Treatment: How Do We Treat Today, Tomorrow and in the Future?

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Disclosures

Stephen A. Harrison

I disclose the following financial relationship(s) with a commercial interest:

- Scientific advisor or consultant for Akero, Alentis, Altimmune, Arrowhead, Axcella, BMS, Echosens, Fibronostics, Forest Labs, Galectin, Gilead, Hepion, Hepagene, HistoIndex, Intercept, Madrigal, Medpace, Metacrine, NGM Bio, Northsea, Novartis, Novo Nordisk, PathAI, Poxel, Liminal, Sagimet, Terns, Viking.
- Stock options: Akero, Cirius, Galectin, Genfit, Hepion, HistoIndex, PathAI, Metacrine, NGM Bio, Northsea.
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Lifestyle Recommendations for Treating NASH

Caloric intake reduction
≥30% or
~750-1,000 kcal/day
improved insulin resistance and hepatic steatosis
*Limit consumption of fructose-enriched beverages

Weight loss
of 3% to 5% can improve steatosis, but 6% to 10% is needed to improve NASH/fibrosis

Exercise
alone may reduce steatosis, but effect on other histologic features unknown

No heavy alcohol consumption
Insufficient data to guide recommendations regarding nonheavy alcohol consumption
**Drink ≥2 cups of caffeinated coffee daily

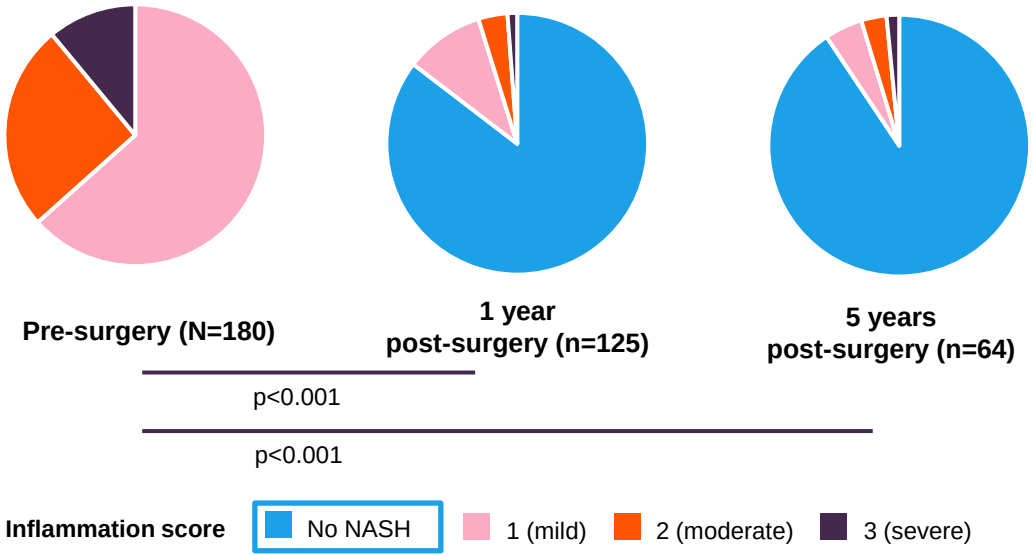
*Fructose increases the odds of the development of nonalcoholic fatty liver in high-risk patients and of nonalcoholic steatohepatitis and more advanced liver fibrosis in patients who already have nonalcoholic fatty liver disease.

**Caffeinated coffee reduces the risk of liver fibrosis in several liver diseases, including nonalcoholic fatty liver disease.

Chalasani N et al. *Hepatology*. 2018;67(1):328-357; Diehl AM, Day C. *New Engl J Med.* 2017; 377:2063-72.

