GI Alliance

Advancing GI Patient Care 2021

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NAFLD/NASH: Current Management & Treatments on the Horizon

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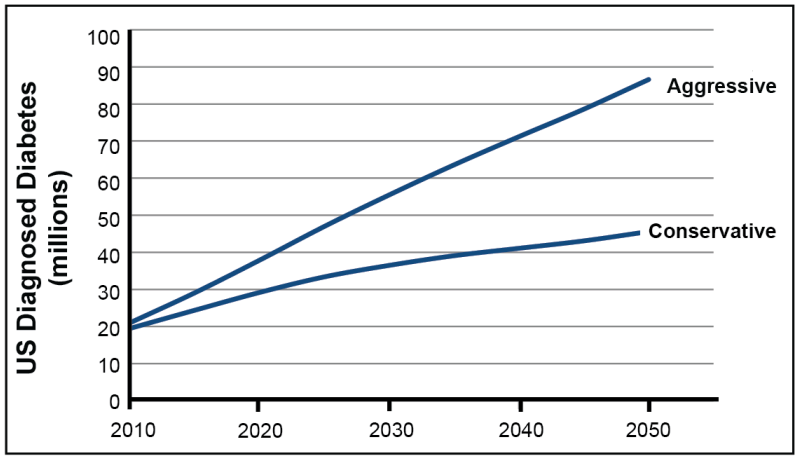
Disclosures

- Scientific advisor or consultant for Akero, Alentis, Altimmune, Arrowhead, Axcella, Canfite, Cirius, CiVi Biopharma, Cymabay, Echosens, Fibronostics, Forest Labs, Galectin, Genfit, Gilead, Hepion, HistoIndex, Intercept, Madrigal, Medpace, Metacrine, NGM Bio, Northsea, Novartis, Novo Nordisk, PathAI, Poxel, Liminal, Ridgeline, Sagimet, Terns, Viking, 89 Bio.
- Stock options: Akero, Cirius, Galectin, Genfit, Hepion, HistoIndex, PathAI, Metacrine, NGM Bio, Northsea.
- Grant/Research support: Akero, Axcella, BMS, Cirius, CiVi Biopharma, Conatus, Cymabay, Enyo, Galectin, Genentech, Genfit, Gilead, Hepion, Hightide, Intercept, Madrigal, Metacrine, NGM Bio, Novartis, Novo Nordisk, Northsea, Pfizer,Sagimet, Viking.

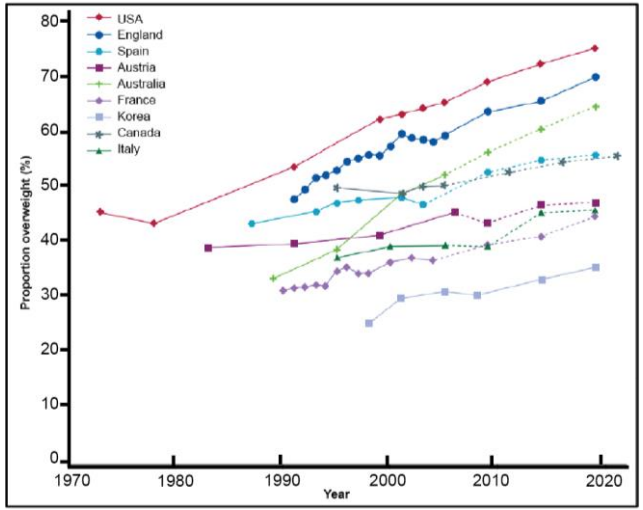
The Disease Burden of NASH Is Expected to Increase Over Time

NASH prevalence could grow along with the rapid increase in diabetes and obesity

DIABETES TRENDS[1]

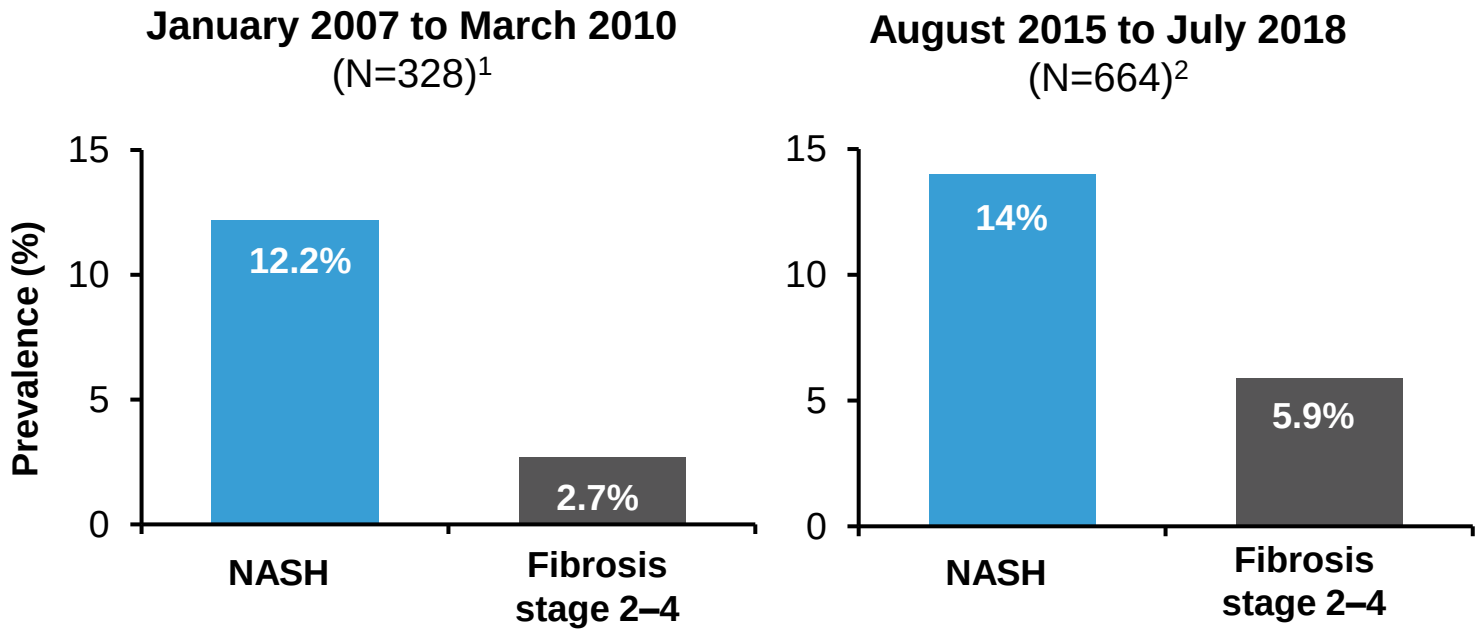


OBESITY TRENDS[2]



1. Boyle JP et al. *Popul Health Metr.* 2010;8:29; 2 Wang YC. *Lancet*. 2011;378(9793):815-825.

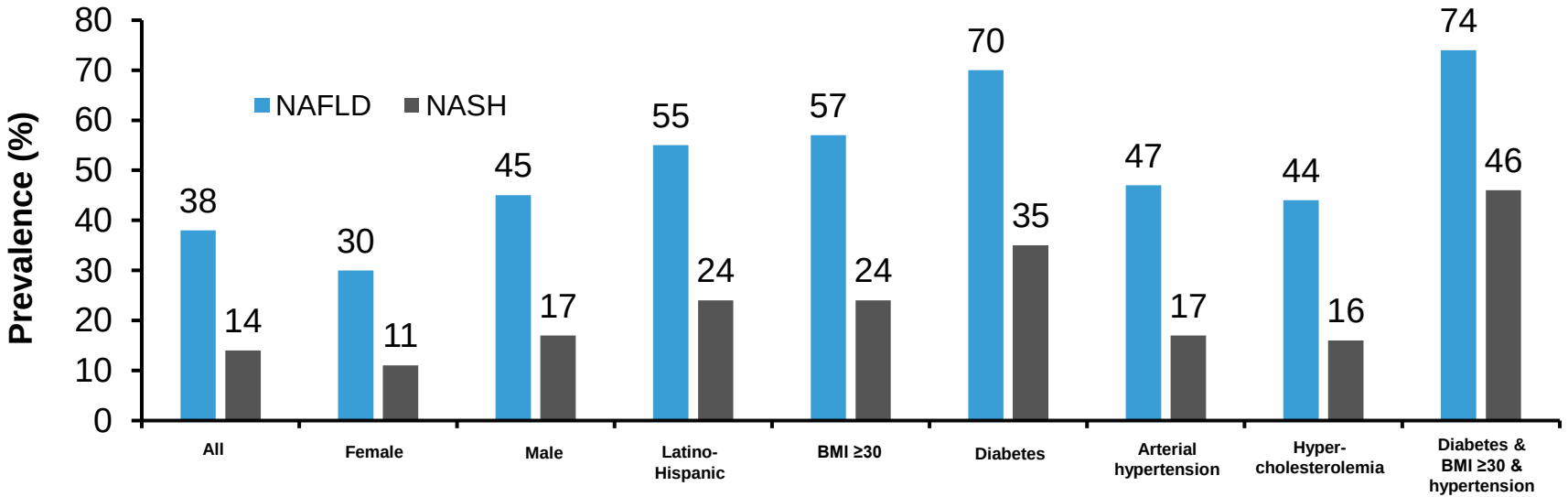
Prevalence of NASH Among US Middle-Aged Cohorts



NASH, non-alcoholic steatohepatitis.

