Malaysian Society of
Gastroenterology & Hepatology

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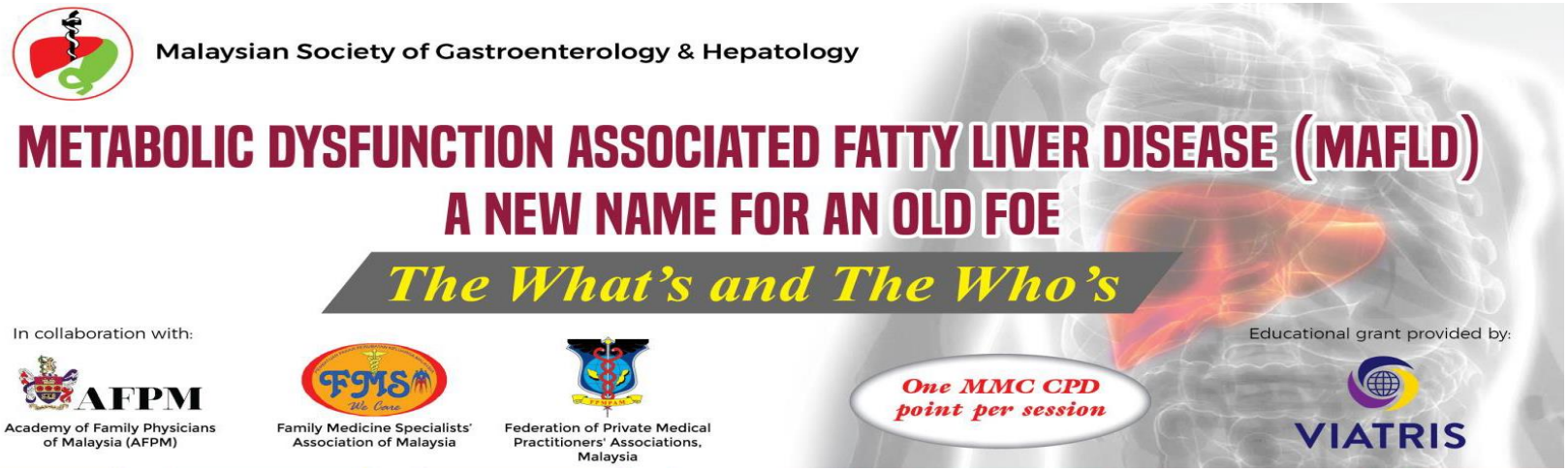


What can we do?

Lifestyle interventions and pharmacological treatments for MAFLD

Wah-Kheong Chan

Steady state

Weight lost

Weight maintained

Weight gain

Energy expenditure

Energy intake

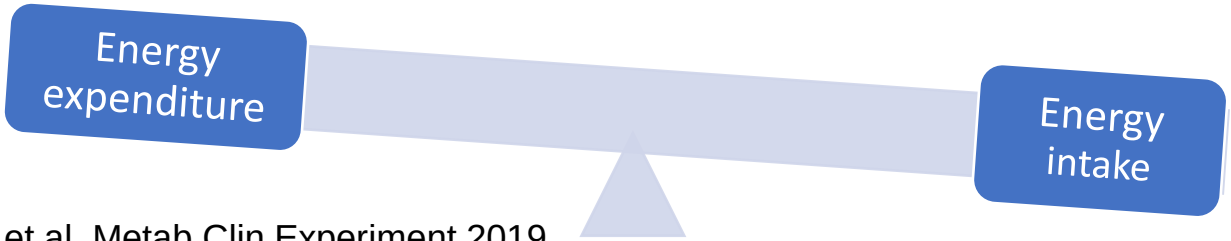
Oussaada SM, et al. Metab Clin Experiment 2019.

Energy intake in excess of expenditure

Weight lost

Weight maintained

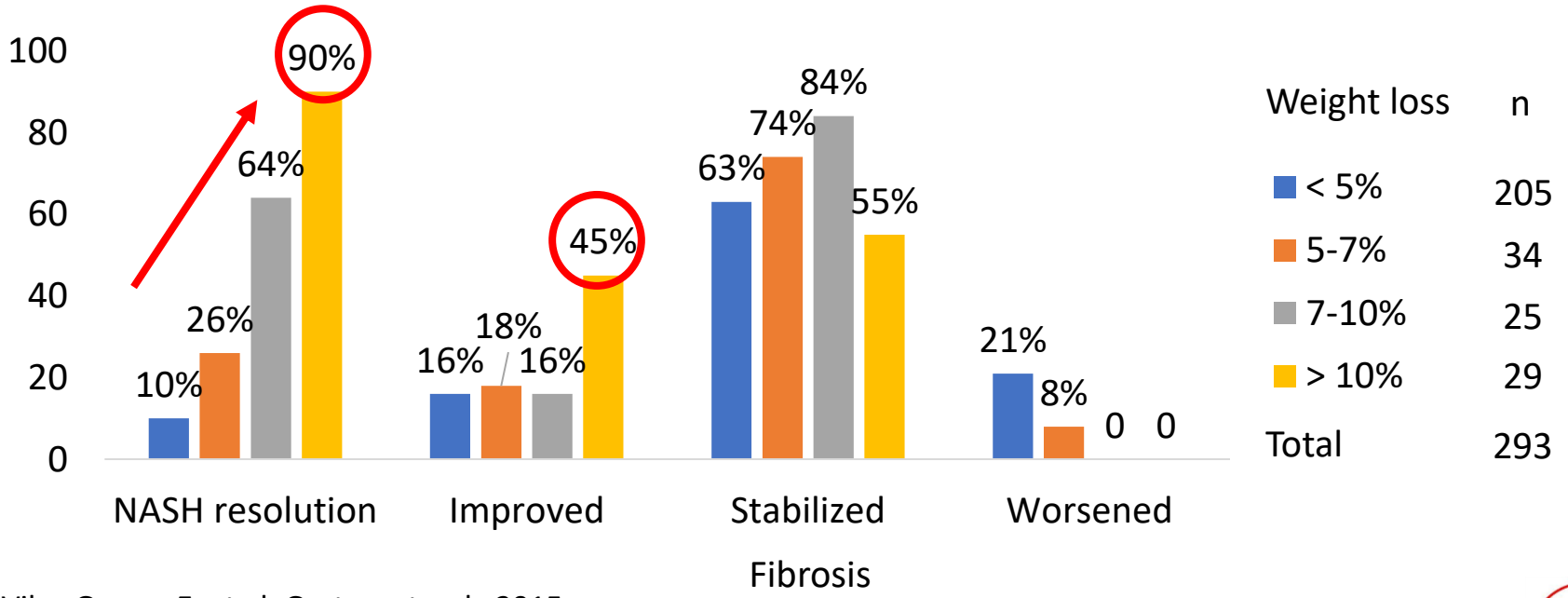
Weight gain



Oussaada SM, et al. Metab Clin Experiment 2019.