Fibrosis Regression Over Time Following Bariatric Surgery in Patients With Severe Obesity and NASH

Distribution of patients with NASH by Brunt inflammation score



NASH resolution with no worsening of fibrosis in **84%** of patients at 5 years post-surgery (p<0.001 vs baseline)

Increased weight loss associated with higher likelihood of NASH resolution

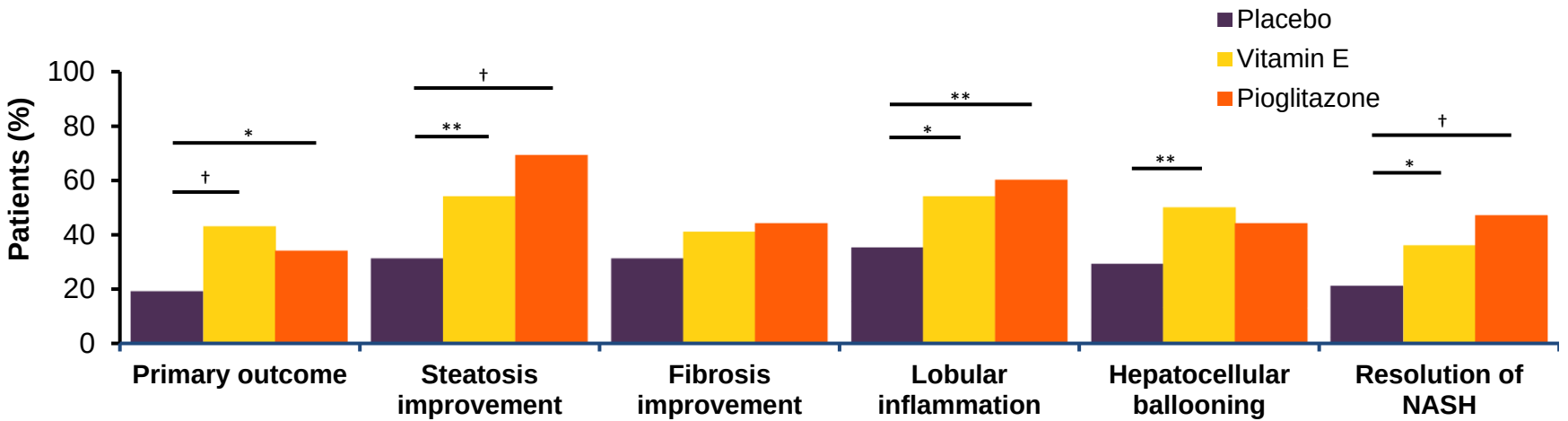
Fibrosis improvement in **70.2%** of patients at 5 years post-surgery

Significant reduction of BMI, AST, ALT, GGT and insulin resistance

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis.

Lassailly G et al. *Gastroenterology*. 2015;149:379–88; Lassailly G et al. *Gastroenterology*. 2020;159:1290–301.