1. Williams CD et al. *Gastroenterology*. 2011;140:124–31; 2. Harrison SA et al. *J Hepatol*. 2021;S0168-8278:00176-8.

NAFLD and NASH Prevalence in Different Groups (US Middle-Aged Cohort, N=664)



BMI measured in kg/m2

BMI, body mass index; NAFLD; non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Harrison SA et al. *J Hepatol*. 2021;S0168-8278:00176-8.

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

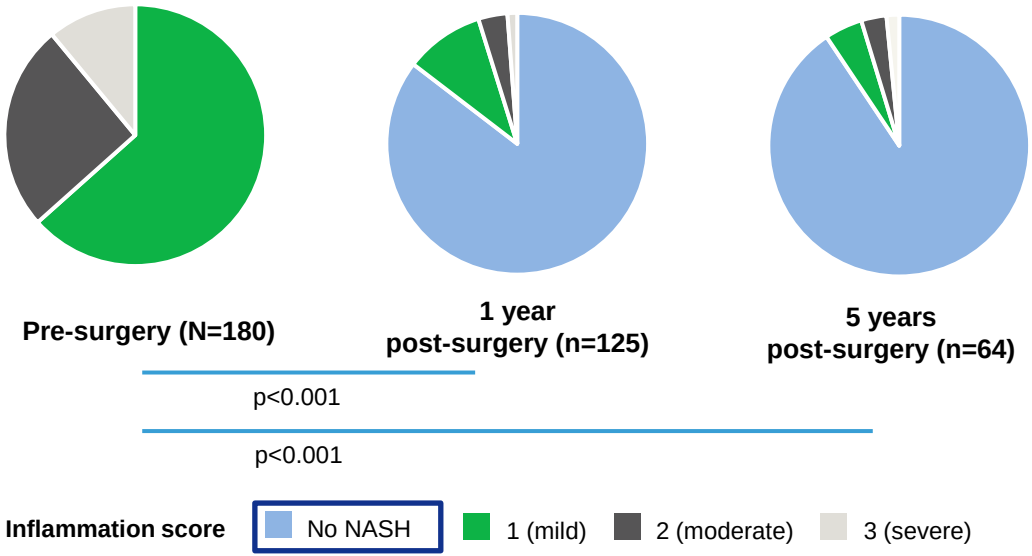
*Fructose increases the odds of the development of nonalcoholic fatty liver in high-risk patients and of nonalcoholic steatohepatitis and more advanced liver fibrosis in patients who already have nonalcoholic fatty liver disease.

**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

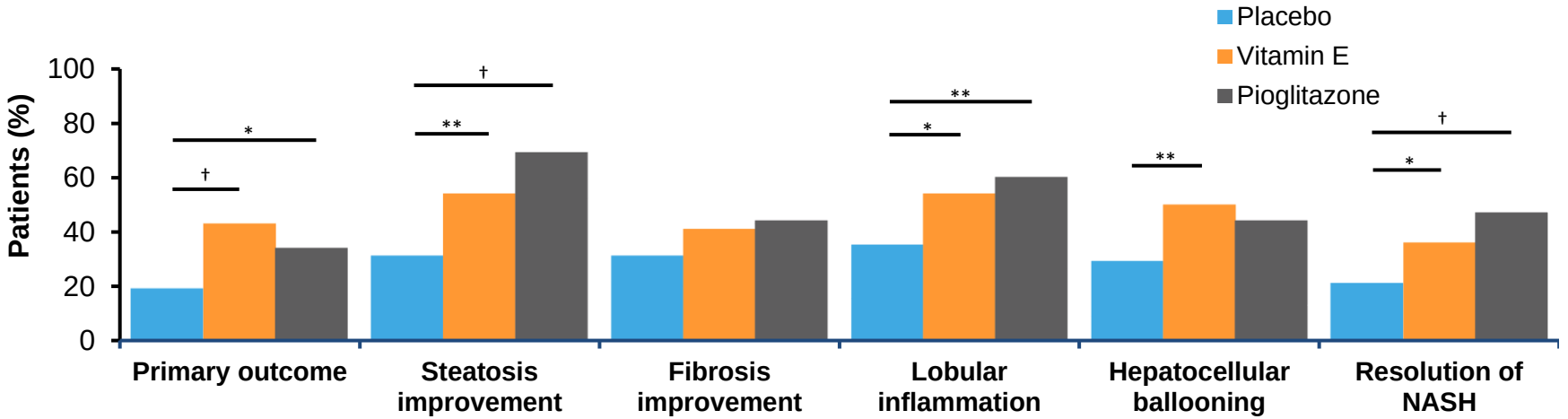
Fibrosis improvement in **70.2%** of patients at 5 years post-surgery

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



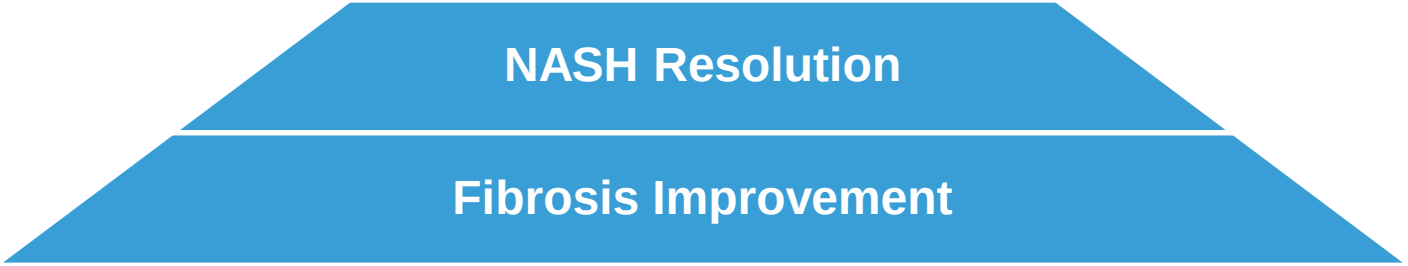
- **Pioglitazone** may improve NASH histology other than fibrosis
- **Vitamin E** may improve histology

*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.

NASH Treatment Outcomes

- NASH progression to **clinical outcomes** takes years, so trials of NASH treatments examine **surrogate outcomes:** histologic endpoints



FDA: Liver Histologic Improvement Endpoints Likely to Predict Clinical Benefit

NASH Resolution

- Resolution of steatohepatitis on overall histopathologic reading

and

- No worsening of liver fibrosis

and/
or

Fibrosis Improvement

- Improvement ≥1 fibrosis stage

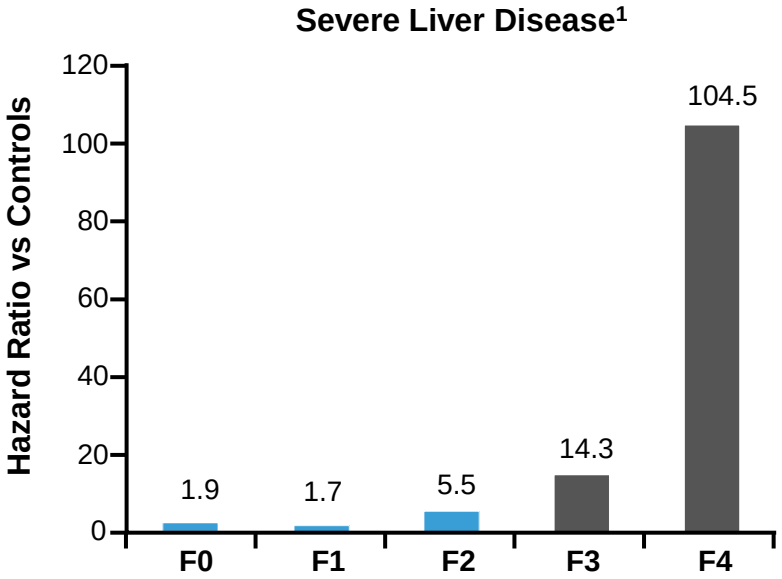
and

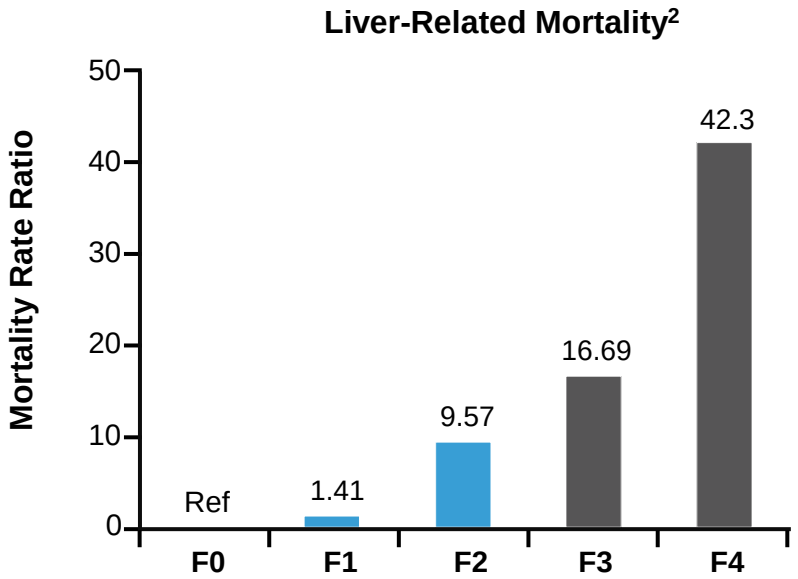
- No worsening of steatohepatitis

"Because of the slow progression of NASH, the FDA recommends liver histological improvements as endpoints reasonably likely to predict clinical benefit to support accelerated approval."

