NASH Core Curriculum: Emerging Management

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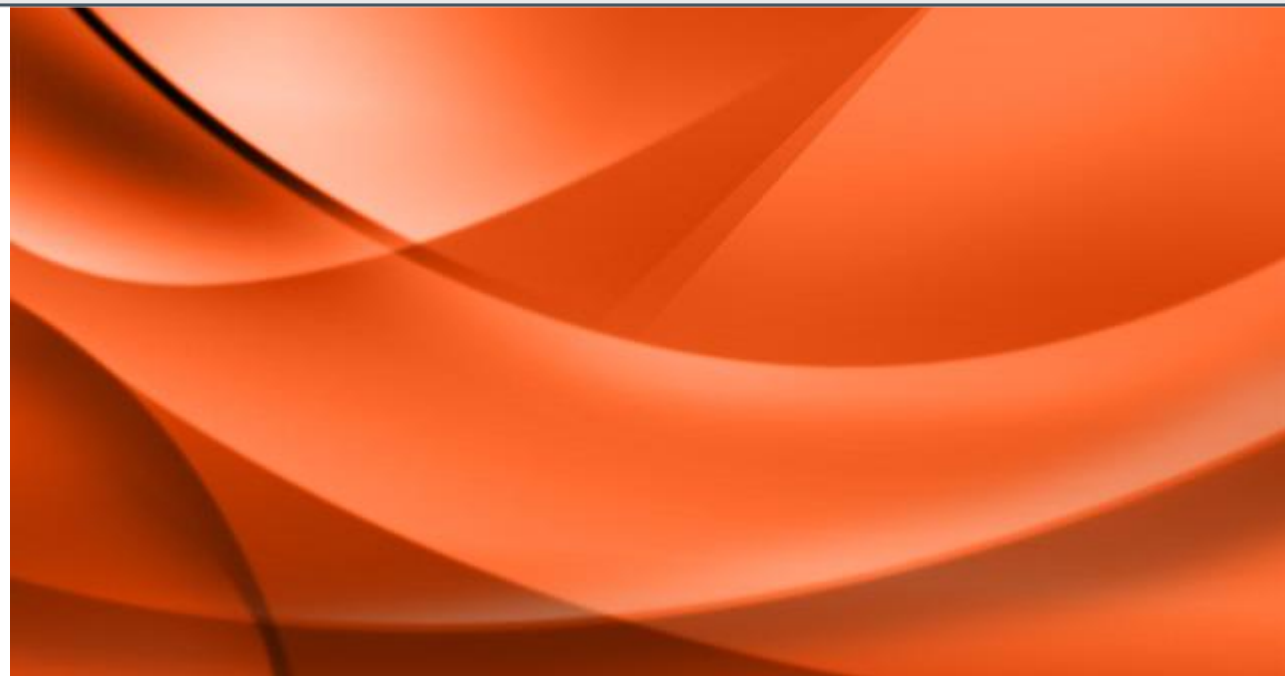

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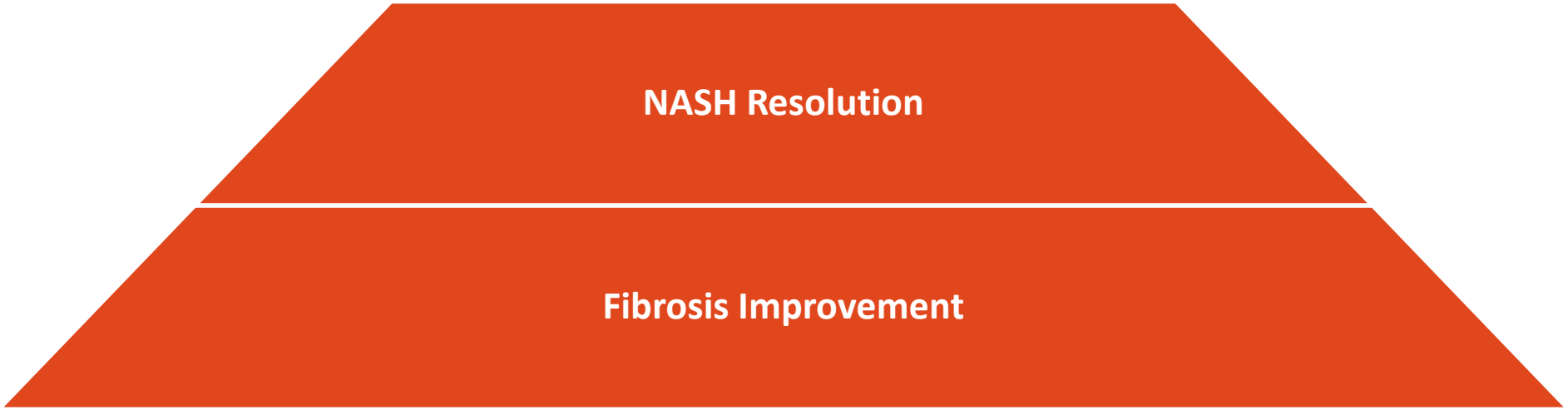
Where Did We Start?