Pharmacological Management of NASH

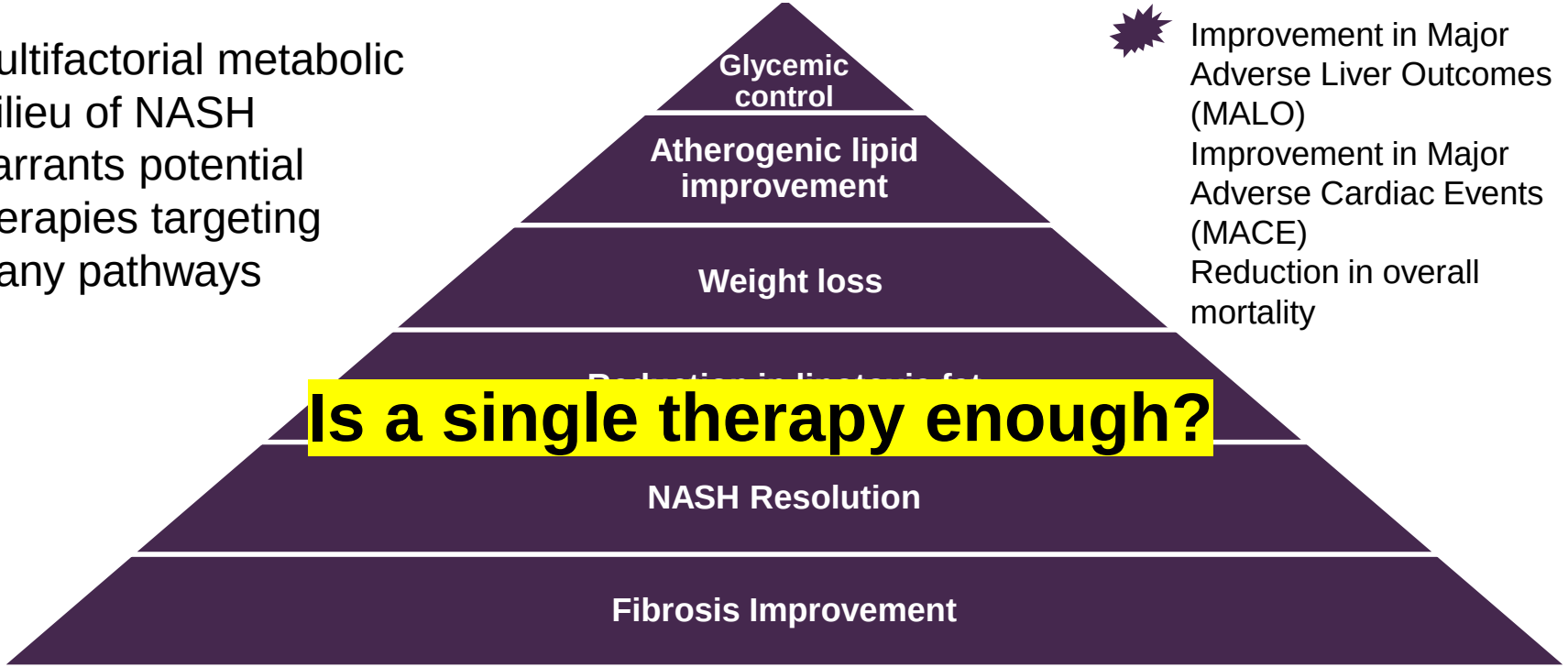


- **Pioglitazone** may improve NASH histology other than fibrosis
- **Vitamin E** may improve histology

*p≤0.05; **p≤0.01; †p≤0.001 vs placebo. N=247; adult patients without diabetes and with biopsy-proven NASH were randomised to pioglitazone 30 mg/day, vitamin E 800 IU/day, or placebo for 96 weeks. The primary outcome was defined as an improvement in histologic findings, which required improvement by 1 or more points in the hepatocellular ballooning score; no increase in the fibrosis score; and either a decrease in the activity score for NAFLD to a score of ≤3 points or a decrease in the activity score of ≤2 points, with ≥1-point decrease in either the lobular inflammation or steatosis score.
NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
Sanyal AJ et al. *N Engl J Med.* 2010;362:1675–85.

Potential Targets for NASH Treatments

Multifactorial metabolic milieu of NASH warrants potential therapies targeting many pathways



Improvement in Major Adverse Liver Outcomes (MALO)
Improvement in Major Adverse Cardiac Events (MACE)
Reduction in overall mortality

Phase 2 / Non-Invasive Endpoints

FXR agonists	• Metacrine (MET409, MET642) • Enyo (EYP001) • Terns (TERN-101)
Cyclophylin inhibitor	• Hepion (CRV431)
Berberine/UDCA	• HighTide (HTD1801)
Mixed Ag/Antag GR/Antag MR	• Corcept (Miricorilant)
FGF21 Agonists	• Boston Pharmaceuticals (BOS-580)
GLP-1 RAs	• GLP-1/glucagon agonists Ex: AstraZeneca (Cotadutide) • GLP1/GR/GIP Ex: Hanmi (HM15211)
Galectin-3 inhibitor	• Galectin (Belapectin – Decompensation outcomes)

Phase 2 / Histological Endpoints

PPAR Agonists	• Zydus (Saroglitazar)
THR-beta agonists	• Viking (VK2809)
FASN Inhibitor	• Sagimet (TVB2640)
Amino Acids	• Axcella (AXA1125)
Mitochondrial Pyruvate Carrier	• Poxel (PXL065)
JNK Inhibitor	• Celgene (CC-90001)
Testosterone Pro-Drug	• Lipocine (LPCN1144)
FGF19 Agonists	• NGM (Aldafermin) ***
FGF21 Agonists	• Akero (Efruxifermin) • BMS (Pegbelfermin) *** • 89 Bio (BIO89-100)
Structurally Engineered Fatty Acids	• Northsea (Icosabutate)
GLP-1 RAs	• GLP-1/GIPs • Lilly (Tirzepatide)
DGAT2 Inhibitor	• Ionis (ION224)