1. FDA. Draft Guidance. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. December 2018.

The Evidence: NAFLD Liver Fibrosis Is a Risk for Adverse Outcomes

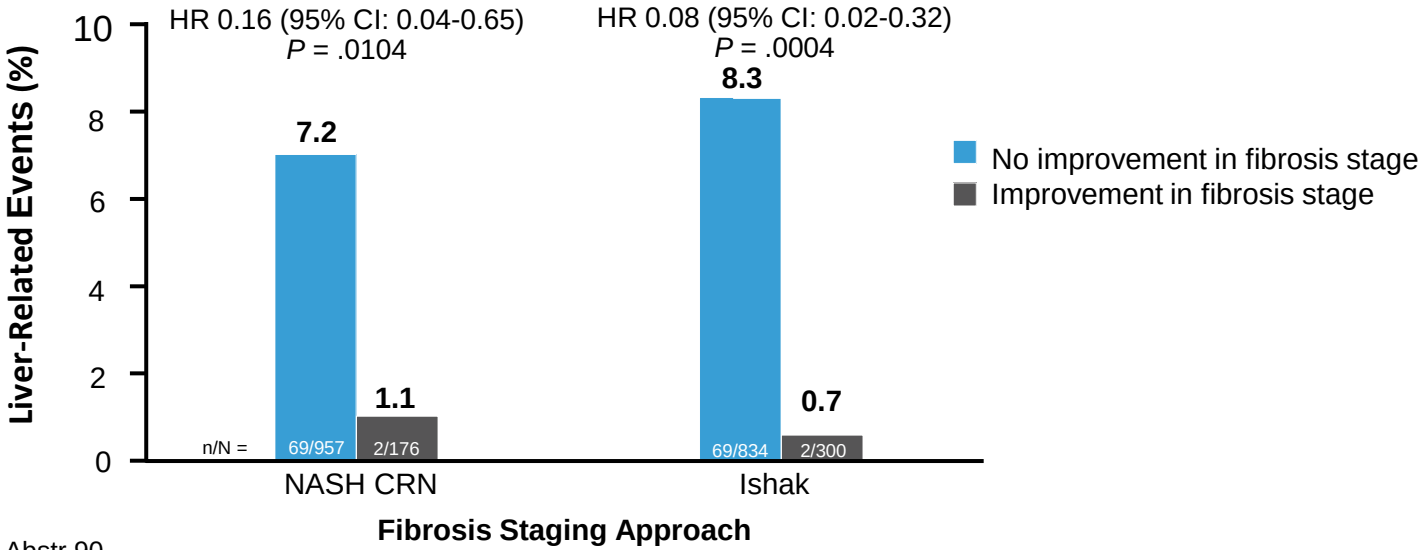




1. Hagström. *J Hepatol*. 2017;67:1265; 2. Dulai. *Hepatology*. 2017;65:1557.

The Evidence: Regression of NASH Cirrhosis Associated With Improved Clinical Outcomes

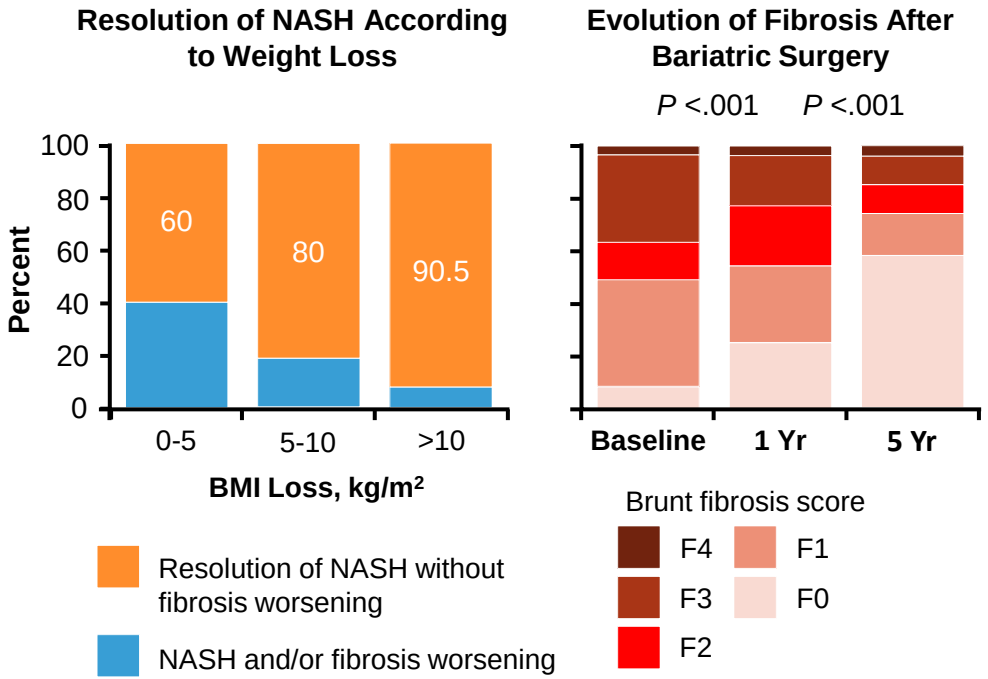
- Pooled analysis of N = 1135 patients with NASH cirrhosis from STELLAR 4 and simtuzumab studies
  - **Improvement in NASH fibrosis stage** was associated with **lower risk of liver-related event**



Sanyal. AASLD 2020. Abstr 90.

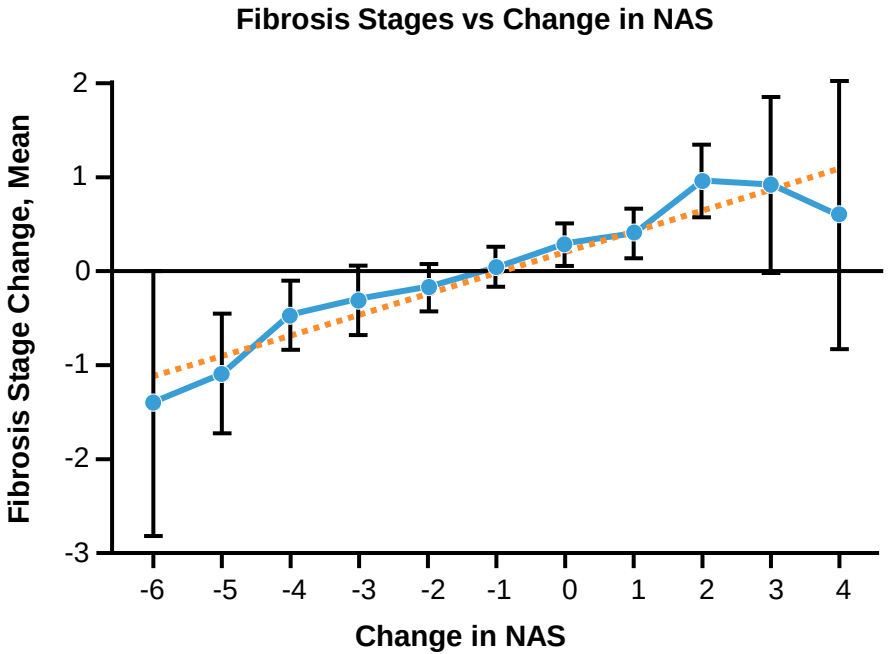
Is NASH Reversible?

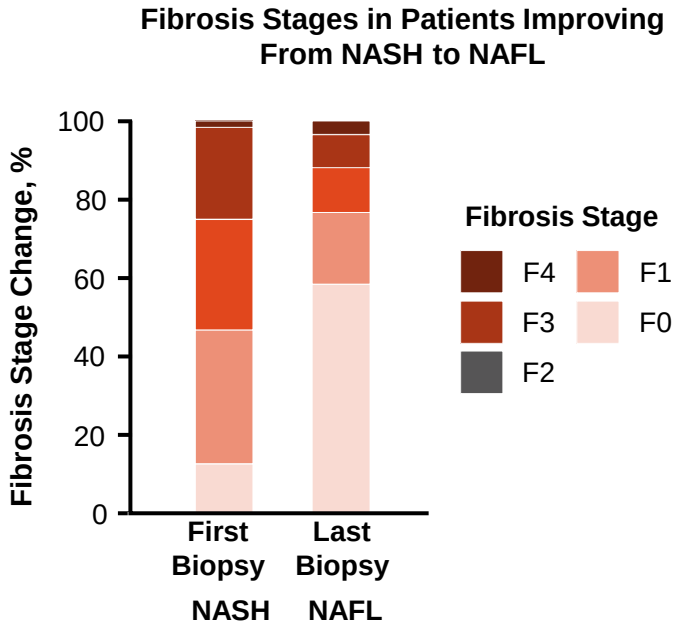
- French single-center study of **bariatric surgery** in severely obese patients with biopsy-confirmed NASH (N = 180)
- At 5 yrs post surgery, 64 of 94 patients (84%) had NASH resolution with no worsening of fibrosis
  - NASH improvement correlated with weight loss



Lassailly. *Gastroenterology*. 2020;159:1290.

