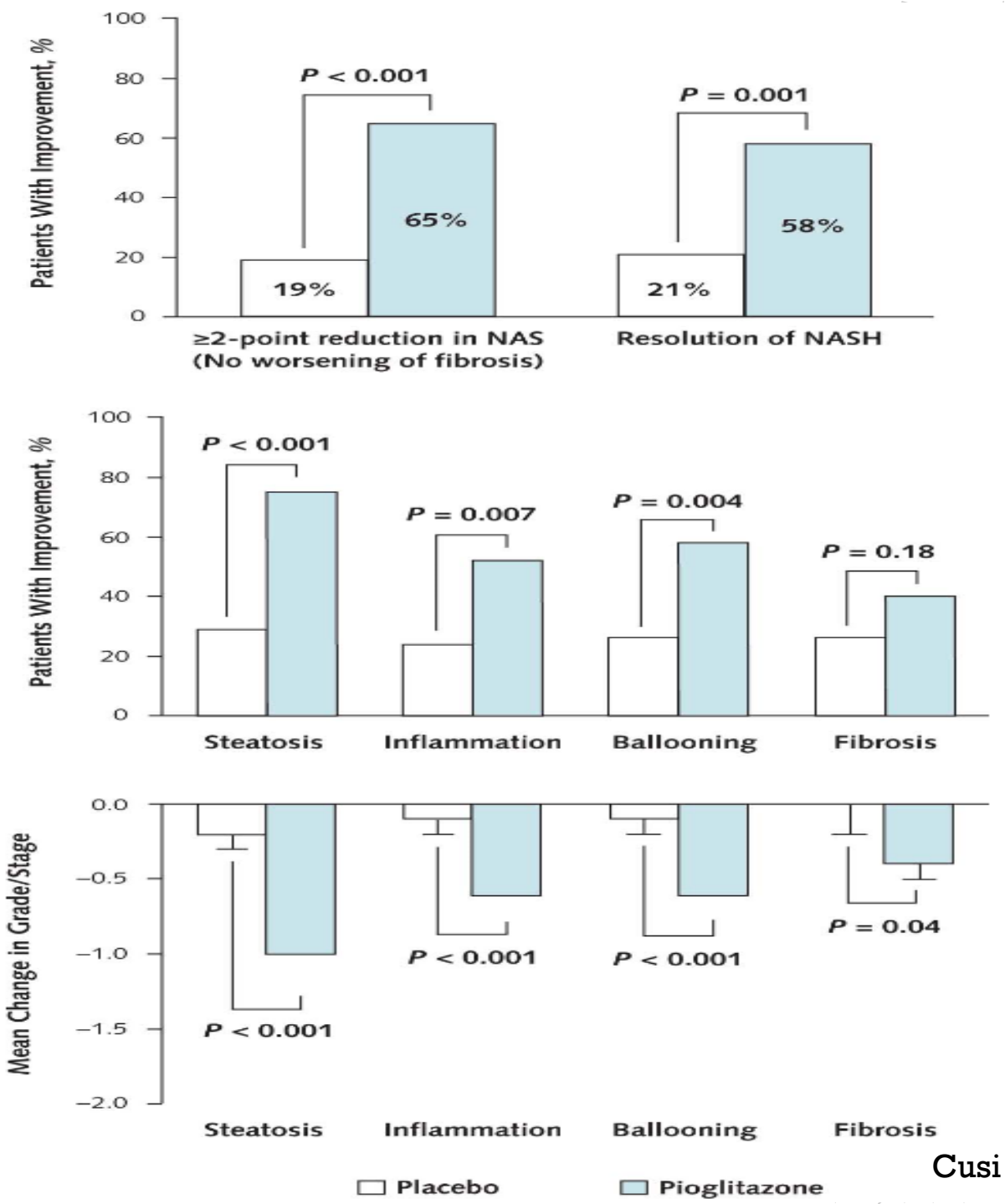
In DM and preDM patients →

From AASLD NAFLD guideline 2018:

Guidance Statements:

24. Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH. Therefore, it may be used to treat these patients. Risks and benefits should be discussed with each patient before starting therapy.