Diet and exercise are both important in MAFLD

Lifestyle intervention in NAFLD



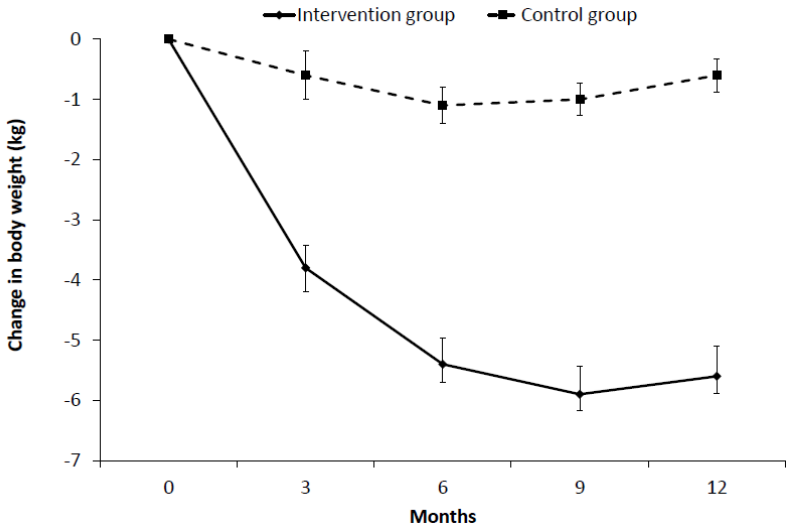
Vilar-Gomez E, et al. Gastroenteroly 2015.

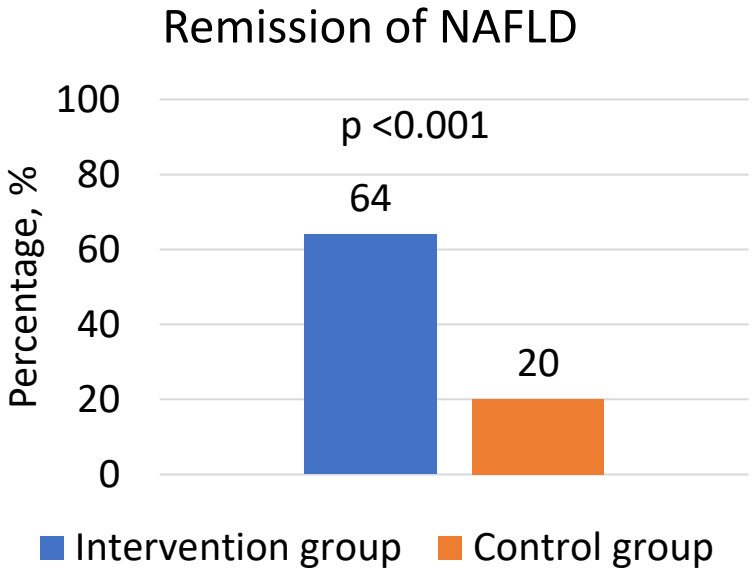
Lifestyle intervention in NAFLD

- Randomized controlled trial
- 154 adults with NAFLD identified during population screening
- Dietitian-led lifestyle modification program vs. usual care
- 12 months
- Primary outcome: Remission of NAFLD as evidenced by intrahepatic triglyceride content <5% based on MRS at Month 12

Wong VW, et al. J Hepatol 2013.