Reversal of NASH Improves Fibrosis Score

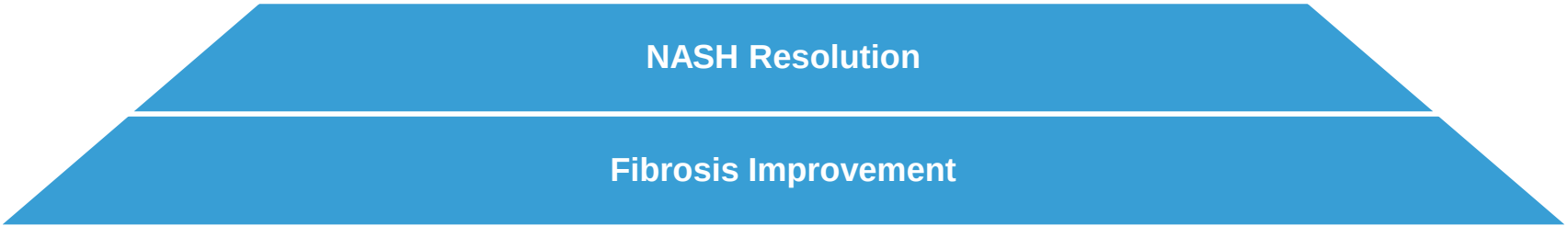




Kleiner. JAMA Network Open. 2019;2:e1912565

Potential Targets for NASH Treatments

Multifactorial metabolic milieu of NASH warrants potential combination therapy targeting many pathways



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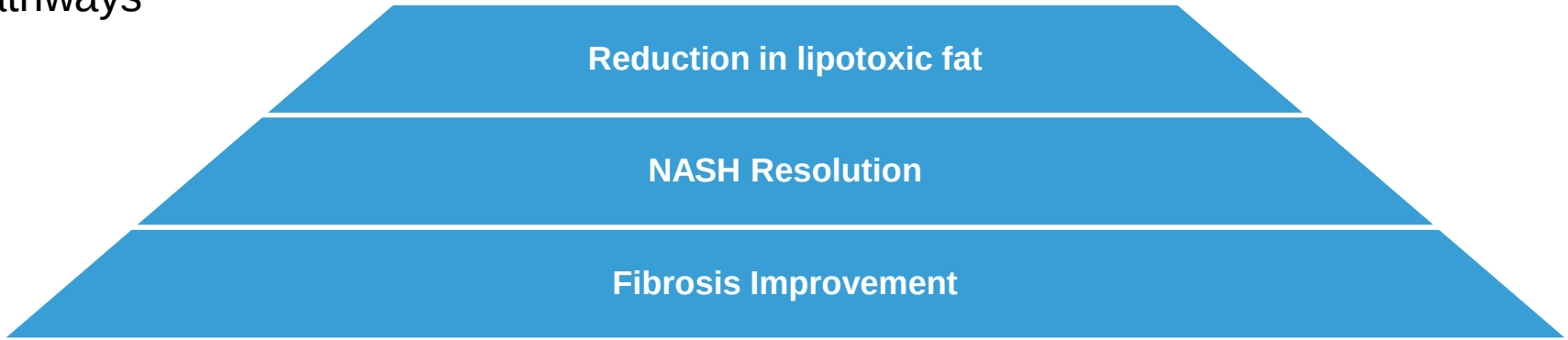

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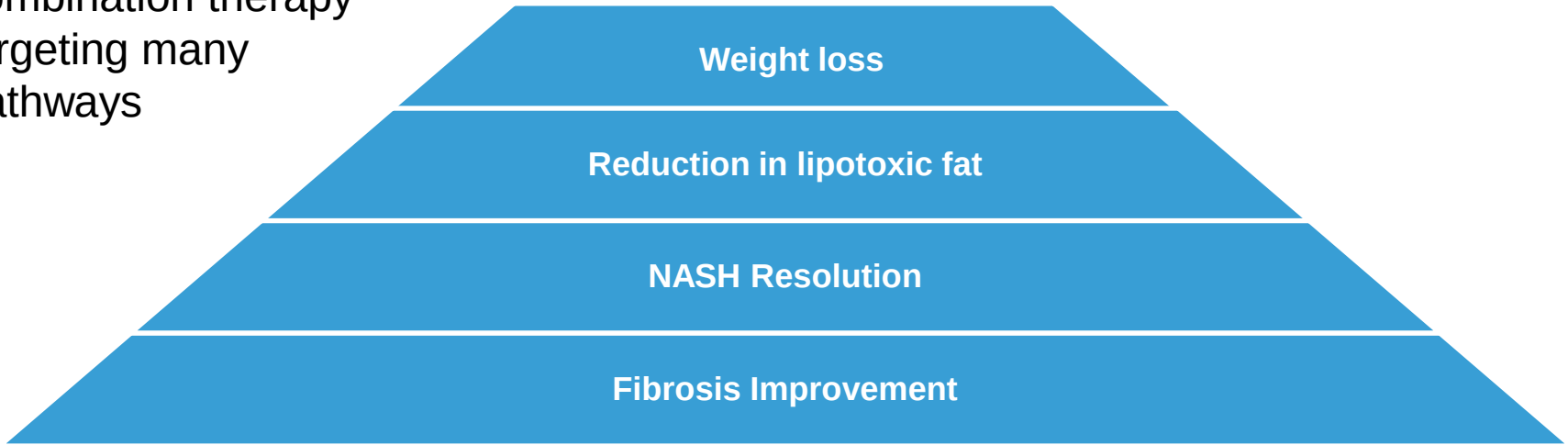

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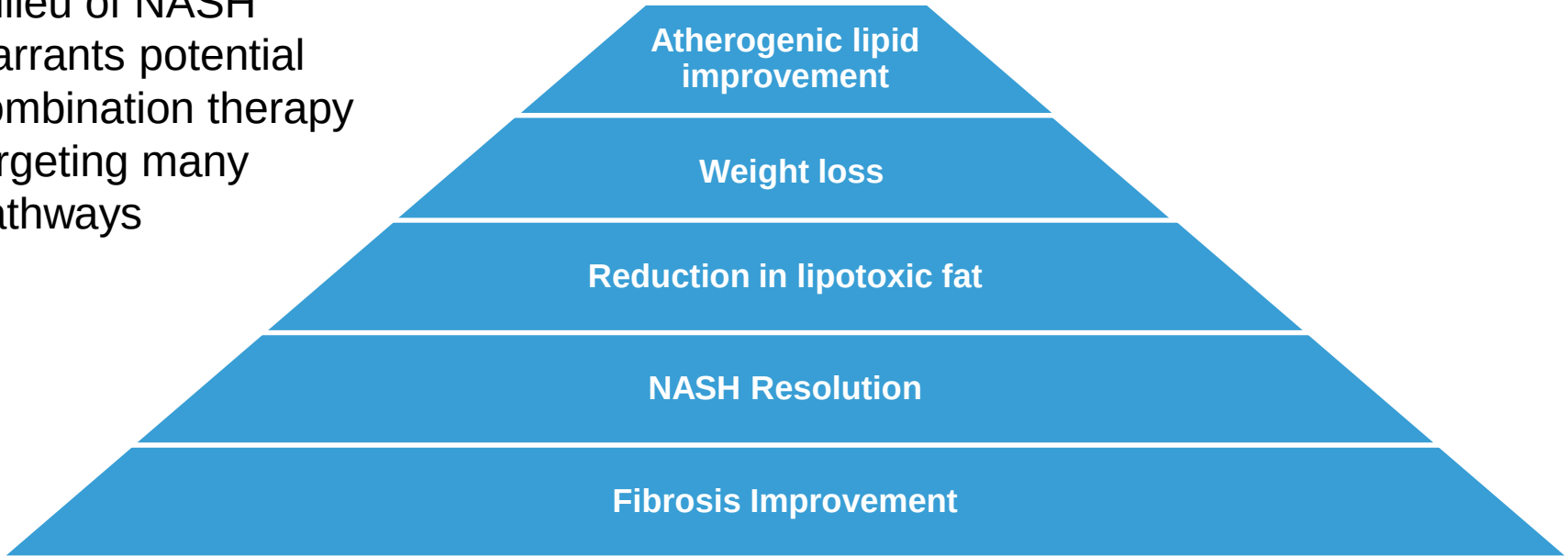