Legends:

*** AASLD Presentation, 2021

Boxed Compounds = Ongoing

Marked with arrows = Readout or Enrollment Finished

Agents in Phase 2 Development-Route of Administration

Oral Agents

FXR agonists	• Metacrine (Met409, Met642), Enyo (EYP001), Terns (Terns 101)
PPAR agonists	• Zydus (Saroglitazar)
THR-beta agonists	• Viking (VK2809)
FASN inhibitor	• Sagimet (TVB2640)
Cyclophylin inhibitor	• Hepion (CRV431)
Structurally engineered fatty acids	• NorthSea (Icosabutate)
Berberine/UDCA	• Hightide (HTD1801)
Mixed Ag/Antag GR/Antag MR	• Corcept (Miricorilant)
Amino Acids	• Axcella (AXA1125)
Mitochondrial pyruvate carrier	• Poxel (PXL065)
JNK inhibitor	• Celgene (CC-90001)
Testosterone prodrug	• Lipocine (LPCN1144)

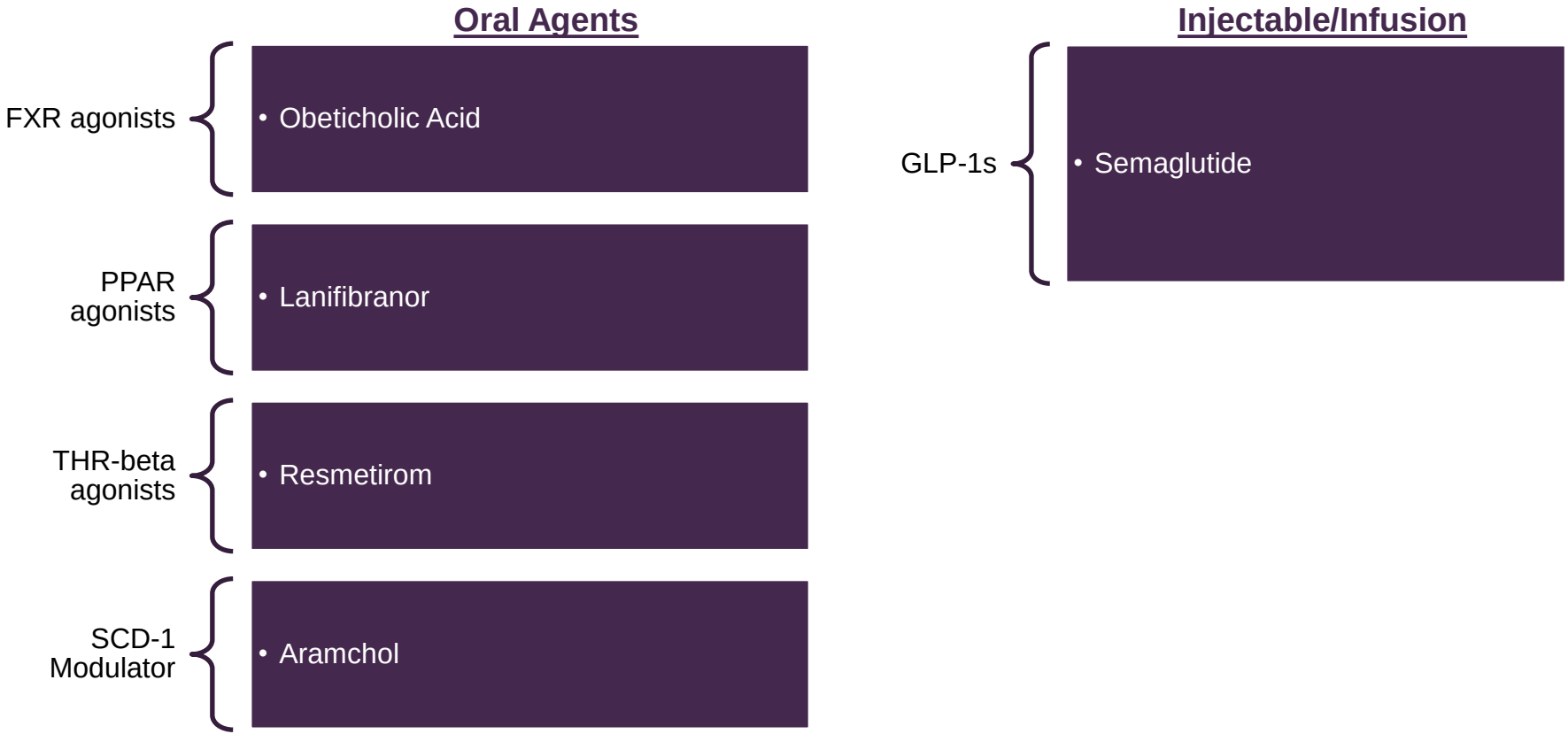
Injectable/Infusion

FGF19 Agonists	• NGM (Aldafermin)
FGF21 Agonists	• Akero (Efruxifermin) • BMS (Pegbelfermin) • 89 Bio (BIO89-100) • Boston Pharmaceuticals (BOS-580)

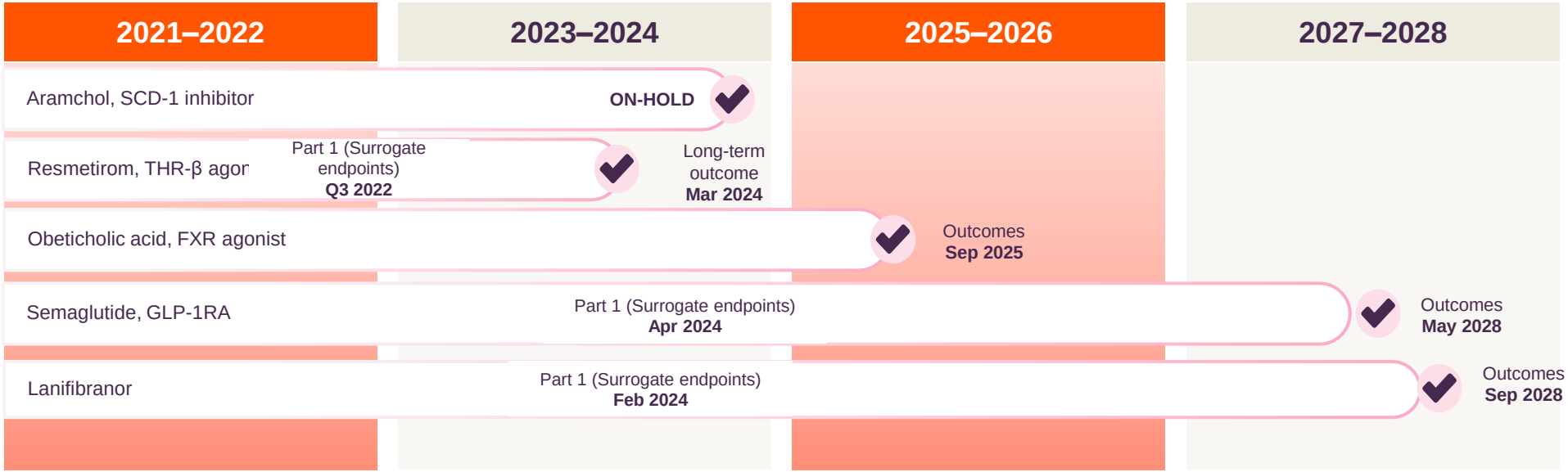
GLP-1 RAs	• GLP-1/GIPs
	  • Lilly (Tirzepatide)
	• GLP-1/glucagon agonists
	  • AstraZeneca (Cotadutide)
	• GLP1/GR/GIP
	  • Hanmi (HM15211)

DGAT2 Inhibitor	• Ionis (ION224)
Galectin-3 inhibitor	• Galectin (Belapectin)