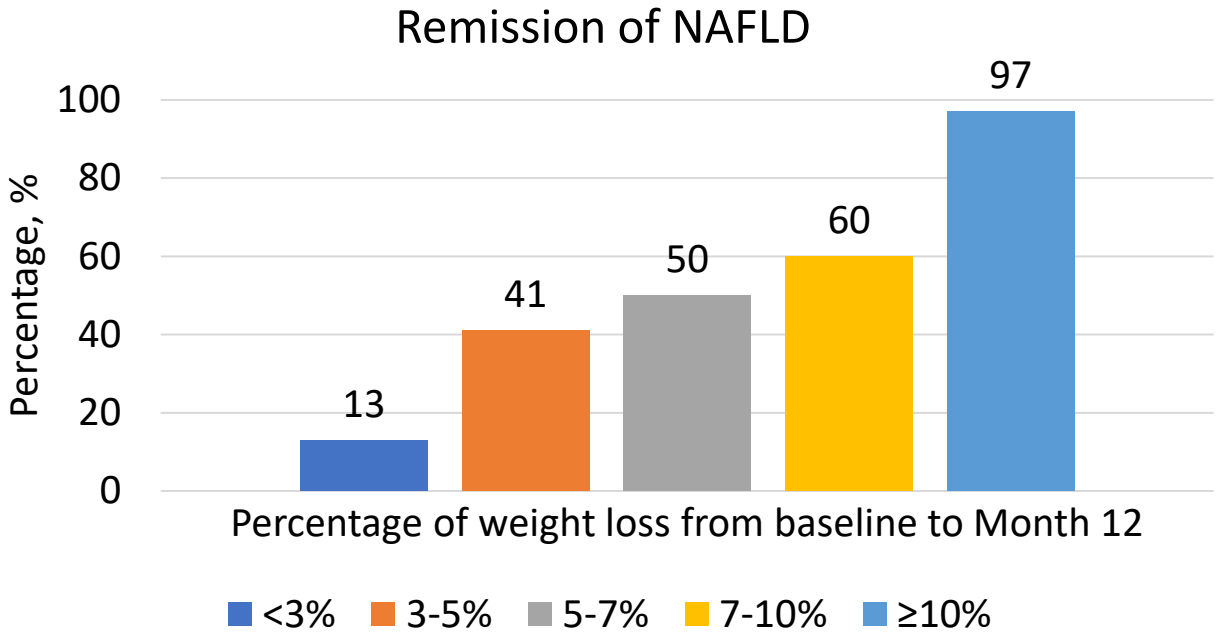
Lifestyle intervention in NAFLD





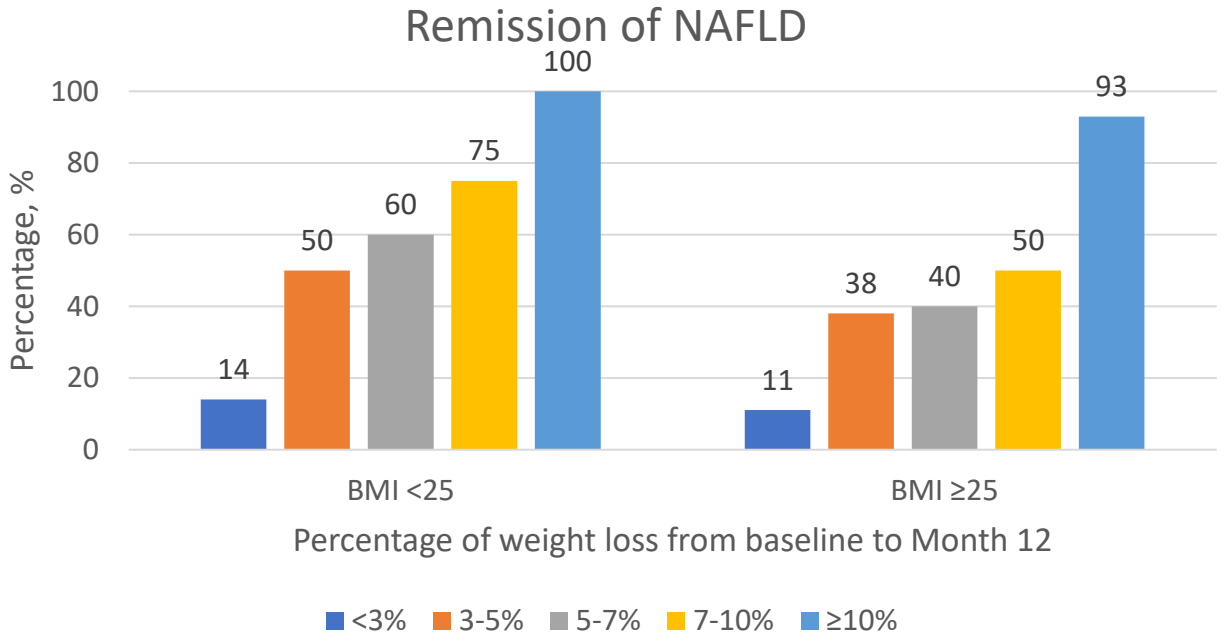
Wong VW, et al. J Hepatol 2013.

Lifestyle intervention in NAFLD



Wong VW, et al. J Hepatol 2013.

Lifestyle intervention in NAFLD



Wong VW, et al. J Hepatol 2018.

Dietary intervention

- Calorie restriction is the most important factor in dietary interventions
- Weight loss results in significant reductions in liver fat and improvement in hepatic insulin resistance

APASL CPG for Diagnosis and Management of MAFLD 2020

- Gradual weight loss (up to 1 kg/week)
- Hypocaloric diet (500–1000 kcal deficit)

Eslam M, et al. Hepatol Int 2020.

Exercise

- Sedentary behaviour is an independent risk factor for NAFLD.

1. Romero-Gommez M, et al. J Hepatol 2017. 2. Ryu S, et al. J Hepatol 2015. 3. Thoma C, et al. J Hepatol 2012.
4. Keating SE, et al. J Hepatol 2012. 5. Hashida R, et al. J Hepatol 2017. 6. Kantartzis K, et al. Gut 2009.

Exercise

- Meta-analysis
- 28 randomized trials
- Physical activity, independent from diet change, was associated with a significant reduction in intrahepatic fat, alanine aminotransferase and aspartate aminotransferase

Orci LA, et al. Clin Gastroenterol Hepatol 2016.

Exercise

- Randomized trial
- 220 subjects with central obesity and NAFLD.
- Vigorous-moderate exercise vs. moderate exercise vs. no exercise for 12 months
- Vigorous-moderate and moderate exercise were equally effective in reducing intrahepatic triglyceride content.
- After adjusting for weight loss, the net changes in intrahepatic triglyceride content were diminished and became nonsignificant between the exercise and control groups

Zhang HJ, et al. JAMA 2016.

Exercise

- Sedentary behaviour is an independent risk factor for NAFLD.
- Exercise, without weight loss, can produce 20-30% relative reduction in intrahepatic fat.
- The effect of exercise is modest in comparison to weight reduction, which can produce >80% reduction in intrahepatic fat.

Cardiorespiratory fitness is a determinant of response to dietary intervention in NAFLD. Those with greater cardiorespiratory fitness have greater response to dietary intervention.

1. Romero-Gommez M, et al. J Hepatol 2017. 2. Ryu S, et al. J Hepatol 2015. 3. Thoma C, et al. J Hepatol 2012.
4. Keating SE, et al. J Hepatol 2012. 5. Hashida R, et al. J Hepatol 2017. 6. Kantartzis K, et al. Gut 2009.

Aerobic or resistance exercise?

- Systematic review
- 13 aerobic and 4 resistance exercise protocols were selected for comparative analysis
- Aerobic exercise: 4.8 METs for 40 minutes/session, 3 times/week for 12 weeks
- Resistance exercise: 3.5 METs for 45 minutes/session, 3 times/week for 12 weeks
- Both aerobic and resistance exercise improved hepatic steatosis
- VO_2 max and energy consumption lower in resistance exercise

Hashida R, et al. J Hepatol 2017.