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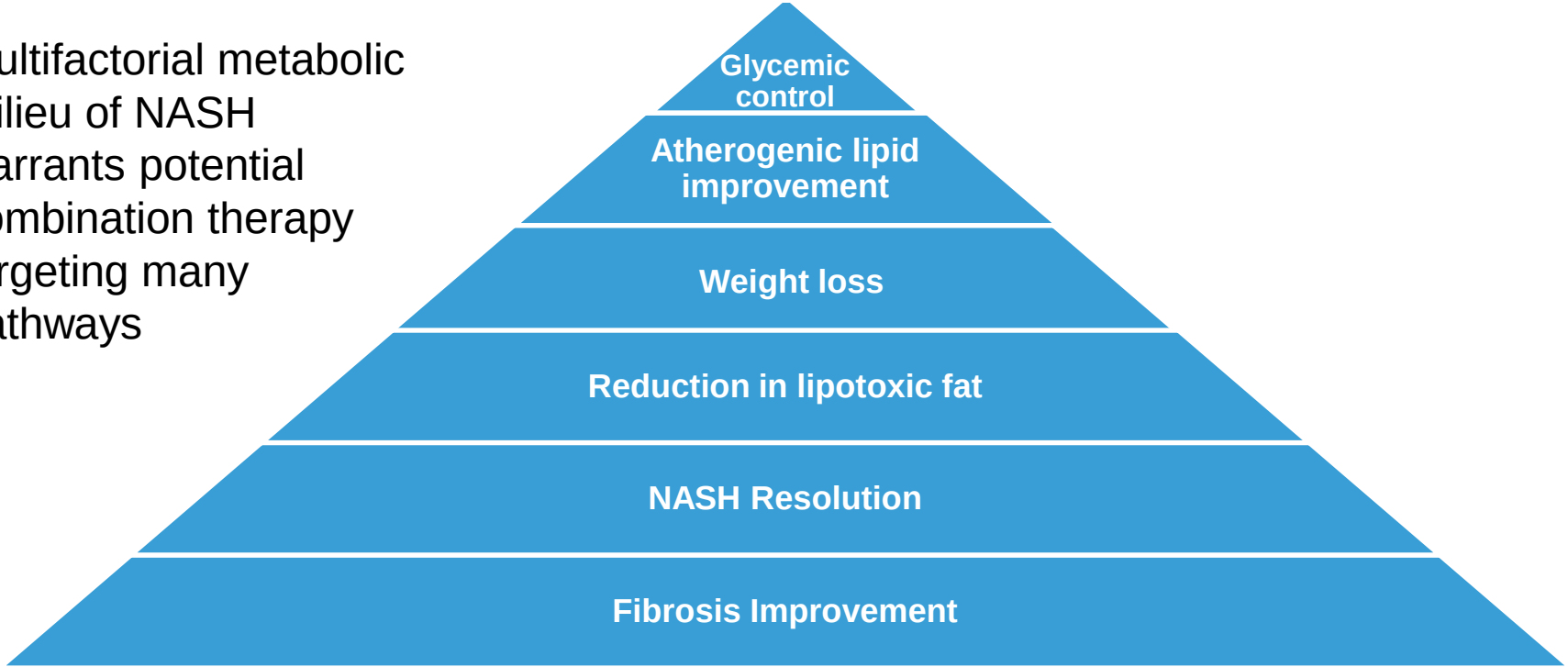
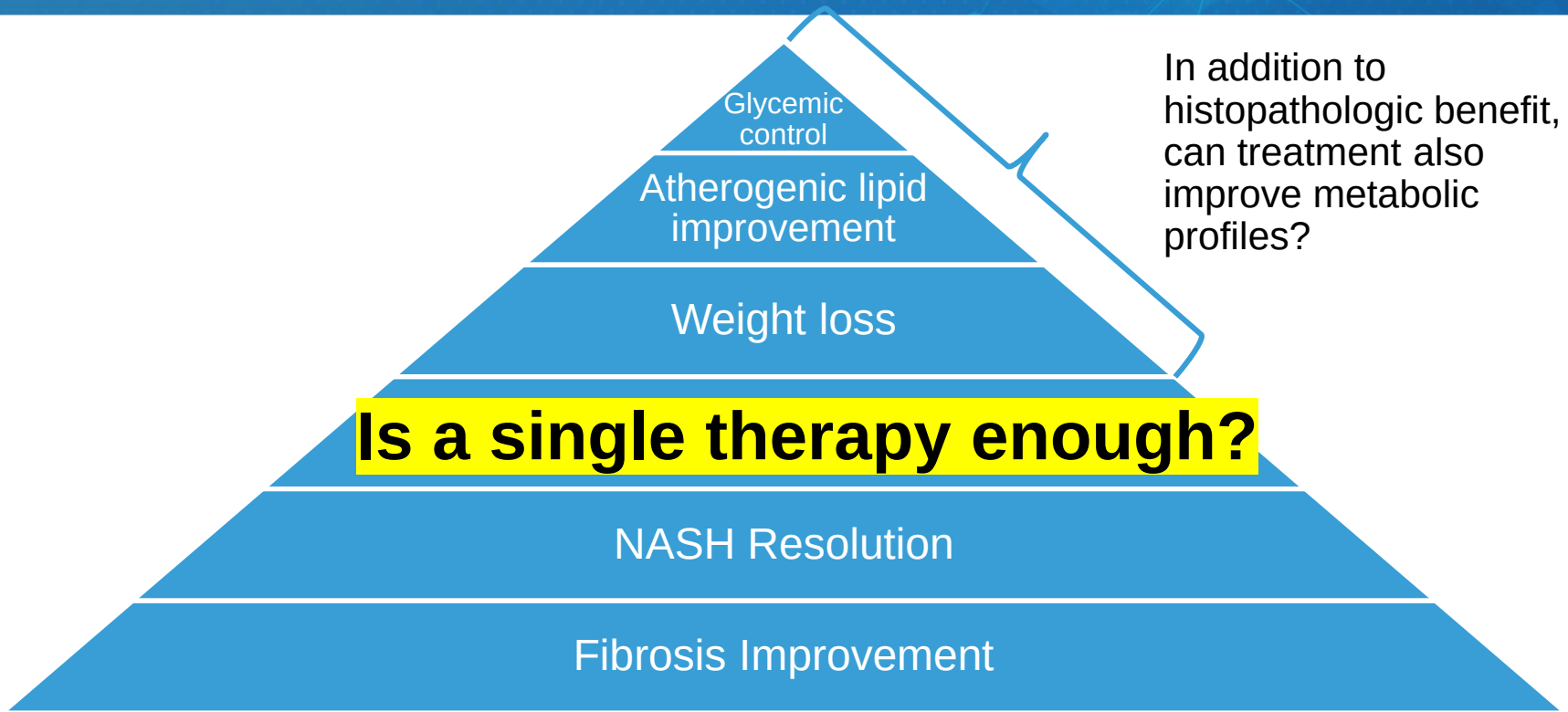
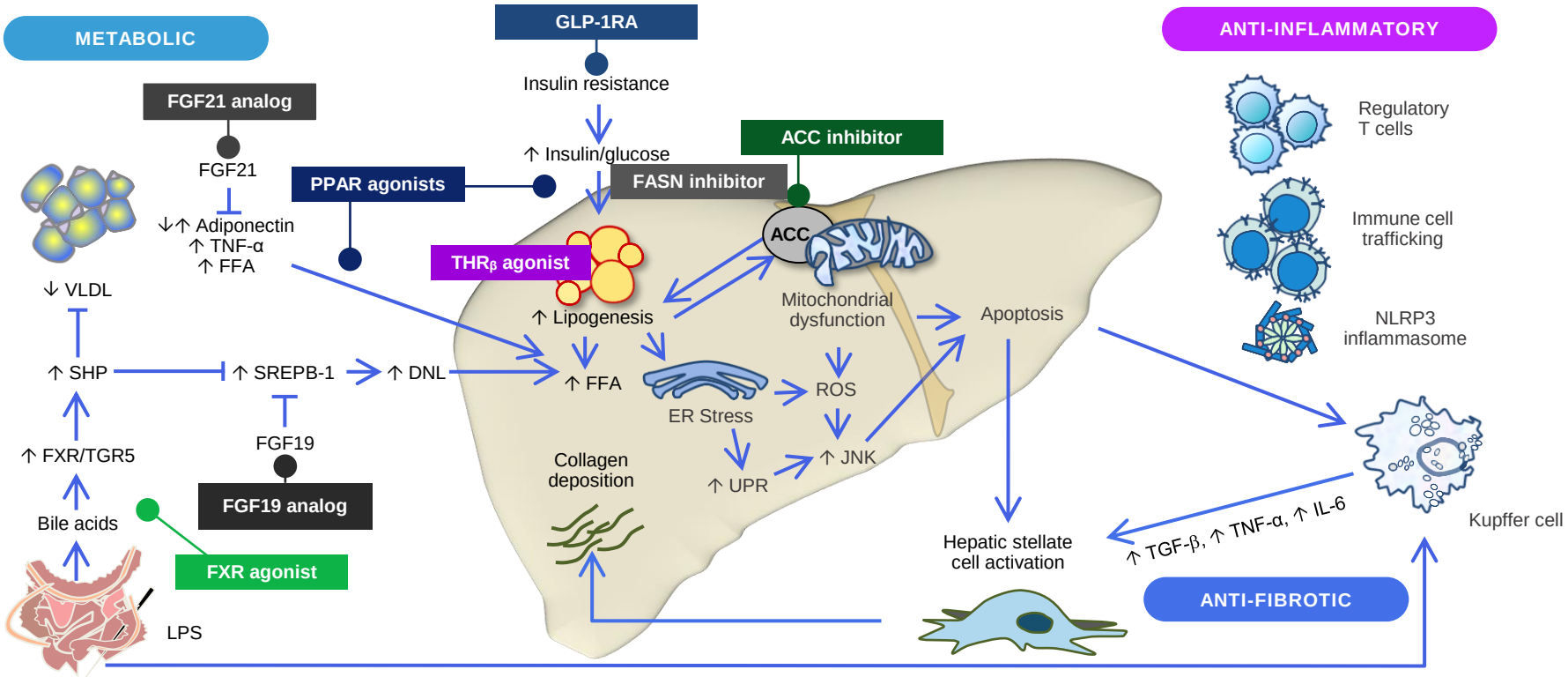


Potential Targets for NASH Therapeutics



In addition to histopathologic benefit, can treatment also improve metabolic profiles?