25. Until further data support its safety and efficacy, pioglitazone should not be used to treat NAFLD without biopsy-proven NASH.



Cusi K, 2016

Glucagon-like Peptide-1 Analogues (GLP's)

- On most recent AASLD guidelines GLP-1's it is too premature to specifically to treat liver disease in patients with NAFLD or NASH.
- Uptodate:
  - **Liraglutide**: 52 patients with NASH at the end NASH resolved in 9 out of 22 patients who received it and in 2 of the placebo patients and those who receive **Liraglutide are less likely to have progression to fibrosis (9 vs 36%)**
  - **Semaglutide**: phase 2 trial with patients with biopsy –proven NASH and liver fibrosis resulted in higher rates of histologic resolution of NASH compared with placebo at 72 weeks at 0.4 mg daily, lower dosages were less effective, but better than palacebo. **However, rate of improvement in fibrosis stage were not significantly different between the groups and placebo- more data neededed before recommended routinely for NASH in the absence of other indications**.

However…….. …..New data shows…….

- Semaglutide may not only be for DM, and weight loss, but also histological improvement in NASH

  - ✓ AI assessed continuous fibrosis score shows significant reduction in fibrosis with semaglutide 0.4 mg vs placebo

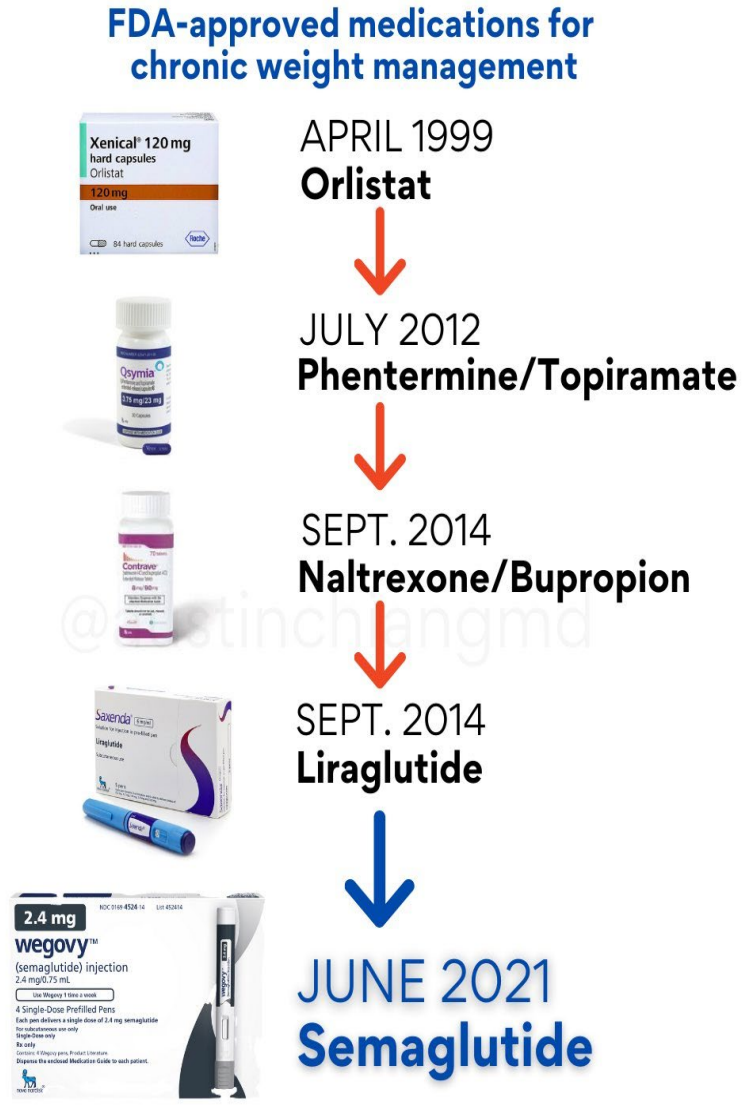
  - ✓ Semaglutide weight loss accounts for most- but not all- of the histological improvement seen in patients with NASH