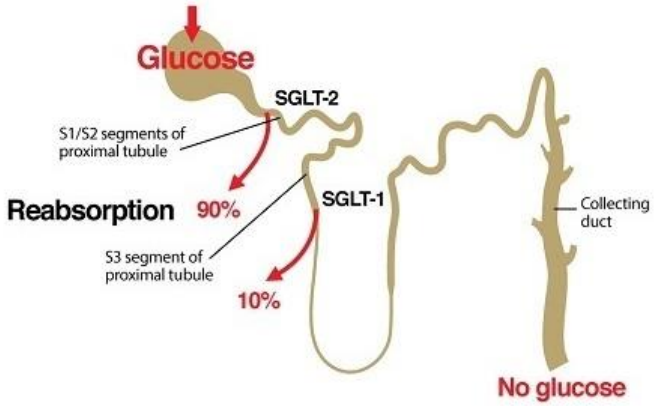
In patients with lower cardiorespiratory fitness, resistance exercise is an option.

Pharmacological treatments for MAFLD

- There is currently no FDA approved treatment for MAFLD

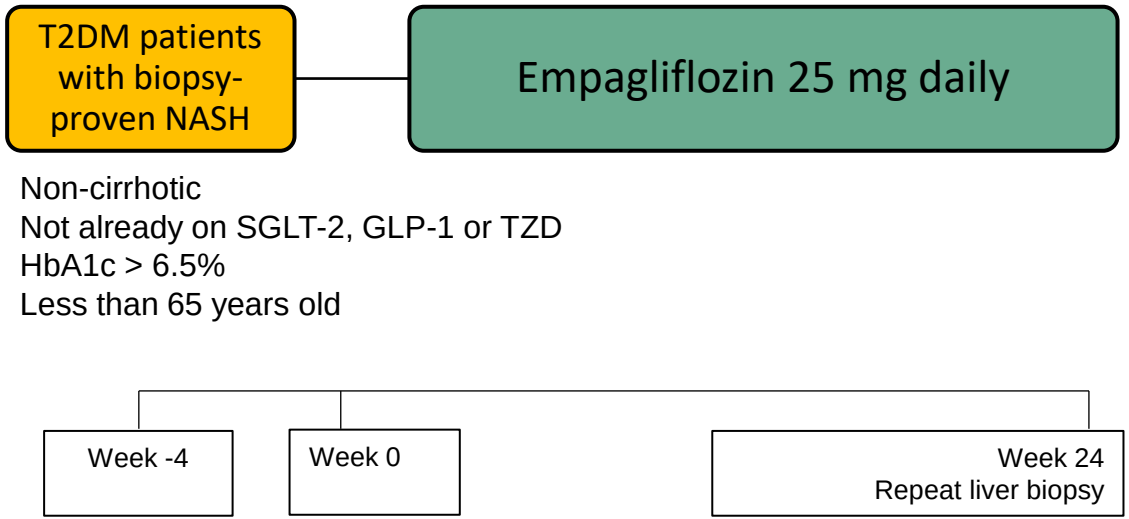
Sodium-glucose co-transporter 2 (SGLT-2) inhibitor

- Blocks reabsorption of glucose in the kidney, increase glucose excretion, and lower blood glucose levels
- Adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus



Empagliflozin for treatment of NASH in T2DM patients

- Investigator-initiated, single-arm, open-label pilot study



Lai LL, et al. Dig Dis Sci 2019.

	Median change	p
BMI, kg/m^2	-0.7	0.011
WC, cm	-3	0.033
SBP, mmHg	-9	0.024
DBP, mmHg	-6	0.033
FBS, mmol/L	-1.7	0.008
Total cholesterol, mmol/L	-0.5	0.011
GGT, U/L	-19	0.013
Volumetric liver fat fraction, %	-7.8	0.017
Steatosis grade	-1	0.014
Ballooning grade	-1	0.034
Fibrosis stage	0	0.046

Lai LL, et al. Dig Dis Sci 2019.

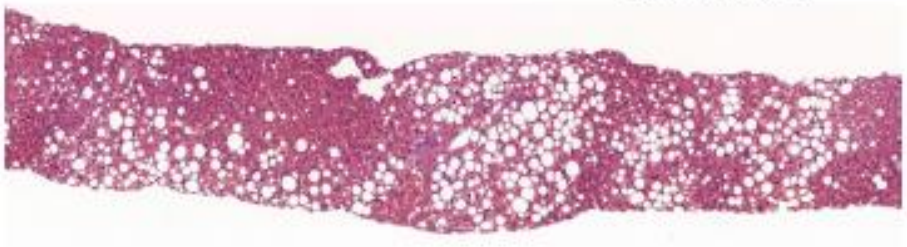
Subject 001

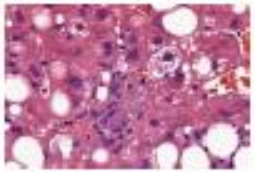
	Baseline	Follow-up
Liver biopsy length, mm	15	10
Number of portal tracts	5	6
Steatosis grade	2	1
Lobular inflammation grade	1	1
Hepatocyte ballooning grade	1	0
Fibrosis stage	1	0
NASH	Yes	No

Lai LL, et al. Dig Dis Sci 2019.