NASH: Potential Therapeutic Targets

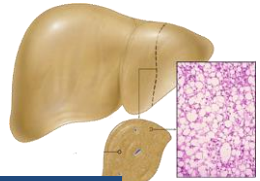
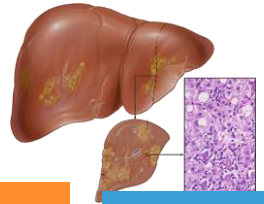
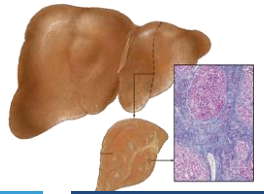


See slides notes for abbreviations.

Adapted from: Konerman MA et al. *J Hepatol*. 2018;68:362–375.

Targeting Pathophysiological Processes

NORMAL LIVER	STEATOSIS	STEATOHEPATITIS	CIRRHOSIS

Targets related to insulin resistance and/or lipid metabolism

PPARγ:	Pioglitazone
GLP-1:	Liraglutide, Semaglutide
GLP-1/GR:	MEDI0382, BI456906
ACC:	GS-0976, PF-05221304
SCD1:	Aramchol
SGLT1/2:	LIK066
FGF21:	BMS-986036, AKR-001,BIO89-100
THR-β:	MGL-3196, VK2809
FGFR1/KLB	BFKB8488A
MPC	MSDC-0602K, PXL065
Mixed ag-antagonist GR and antag MR	Miricorilant
MGAT2 Inhib	BMS963272
Fatty acid	Icosabutate
FASN Inh	TVB-2640
GHRH analog	Tesamorelin

Targets related to lipotoxicity & oxidative stress

PPARα/∂:	Elafibranor
PPARα/∂/γ:	Lanifibranor
PPARα/γ:	Saroglitazar
MPC	MSDC-0602K, PXL065
FXR:	OCA, GS-9674, tropifexor, LMB-763, EYP001, MET409
TGR5:	INT-767, INT-777
ASBT:	Volixibat
FGF19:	NGM282
Vitamin E	

Targets related to inflammation and immune activation

CCR2/5:	Cenicriviroc
AOC3:	BI 1467335
TLR4:	JKB-121
Anti-LPS:	IMM-124E
CRV431	

Targets related to cell death (apoptosis and necrosis)

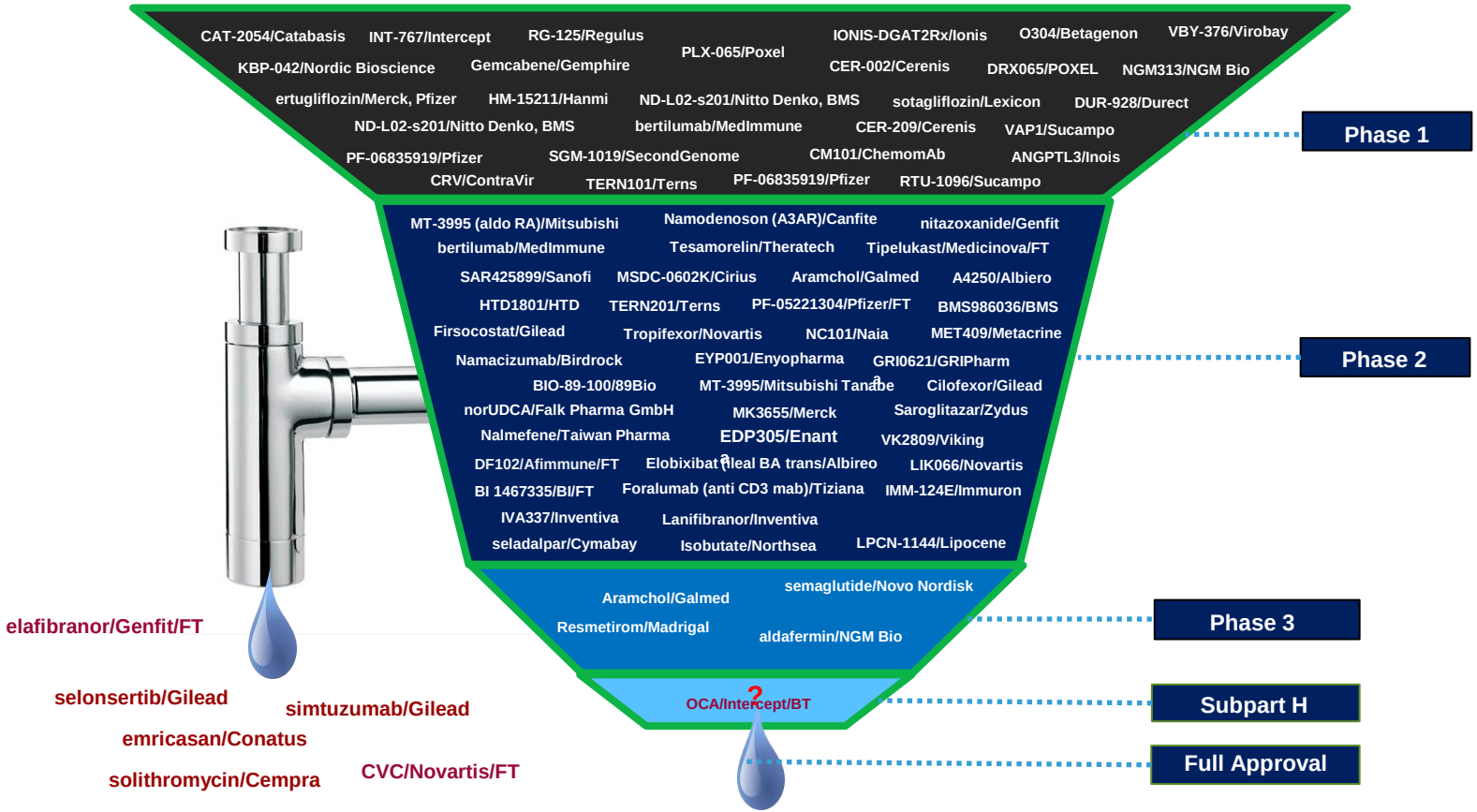
ASK1	Selonsertib
Caspase	Emricasan
CRV431	

Targets related to fibrogenesis & collagen turnover

LOXL2:	Simtuzumab
Galectin	GR-MD-02
CRV431	

Some drugs have pleiotropic effects

Global Pipeline for NASH



GI Alliance

“Prediction is very difficult, especially about the future”

Niels Bohr, Nobel Laureate in Physics, 1922

Photo from the Nobel Foundation archive.

Multiple Agents in Development

Oral Agents

- FXR agonists
  - Ex: obeticholic acid
- PPAR agonists
  - Ex: pioglitazone, elafibranor, lanifibranor, seladelpar
- THR-beta agonists
  - Ex: resmetirom
- Metabolic enzyme inhibitors
  - Ex: SCD-1 inhibitor aramchol
- ACC inhibitor
- FASN inhibitor
- Mitochondrial pyruvate carrier inhibitor
- Pancyclophylin inhibitor
- Structurally engineered fatty acid (SEFAs)

Injectable/Infusion

- FGF19 agonists
  - Ex: aldafermin
- FGF21 agonists
  - Ex: efruxifermin, pegbelfermin
- GLP-1 RAs
  - Ex: semaglutide
  - Theoretical: GLP-1/GIPs (eg, tirzepatide), GLP-1/glucagon agonists (eg, cotadutide)
- Galectin-3 inhibitor
  - Ex: belapectin infusion
  - Targeting prevention of esophageal varices

Injectable/Infusion Approaches

Effects

- Potentially very potent effect on **histopathology**
  - Unknown effect of GLP1-RAs on fibrosis: potential slowing of progression of fibrosis
- Potential impact on **metabolic profiles**?

Practical Considerations

- GI tolerability

Possible uses

- Short-term induction therapy in F3/F4?
- Use in F2 with rapid fibrosis progression risk factors or with significant metabolic comorbidities?