Semaglutide, NASH, and Mice

- ✓ Semaglutide reduces body weight, adiposity, and hepatomegaly
- ✓ Improves glucose tolerance and hyperinsulinemia
- ✓ Improvement in plasma and liver biochemistry
- ✓ NAFLD Activity score improves by **>2 point**
- ✓ Fibrosis stage was unaffected
- ✓ Reduces quantitative histological markers of steatosis, inflammation and fibrosis

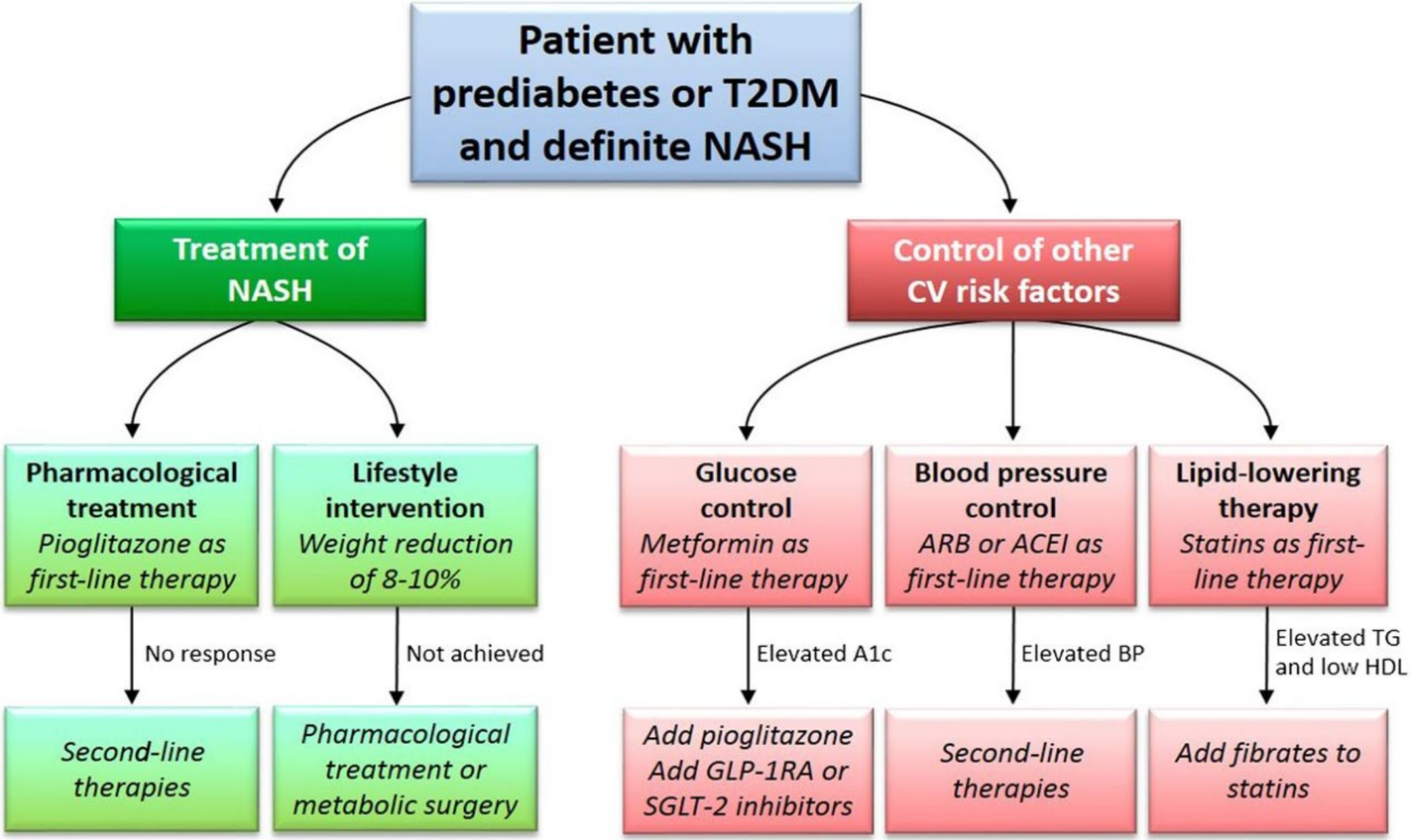
GLP's and Weight loss dosing

- Liraglutide/Saxenda daily
  - 0.6mg, 1.2 mg, 1.8 mg, 2.4 mg, 3 mg
- Semaglutide /Wegovy weekly
  - 0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg