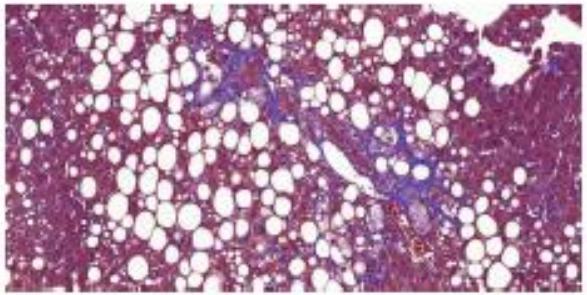
Subject 001

Pre-treatment (H&E 5x):
Grade 2 Steatosis





Pre-treatment (H&E 20x):
Focal hepatocyte ballooning and inflammation

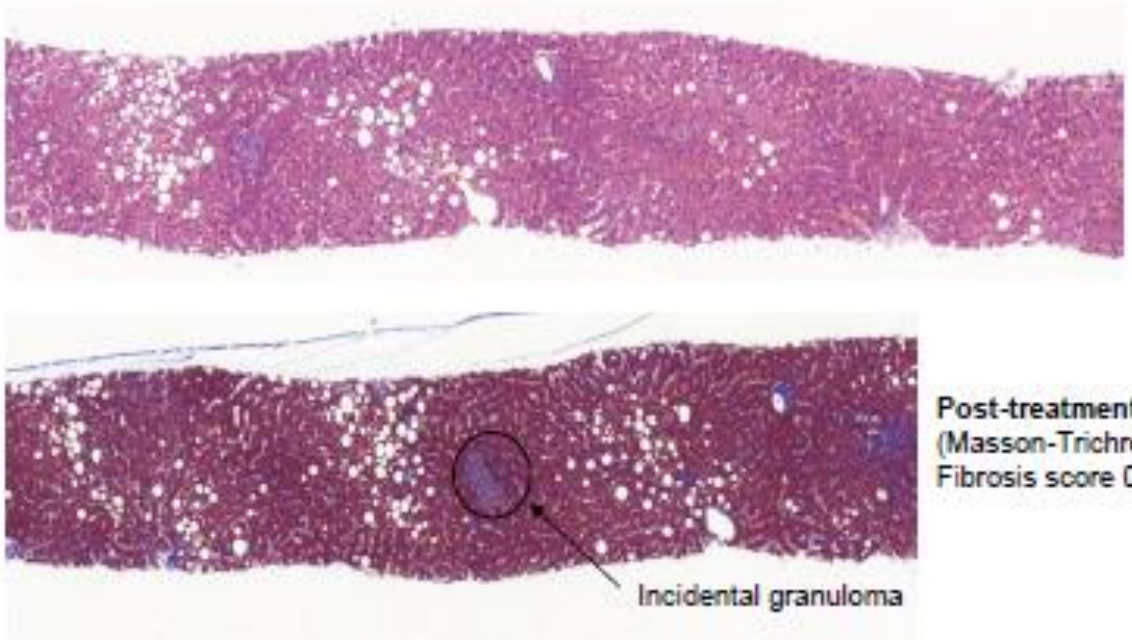


Pre-treatment (Masson-Trichrome 10x):
Focal zone 3 perisinusoidal fibrosis (score 1a)

Lai LL, et al. Dig Dis Sci 2019.

Subject 001

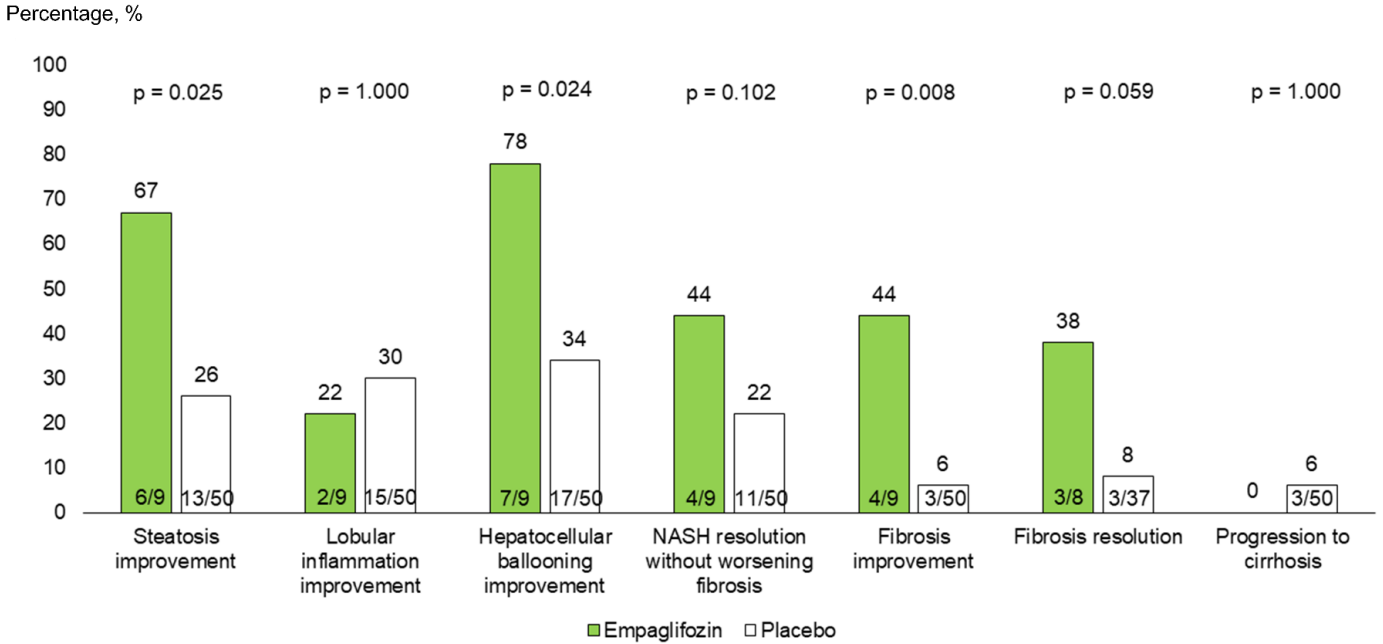
Post-treatment (H&E 5x):
Grade 1 Steatosis



Post-treatment
(Masson-Trichrome 5x):
Fibrosis score 0

Lai LL, et al. Dig Dis Sci 2019.

Empagliflozin vs. historical placebo



Lai LL, et al. Dig Dis Sci 2019.