Oral Approaches

Effects

- Variable effect on **histopathology**
- Variable effects on **metabolic profiles**

Practical Considerations

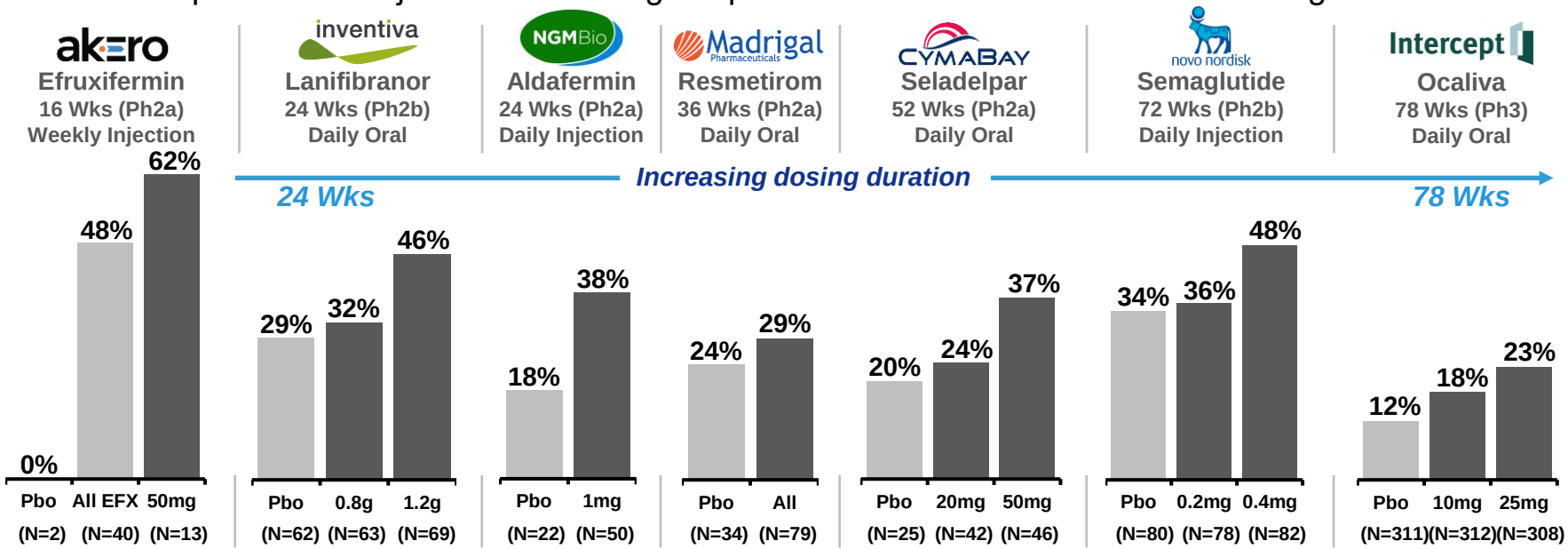
- Favorable route of administration
- Generally well tolerated
  - Mild GI AEs
  - LDL increase and pruritus (FXR agonists)
  - Elevated triglycerides – ACC inhibitor

Possible Uses

- Long-term treatment/maintenance therapy in F1-F3?
  - Role in F4 unclear
- Fixed dose combination

NASH Development Landscape: Fibrosis Improvement

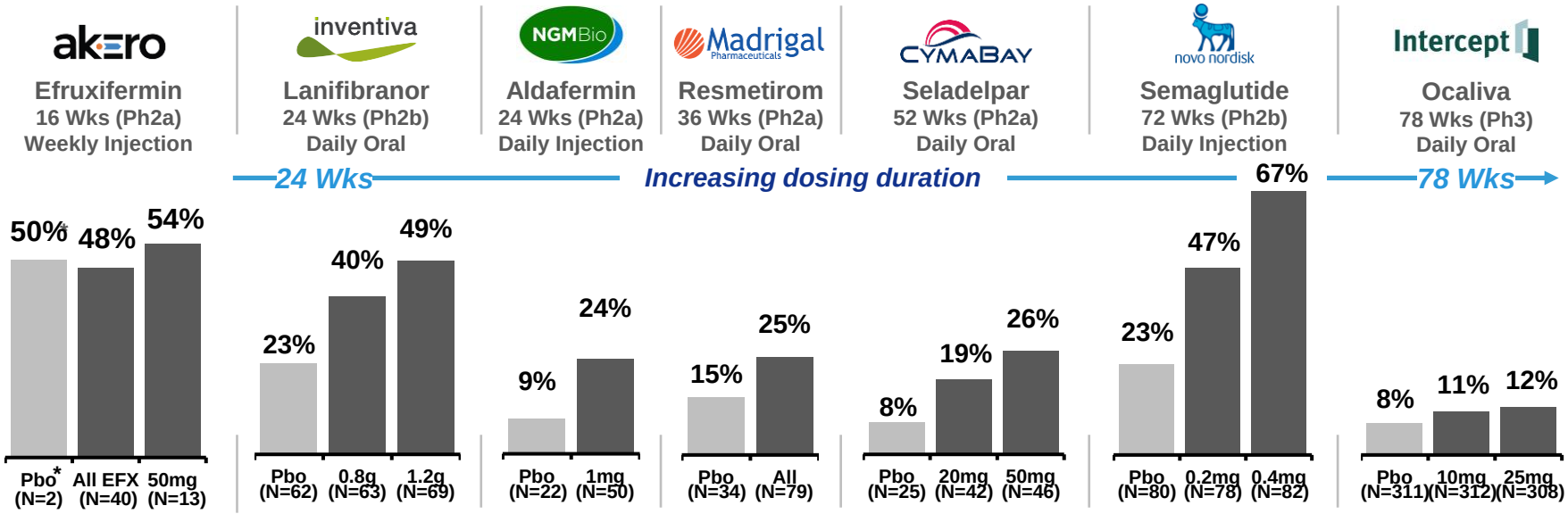
Proportion of Subjects With ≥1 Stage Improvement in Fibrosis and No Worsening of NAS[1]



Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. No head-to-head clinical trials have been conducted. Inventiva (2020) June 16 Corporate Presentation; NGM Bio (2020) June 3 Corporate Presentation; Harrison S et al. *Lancet*. 2019. 394(10213):2012-24; CymaBay (2020) March 12 Press Release; Novo Nordisk (2020) June 19 R&D Investor Presentation; Younossi Z et al. *Lancet*. 2019. 394(10215):2184-96. All trademarks are the property of their respective owners. 1 FDA Guidance for Industry: Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment (2018).

NASH Development Landscape: NASH Resolution

Proportion of Subjects with Resolution of NASH and No Worsening of Fibrosis[1]



* A single placebo responder lost 25 pounds over 16 weeks (11% weight reduction).

Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. No head-to-head clinical trials have been conducted. Inventiva (2020) June 16 Corporate Presentation; NGM Bio (2020) June 3 Corporate Presentation; Harrison S et al. Lancet. 2019. 394(10213):2012-24; CymaBay (2020) March 12 Press Release; Novo Nordisk (2020) June 19 R&D Investor Presentation; Younossi Z et al. Lancet. 2019.394 (10215):2184-96. All trademarks are the property of their respective owners. 1 FDA Guidance for Industry: Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment (2018)

Both NASH Resolution AND Fibrosis Improvement

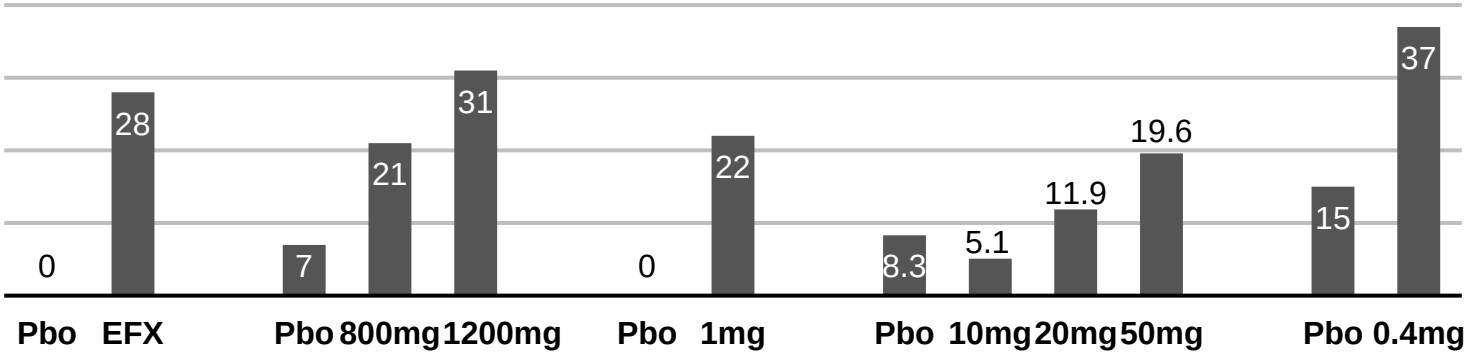
Efruxifermin
16 Weeks
Phase 2a
Weekly Injection