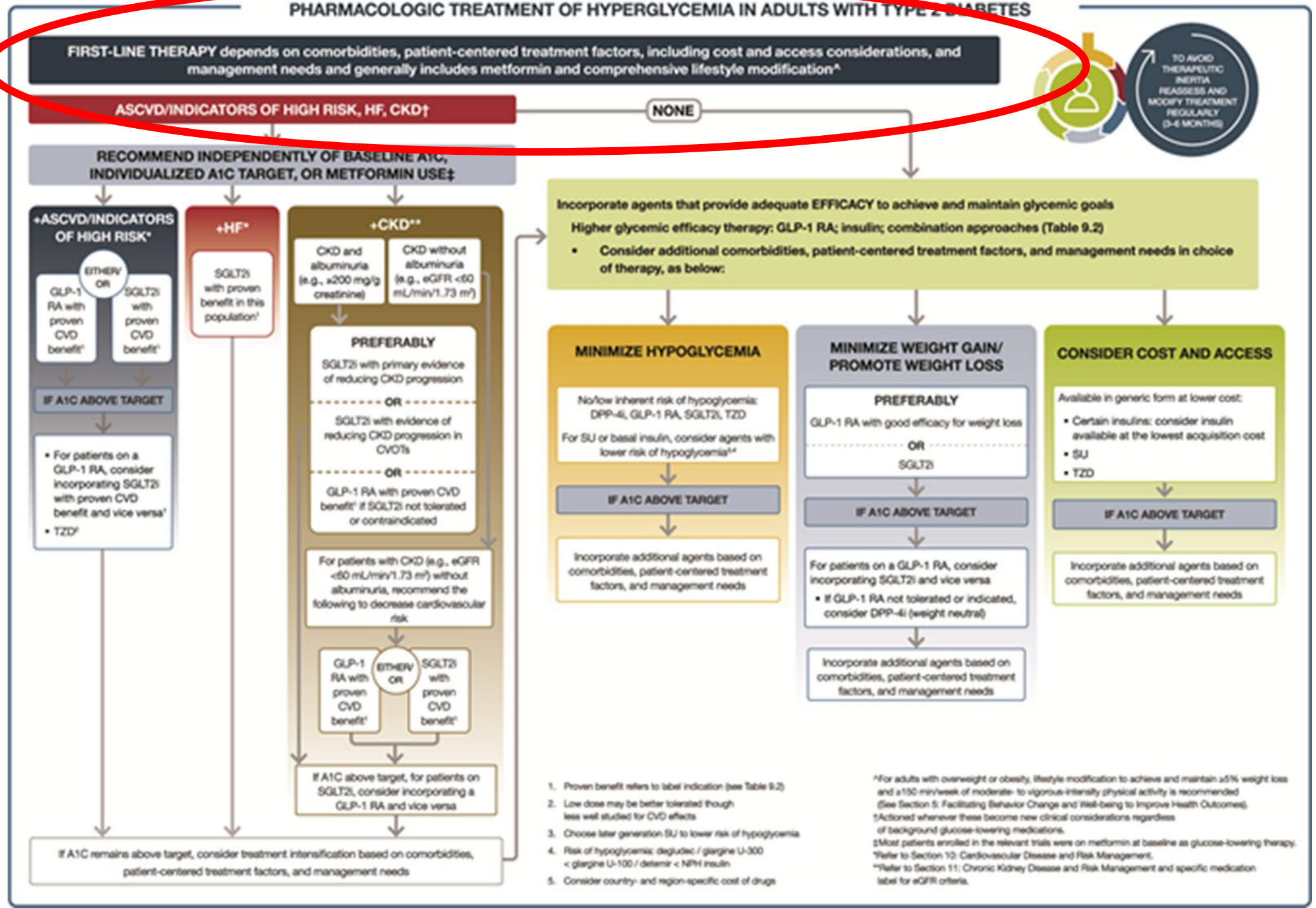


Possibility of SGLT2 inhibitors in NAFLD

- Mitsui Memorial Hospital
  - 161 Japanese NAFLD patients with T2DM administered SGLT2 between 2014-2019 and based on body weight reductions divided into 2 groups <3% & >3%
  - Both groups showed improved
    - Fib 4- index
    - ALT
    - Fasting glucose
    - A1C
  - Cumulative normalization rate of ALT differed significantly between 2 groups
    - Determined reduced body weight equal or more than >3% for 8 weeklys independent factor to normalization of ALT
  - During follow up period 55 of 109 patients ALT's re-exacerbated- weight gain was independently related to this (1.08 per 1% gain of BW)



Diabetes Care 2017 Mar; 40(3): 419-430.
https://doi.org/10.2337/dc16-1787


PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES
FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification^
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
ASCVD/INDICATORS OF HIGH RISK, HF, CKD†
NONE
RECOMMEND INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE‡
+ASCVD/INDICATORS OF HIGH RISK*
EITHER/OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1]
IF A1C ABOVE TARGET
• For patients on a GLP-1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa[1]
• TZD[2]
+HF*
SGLT2i with proven benefit in this population[1]
+CKD**
CKD and albuminuria (e.g., ≥200 mg/g creatinine)
CKD without albuminuria (e.g., eGFR <60 mL/min/1.73 m²)
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
OR
SGLT2i with evidence of reducing CKD progression in CVOTs
OR
GLP-1 RA with proven CVD benefit[1] if SGLT2i not tolerated or contraindicated
For patients with CKD (e.g., eGFR <60 mL/min/1.73 m²) without albuminuria, recommend the following to decrease cardiovascular risk
GLP-1 RA with proven CVD benefit[1]
EITHER/OR
SGLT2i with proven CVD benefit[1]
If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA and vice versa
If A1C remains above target, consider treatment intensification based on comorbidities, patient-centered treatment factors, and management needs