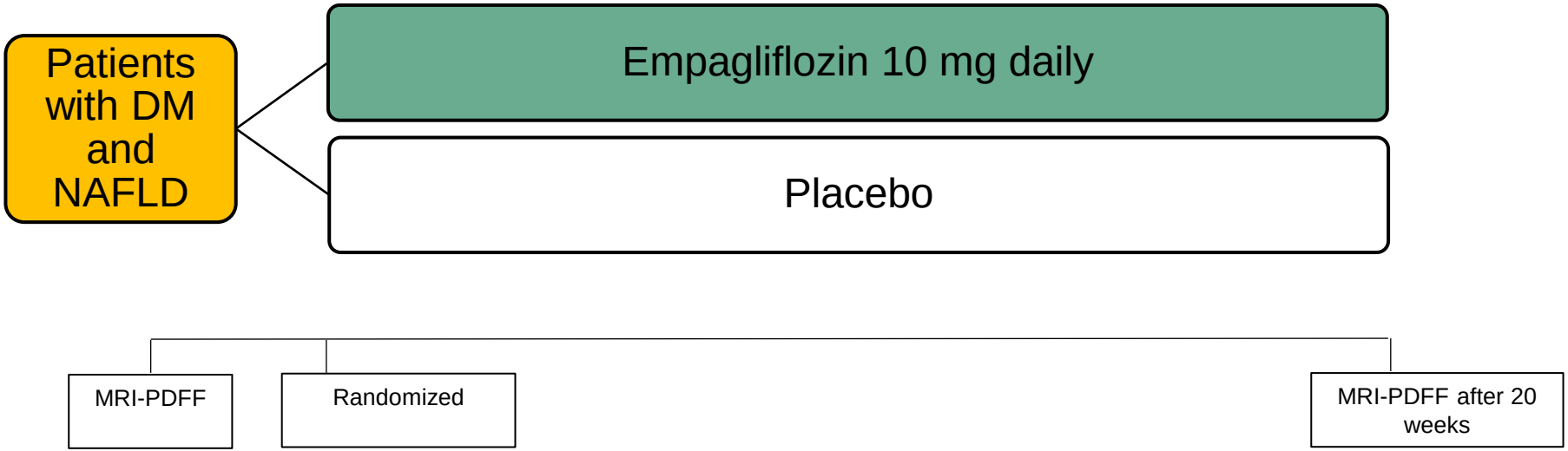
Adverse events

- Six of 9 patients experienced minor hypoglycemia. All 6 patients were on concomitant insulin therapy. No patients experienced severe hypoglycemia.

- None of the patients developed genitourinary infection, but one patient experienced pruritus vulvae which resolved spontaneously with perineal hygiene.

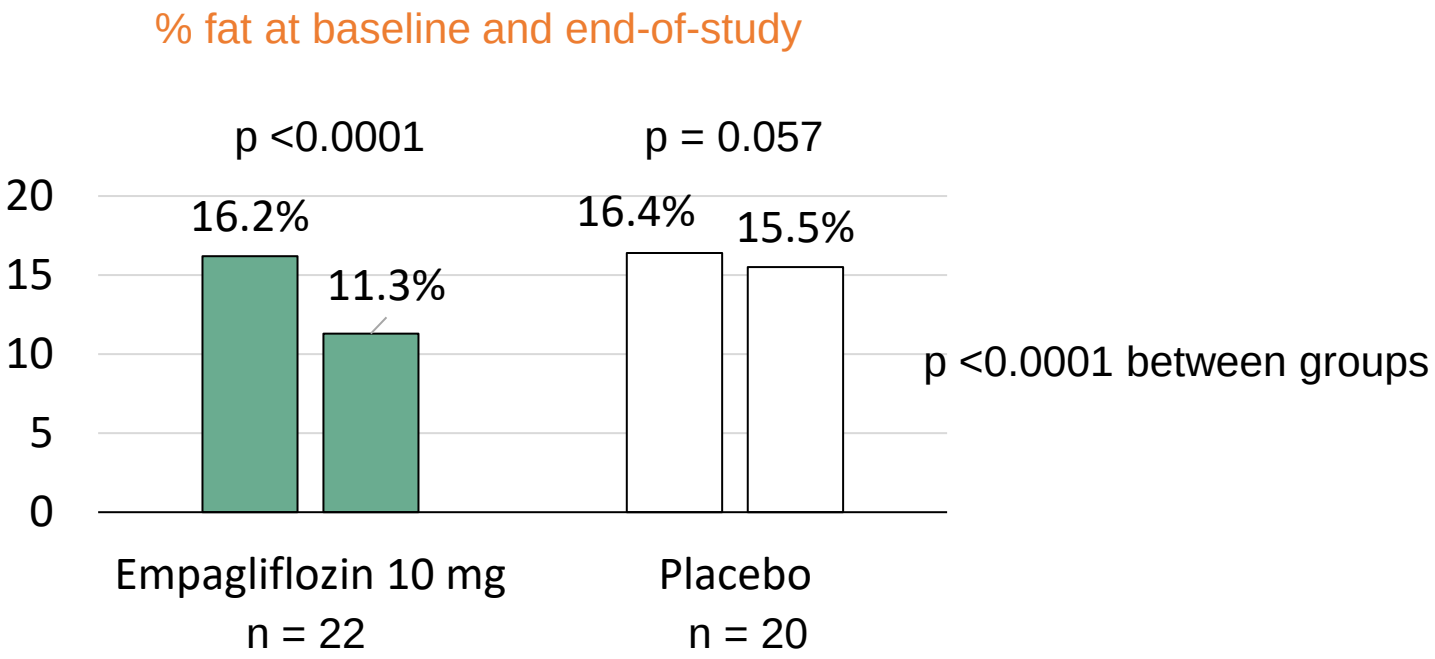
Lai LL, et al. Dig Dis Sci 2019.

E-LIFT Trial



Kuchay MS, et al. Diabetes Care 2018.

E-LIFT Trial



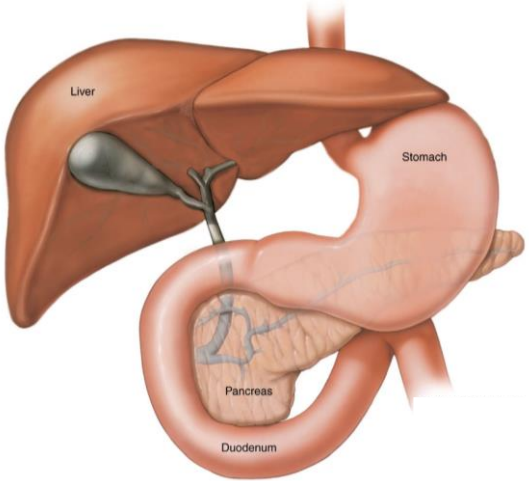
Kuchay MS, et al. Diabetes Care 2018.

Empaglifozin, cardiovascular outcomes and mortality in T2DM

- N = 7020
- Randomly assigned to 10 mg or 25 mg of empaglifozin or placebo
- Median observation 3.1 years
- Significantly lower rates of death from cardiovascular causes (3.7% vs. 5.9%), hospitalization for heart failure (2.7% vs. 4.1%) and death from any cause (5.7% vs. 8.3%)

Zinman B, et al. N Engl J Med 2015.