Agents in Phase 3 Development

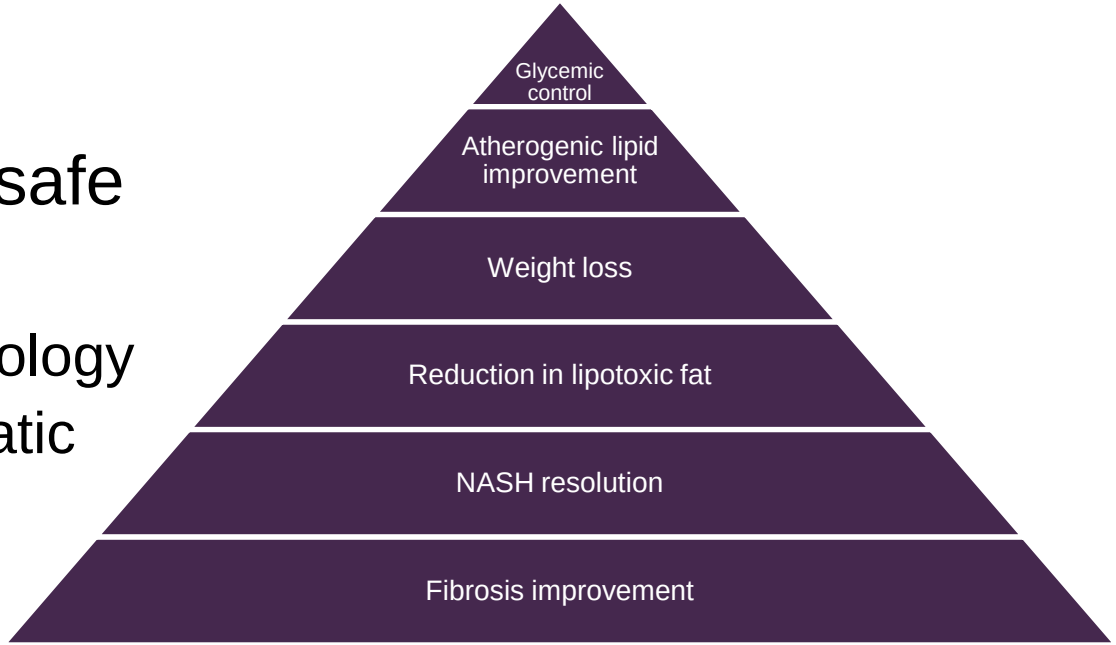


The Future of NASH Therapeutics
Ongoing Phase 3 Trials

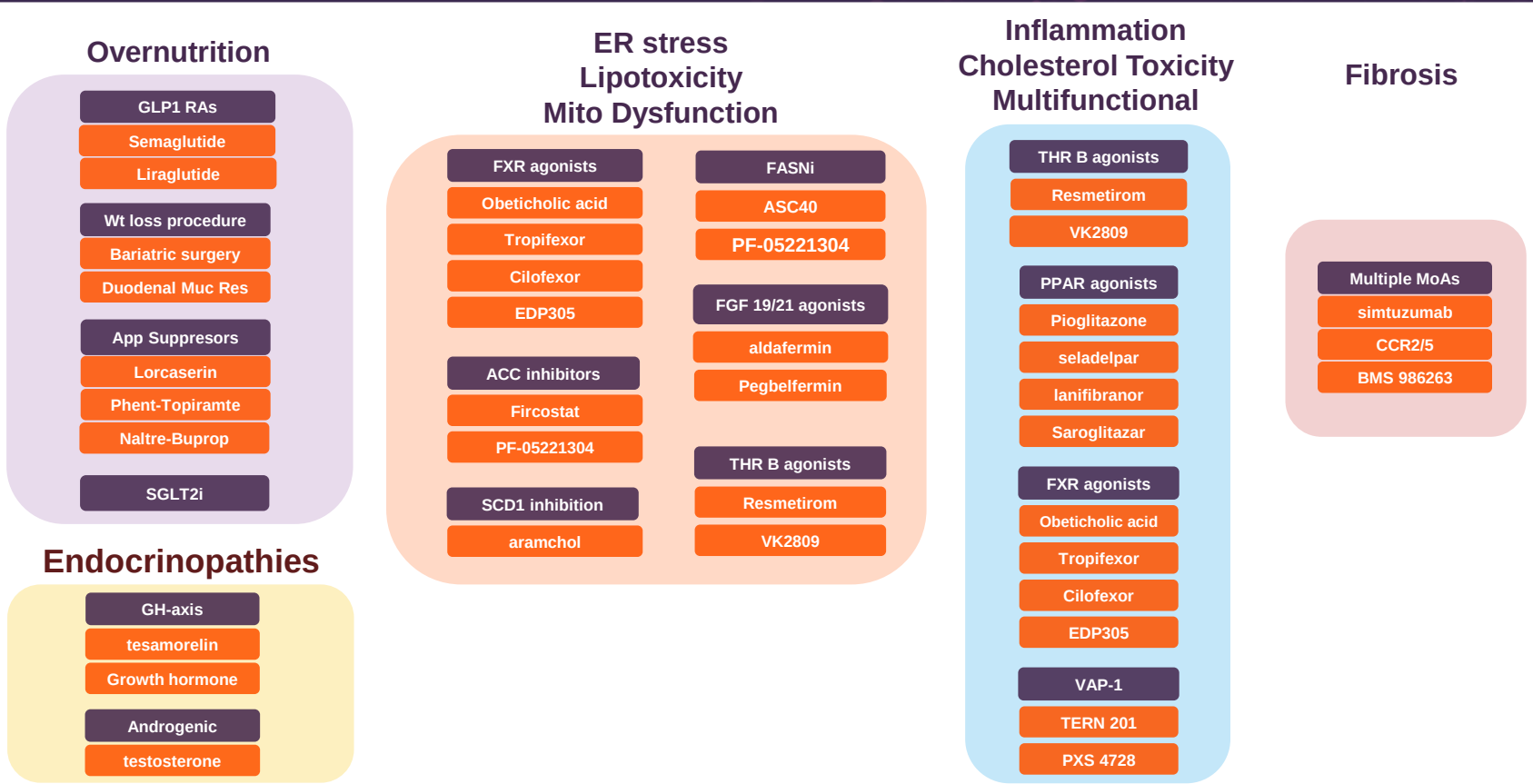


Ideal Combination

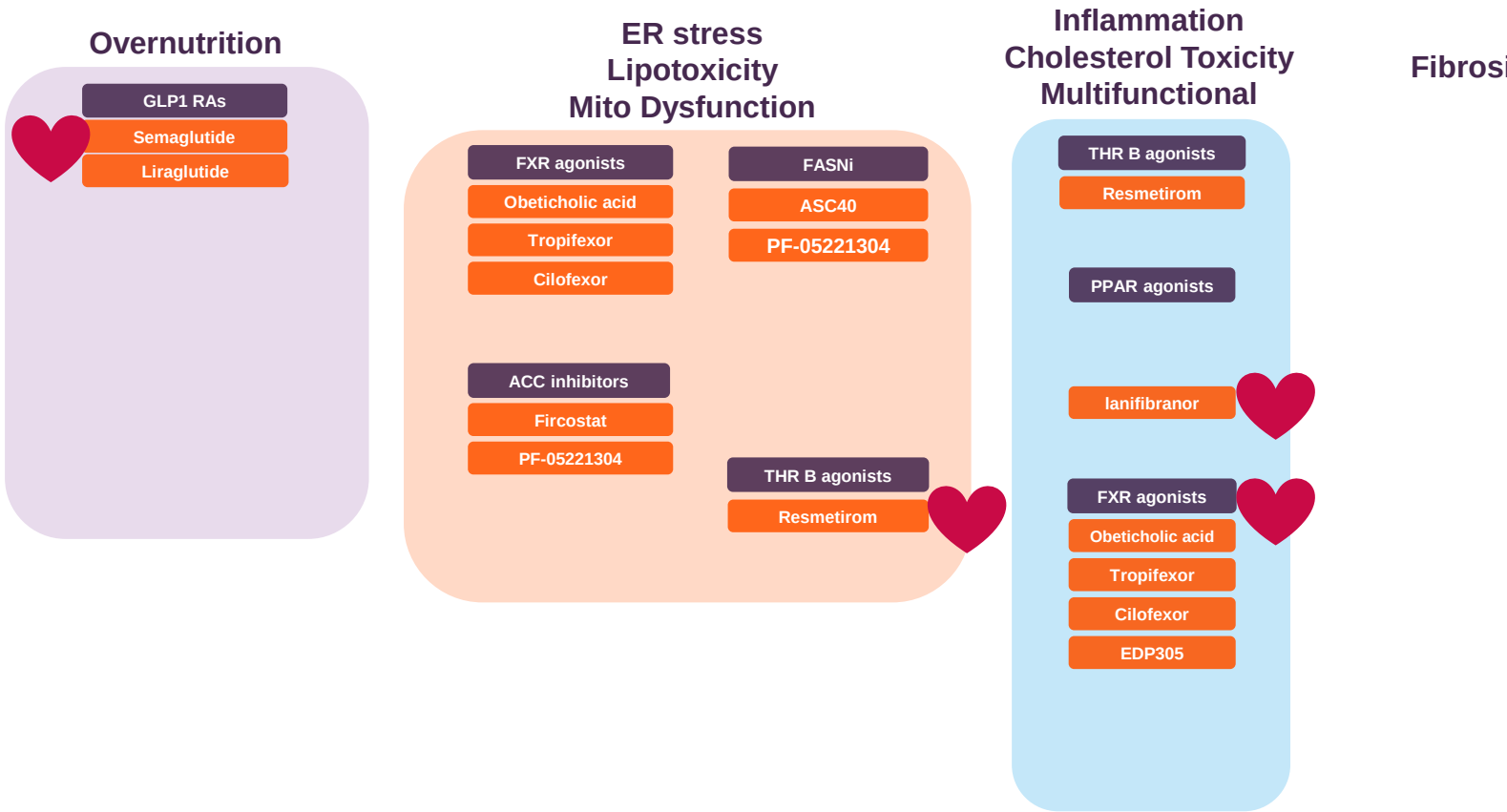
- Oral
- Well tolerated and safe
- Synergistic
  - Improves histopathology
  - Improves extrahepatic metabolic profiles
- Enhances long term outcomes



NASH Therapeutics by MoA



NASH Therapeutics by MoA



Jamaican 4x100m Relay World Record
Seoul, Sept 4th 2011

All:

- World class sprinters in their own right
- Got along well with each other
- Had complementary strengths
- Similar endurance