Incorporate agents that provide adequate EFFICACY to achieve and maintain glycemic goals
Higher glycemic efficacy therapy: GLP-1 RA; insulin; combination approaches (Table 9.2)
• Consider additional comorbidities, patient-centered treatment factors, and management needs in choice of therapy, as below:
MINIMIZE HYPOGLYCEMIA
No/low inherent risk of hypoglycemia: DPP-4i, GLP-1 RA, SGLT2i, TZD
For SU or basal insulin, consider agents with lower risk of hypoglycemia[3,4]
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
MINIMIZE WEIGHT GAIN/ PROMOTE WEIGHT LOSS
PREFERABLY
GLP-1 RA with good efficacy for weight loss
OR
SGLT2i
IF A1C ABOVE TARGET
For patients on a GLP-1 RA, consider incorporating SGLT2i and vice versa
• If GLP-1 RA not tolerated or indicated, consider DPP-4i (weight neutral)
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
CONSIDER COST AND ACCESS
Available in generic form at lower cost:
• Certain insulins: consider insulin available at the lowest acquisition cost
• SU
• TZD
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
1. Proven benefit refers to label indication (see Table 9.2)
2. Low dose may be better tolerated though less well studied for CVD effects
3. Choose later generation SU to lower risk of hypoglycemia
4. Risk of hypoglycemia: degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
5. Consider country- and region-specific cost of drugs
^For adults with overweight or obesity, lifestyle modification to achieve and maintain ≥5% weight loss and ≥150 min/week of moderate- to vigorous-intensity physical activity is recommended (See Section 5: Facilitating Behavior Change and Well-being to Improve Health Outcomes).
†Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
‡Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.
*Refer to Section 10: Cardiovascular Disease and Risk Management.
**Refer to Section 11: Chronic Kidney Disease and Risk Management and specific medication label for eGFR criteria.