Glucagon-like peptide-1 (GLP-1) receptor agonist



1. Delays gastric emptying
2. Increase insulin secretion
3. Decrease hepatic gluconeogenesis by decreasing glucagon secretion

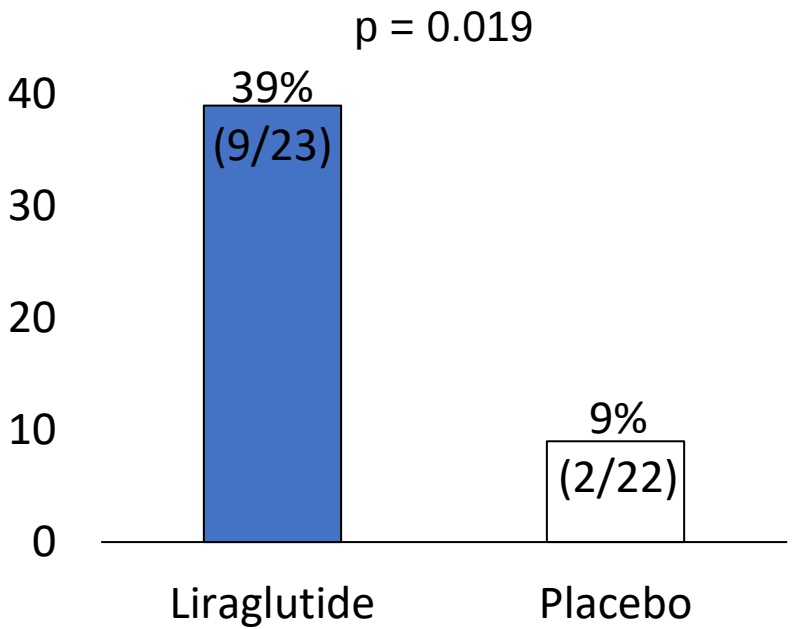
Baggio, et al. Gastroenterology 2007.

Liraglutide Efficacy and Action in Non-Alcoholic Steatohepatitis (LEAN)

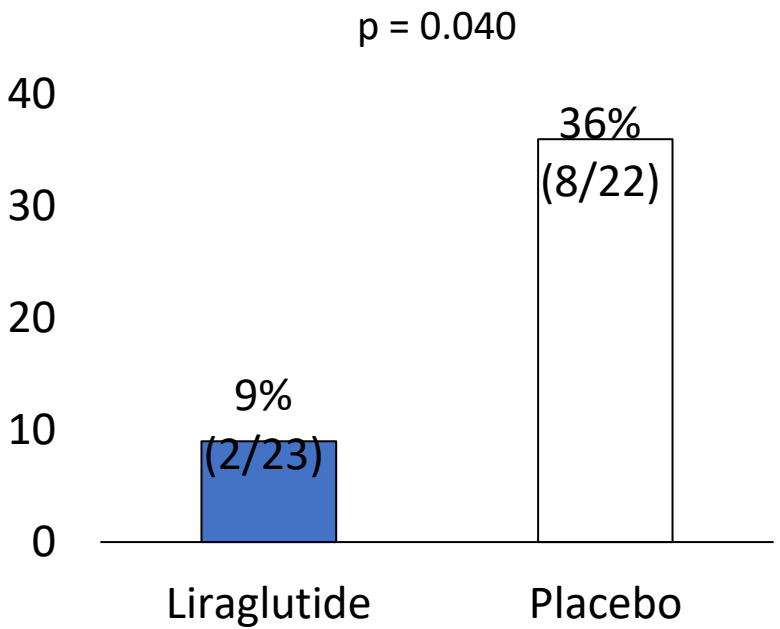
- Multicentre, randomized, double-blinded, placebo-controlled trial
- Overweight (BMI ≥ 25 kg per m^2) and biopsy-proven NASH
- Liraglutide 1.8 mg daily vs. placebo for 48 weeks
- Primary efficacy outcome: resolution of definite NASH (disappearance of hepatocyte ballooning) with no worsening in fibrosis
- Percentage of patients with diabetes mellitus: 33%
- Percentage of patients with fibrosis stage F3, 40% ; F4, 12%

Armstrong, et al. Lancet 2016.

Resolution of definite NASH



Progression of fibrosis



Armstrong, et al. Lancet 2016.

	Mean change	p*
BMI, kg/m^2	-1.6	0.005
FBS, mmol/L	-1.7	0.005
HbA1c, %	-0.5	0.030
HDL cholesterol, mmol/L	+0.13	0.010
GGT, U/L	-23	0.010

*p values and adjusted treatment changes determined by linear regression analysis regressing change on the baseline characteristic score and treatment

Armstrong, et al. Lancet 2016.