Lanifibranor
24 Weeks
Phase 2b
Daily oral

Aldafermin
24 Weeks
Phase 2a
Daily Injection

Seladelpar
52 Weeks
Phase 2
Daily oral

Semaglutide
72 Weeks
Phase 2b
Daily Injection



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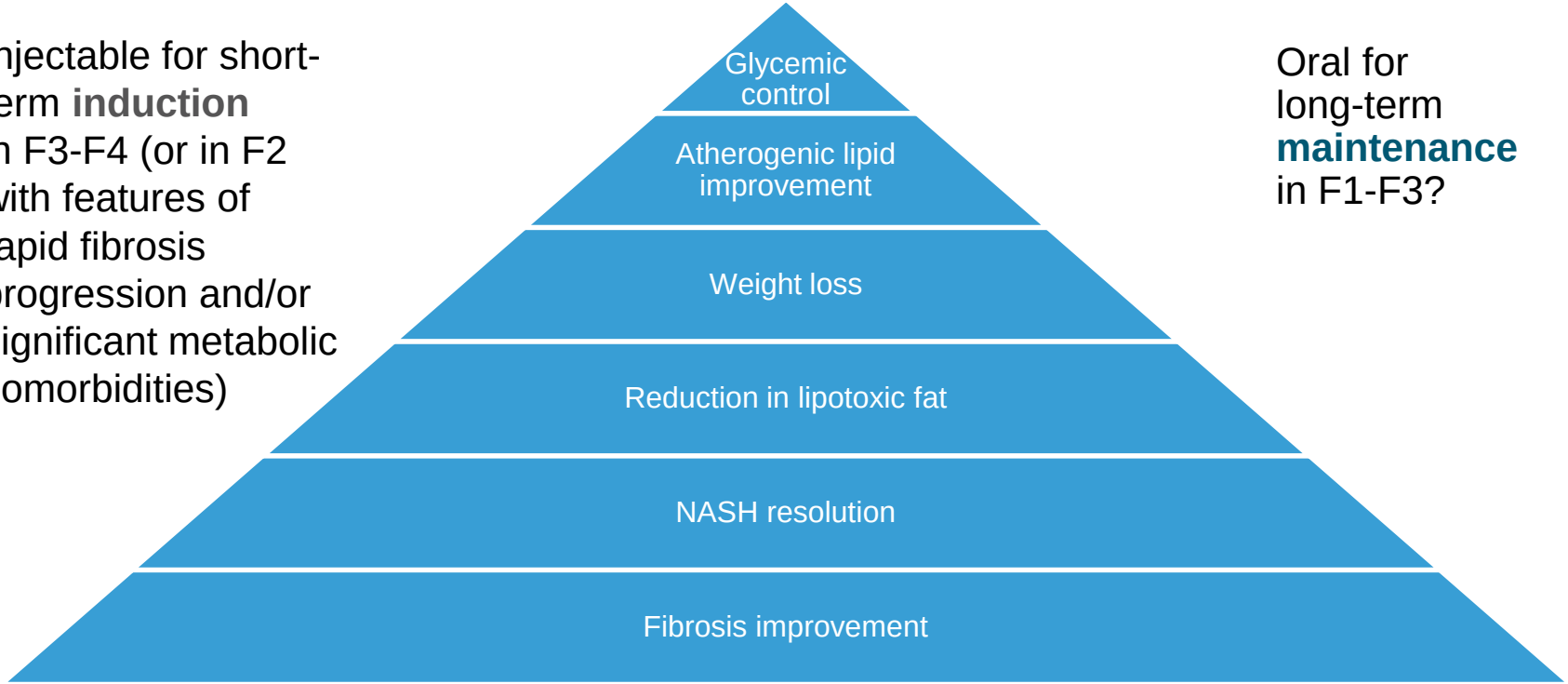
Potential Targets for NASH Treatments

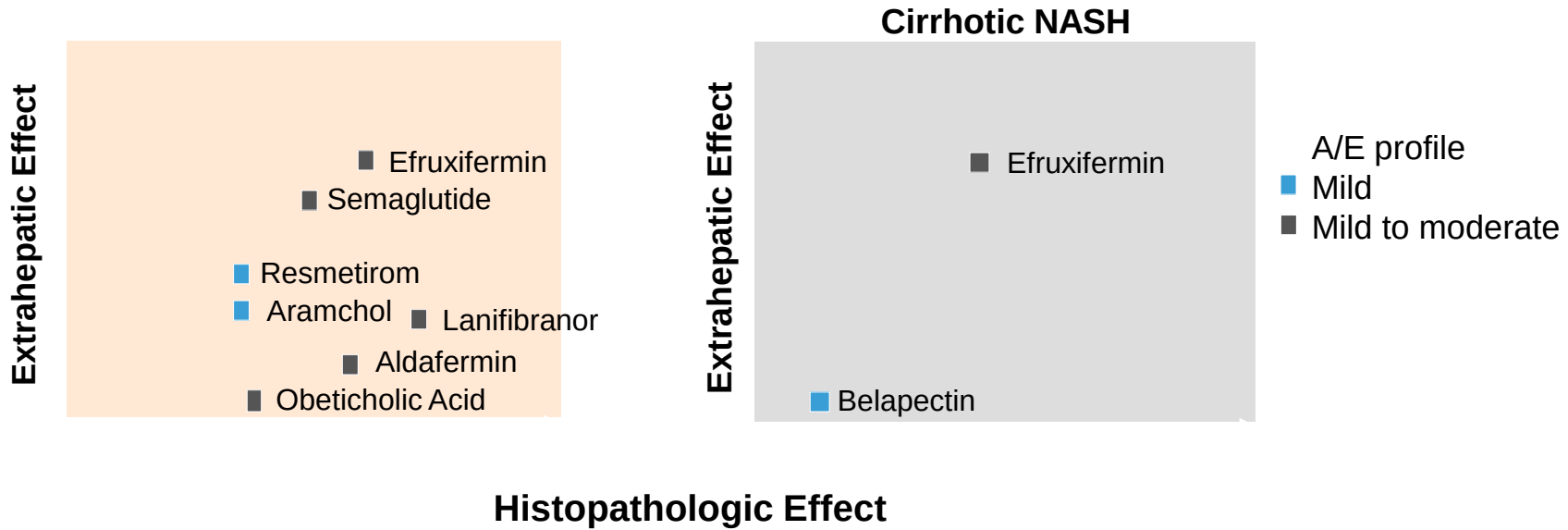
Injectable for short-term **induction** in F3-F4 (or in F2 with features of rapid fibrosis progression and/or significant metabolic comorbidities)



Oral for long-term **maintenance** in F1-F3?

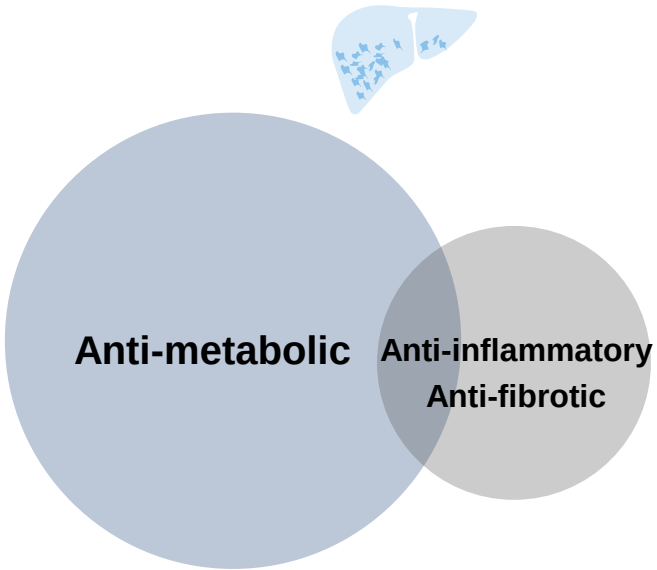
My Perspective: Histopathologic and Extrahepatic Profiles

- Agents may have different profiles of **histopathologic effects** (fibrosis, NASH resolution) vs **extrahepatic effects** (weight loss, atherogenic lipid improvement and glycemic control)

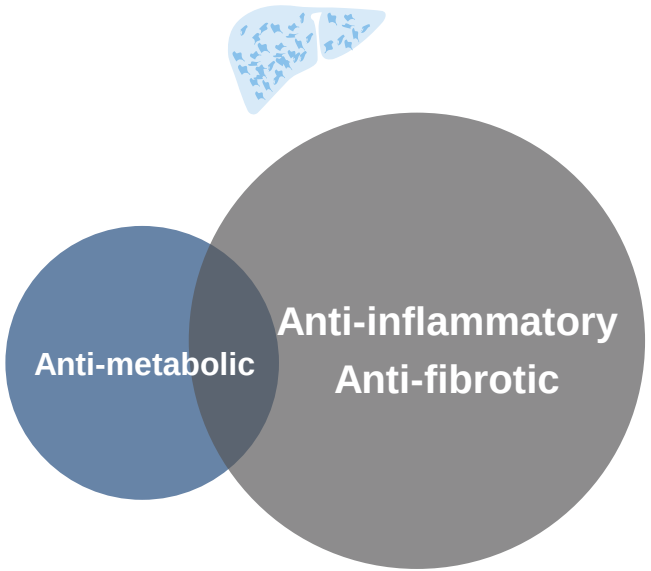


The Future of Combination Therapy

Patients without cirrhosis



Patients with cirrhosis



Thank You

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