Statins and NAFLD and abnormal LFT's

- Strong association of NAFLD and increase risk of CVD
  - Lipid profile tends to have high triglycerides, increased LDL and low HDL
- Reluctance to use statins in chronic liver disease, but studies show safety
  - GREACE and IDEAL
  - Severe hepatitis due to statins idiosyncratic and very rare
  - Kaiser study 23,000 persons incidence of ALT > 10 x ULN due to statins was 0.1% (1 per 1,000)
- Black Box warning has been removed
- Lipophilic statins (not hydrophilic) have recently been shown to decrease the risk of HCC

Am J Med 2005;118:618-24

http://aasldv2019stg.aasld.org/sites/default/files/2019-06/NAFLD%20Guidance%202018.pdf

STATIN Recommendations

- Due to NAFLD patients being at high risk for CV morbidity and mortality, CVD risk factors need to be aggressively modified in all NAFLD patients
- Statins do not put NAFLD and NASH patients at higher risk for serious liver injury, therefore, they can be used to treat dyslipidemia in patients with NAFLD and NASH.
- They should be avoided in decompensated cirrhosis.

http://aasldv2019stg.aasld.org/sites/default/files/2019-06/NAFLD%20Guidance%202018.pdf

Bariatric Surgery Improves Clinical Parameters

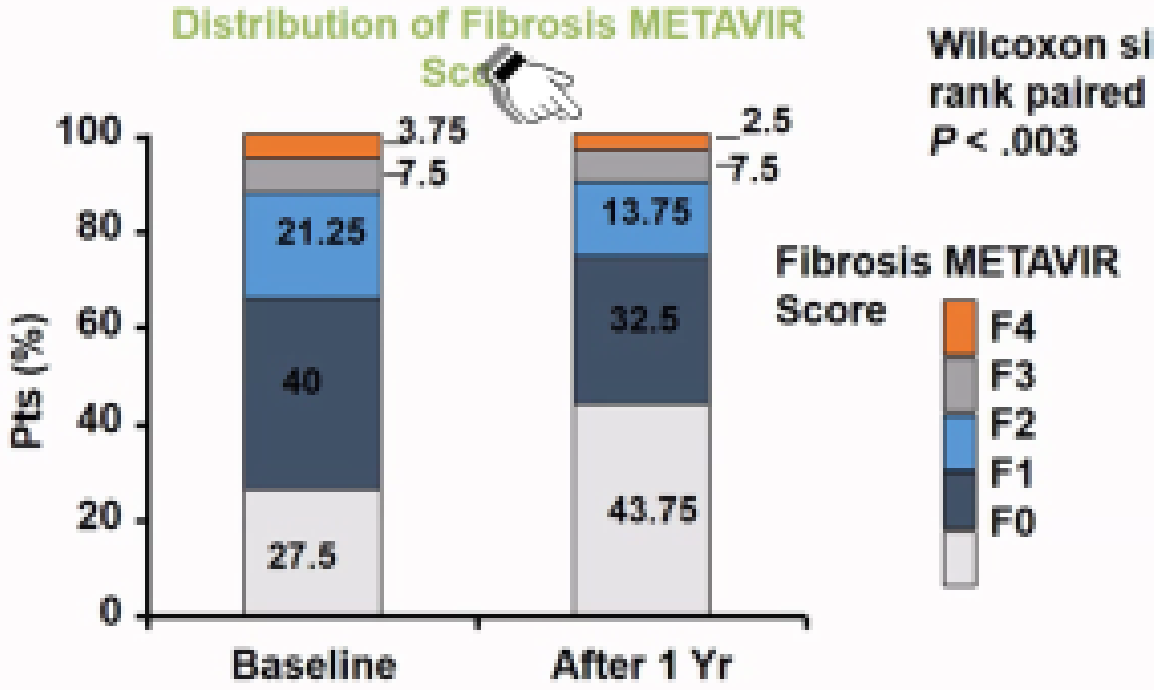
Liver biopsies assessed by 2 blinded reviewers for fibrosis (F0-4), NAFLD scoring to determine NASH (≥ 3, probable or definite; ≥ 5, definite)