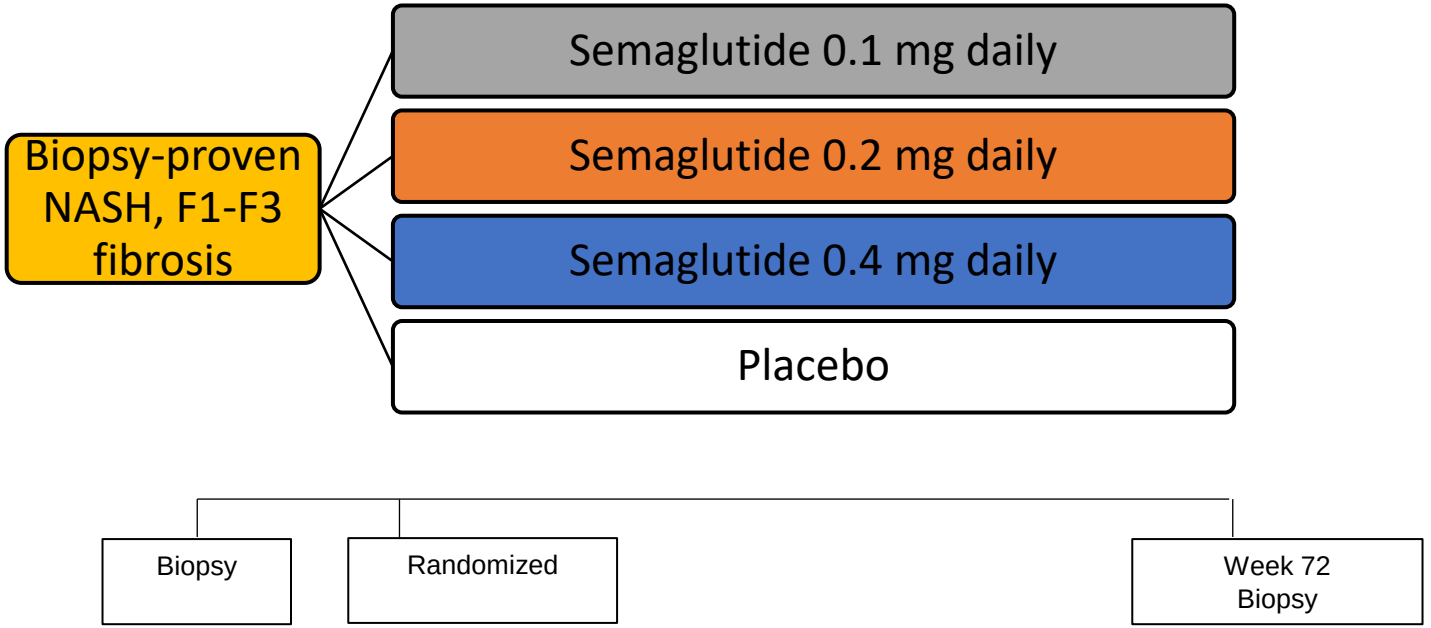
Adverse events

- Similar adverse event profile to placebo, with the exception of predictable gastrointestinal symptoms (mainly diarrhoea, constipation, and loss of appetite), which were mainly transient and mild-to-moderate in severity

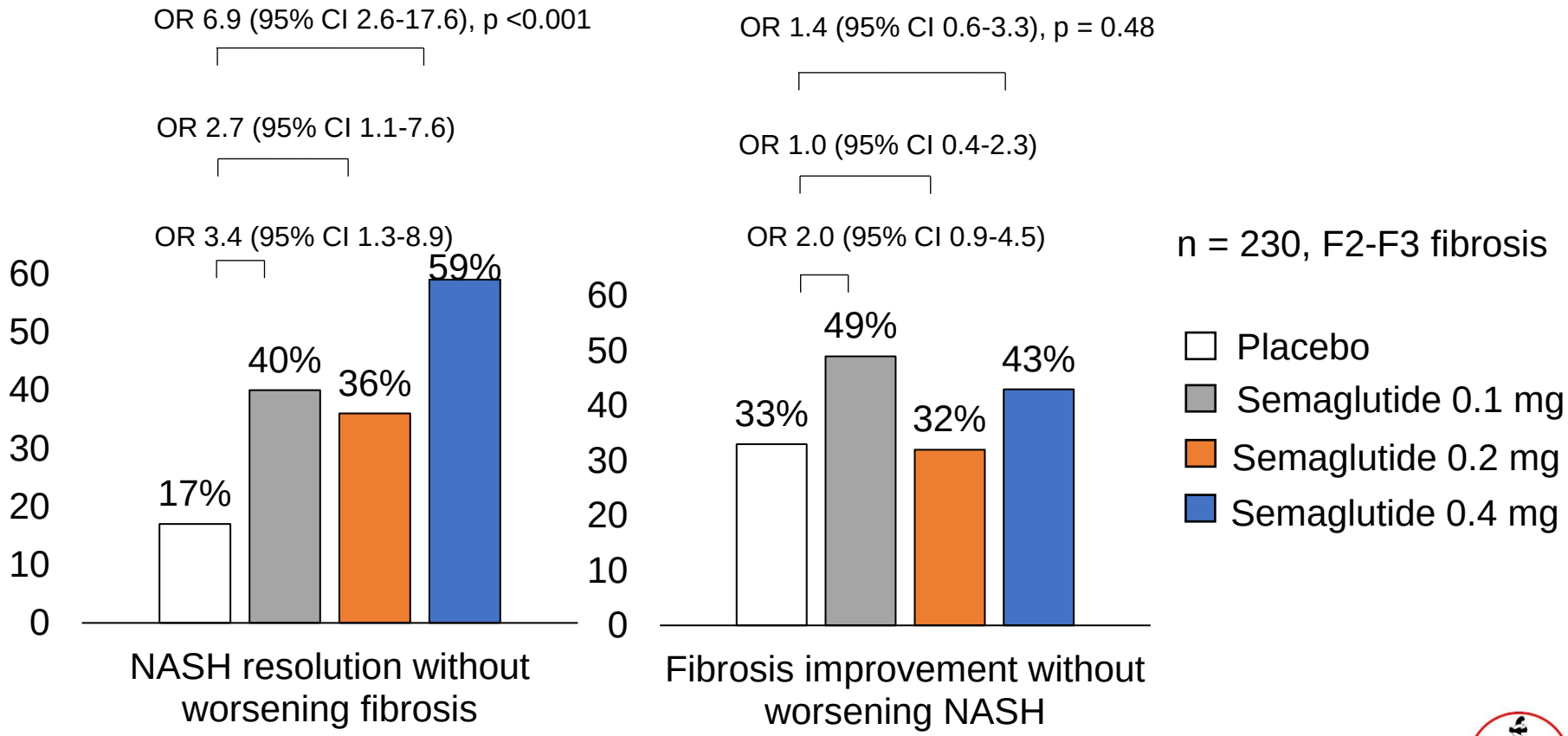
- Contraindicated in patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2

Armstrong, et al. Lancet 2016.

Semaglutide



Newsome, et al. NEJM 2020.



Newsome, et al. NEJM 2020.

Semaglutide significantly reduced adverse cardiovascular events

- 3297 patients
- Randomized to semaglutide once weekly injection (0.5 mg or 1.0 mg) or placebo for 104 weeks
- Primary outcome: First occurrence of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke
- Primary outcome occurred in 6.6% in semaglutide groups vs. 8.9% in the placebo group ($p < 0.001$)

Marso, et al. NEJM 2016.

Conclusion

- Lifestyle intervention is the mainstay for treatment for MAFLD.
- Weight loss of ≥10% can lead to NASH resolution in most patients and fibrosis improvement in many.
- There is currently no FDA approved pharmacological treatment for MAFLD.
- However, there is emerging evidence of benefit of SGLT inhibitors and GLP-1 receptor agonists in MAFLD.