- Same home

Future Therapeutic Considerations

- Addition of precision medicine to attack fibrosis
  - CAR-T
  - Therapeutic oligonucleotides
  - Microbiome
  - Genetic polymorphisms
    - HSD17B13
    - PNPLA3

Table 1. Liver metabolic targets of the therapeutic oligonucleotides.

Disease	Targeted gene	Targeting oligonucleotide(s)
NASH	miR-132	Anti-miR
NASH	PNPLA3	Antisense
NASH	STK25	Antisense
NASH	DGAT2	Antisense
A1AT D	AAT	siRNA
HHC	TMPRSS6	siRNA
TTR amyloidosis	TTR	siRNA, Antisense
AIP	ALAS1	siRNA
Liver Fibrosis	HSP47	siRNA

PNPLA3 =; miRs = microRNAs; NASH = nonalcoholic steatohepatitis; STK25 = serine/threonine protein kinase-25; siRNA – short interfering RNA; A1AT D = alpha 1 antitrypsin deficiency; HHC = hereditary hemochromatosis; AIP = acute intermittent porphyria; TTR = transthyretin; ALAS1 = aminolevulinic acid synthase 1; HSP 47 = heat shock protein 47.

Amor C. *Nature*. 2020; Alkhouri. *Exp Opin Invest Drugs*. 2021.

Summary

- As our understanding of NASH pathogenesis improves, the number of targets in NASH drug development continues to expand
- Therapies aimed at both histopathology and dysregulated metabolism are ideal
- Synergistic combination approaches-potentially overlaid with precision medicine advances may allow for broad application