Parameter	Before Surgery	After 5 Yrs	*P* Value
Diabetes mellitus, n (%)	94 (24.8)	24 (10.8)	.00001
Arterial hypertension, n (%)	185 (48.8)	85 (37.0)	.0005
Serum triglycerides, mean (g/L)	1.67	1.06	.00001
Fasting glucose, mean (g/L)	1.18	0.94	.00001
Insulin resistance index, mean	3.2	2.83	.00001
ALT, mean (IU/L)	30.1	22.8	.00003
GGT, mean (IU/L)	39.9	29.2	.00001

Mathurin P, et al. Gastroenterology. 2009;137:532-540.

Bariatric Surgery Improves Fibrosis in Pts With NASH

- Prospective study of bariatric surgery in pts who are morbidly obese with biopsy-validated NASH, ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)



Lassailly G, et al. Gastroenterology. 2015;149:379-388.

NASH Treatment: Bariatric Surgery Meta-analysis

- 15 studies: 766 paired liver biopsies

% BMI reduction: 19 – 42%
Steatosis improved 92%
Steatohepatitis improved 81%
Fibrosis improved 66%

➢ **Complete resolution of NASH in 70%**

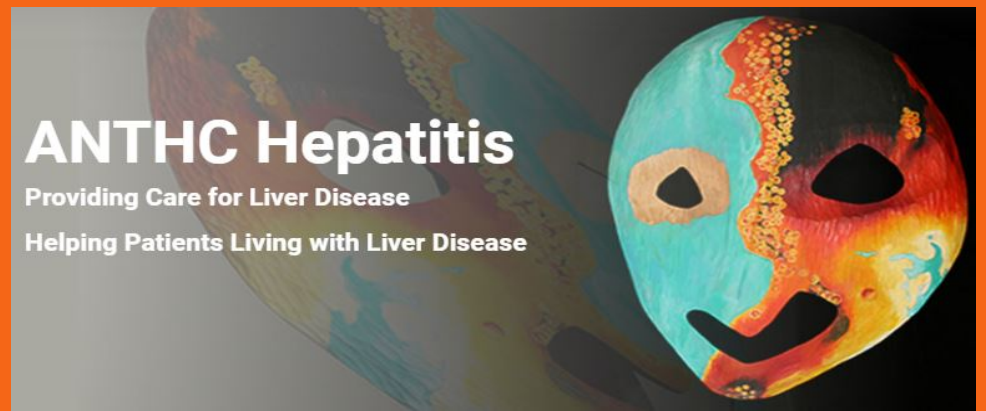
Moummadi; Clin Gastro Hepatol 2008

Conclusions

- No magic drug is available- but are seeing positive results with GLP's
- Wt. loss ~ 10% and 30-60 minutes of exercise 5 days/week
- Important to control diabetes
- Vitamin E in non-diabetics with biopsy proven NASH
- Products to alter biome may be in the future: probiotics and stool transplant
- Treat lipid abnormalities with a statin and consider metformin or GLP1 medications for diabetes
- New drugs to prevent NASH and halt or reverse fibrosis are in clinical trials

ADDITIONAL LEARNING OPPORTUNITIES

- AK ID ECHO: HCV, HIV, PrEP, STIs
  - The 2nd Tuesday of every month from 12:00-1:00PM Alaska Standard Time
    - 1CE/CME offered per session
  - anthc.org/project-echo/hcv-hiv-prep-stis-echo
- LiverConnect Webinar Program
  - Second Tuesday of every month 8:00-9:00AM Alaska Standard Time
    - Full Hour didactic topics on Liver Disease and related topics 1CE/CME offered
  - anthc.org/what-we-do/clinical-and-research-services/hep/liverconnect/



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Thank you

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