NASH Treatment Outcomes

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



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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

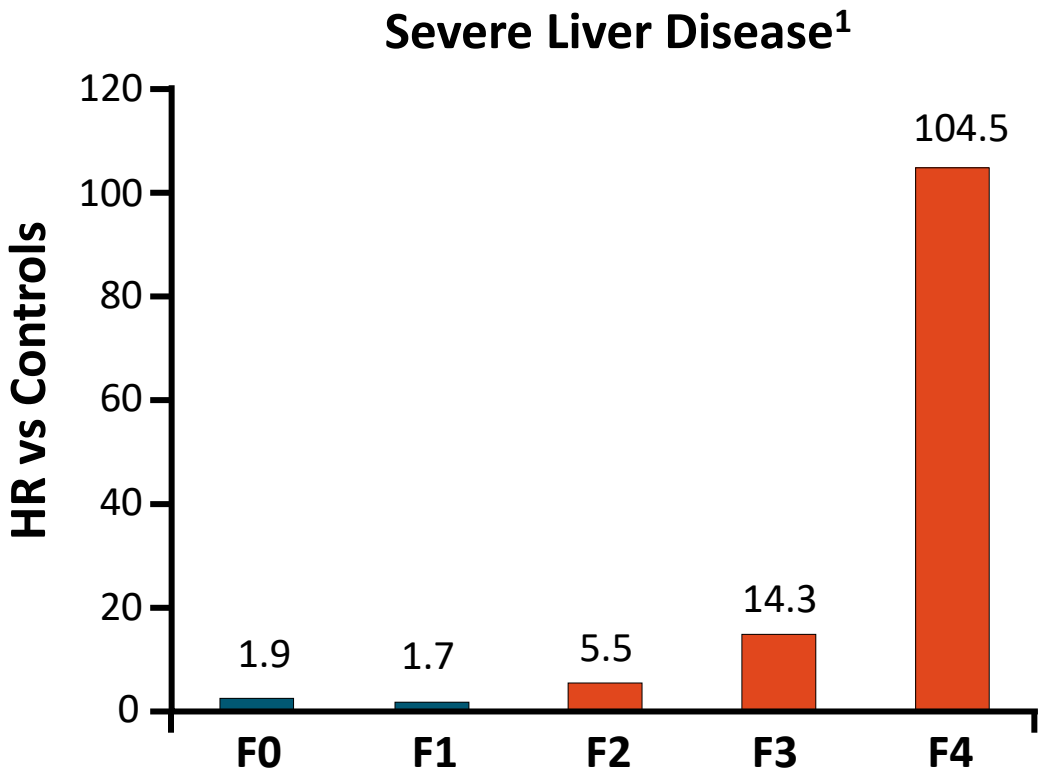
and

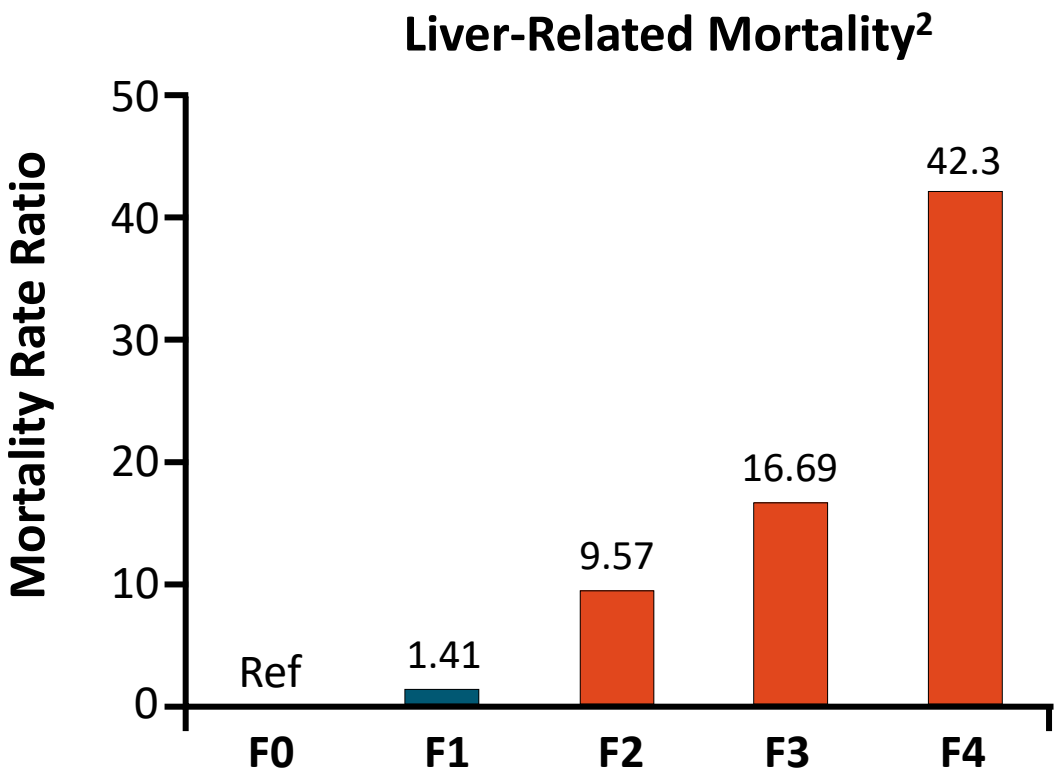
- No worsening of steatohepatitis

"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."

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 Draft Guidance.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.

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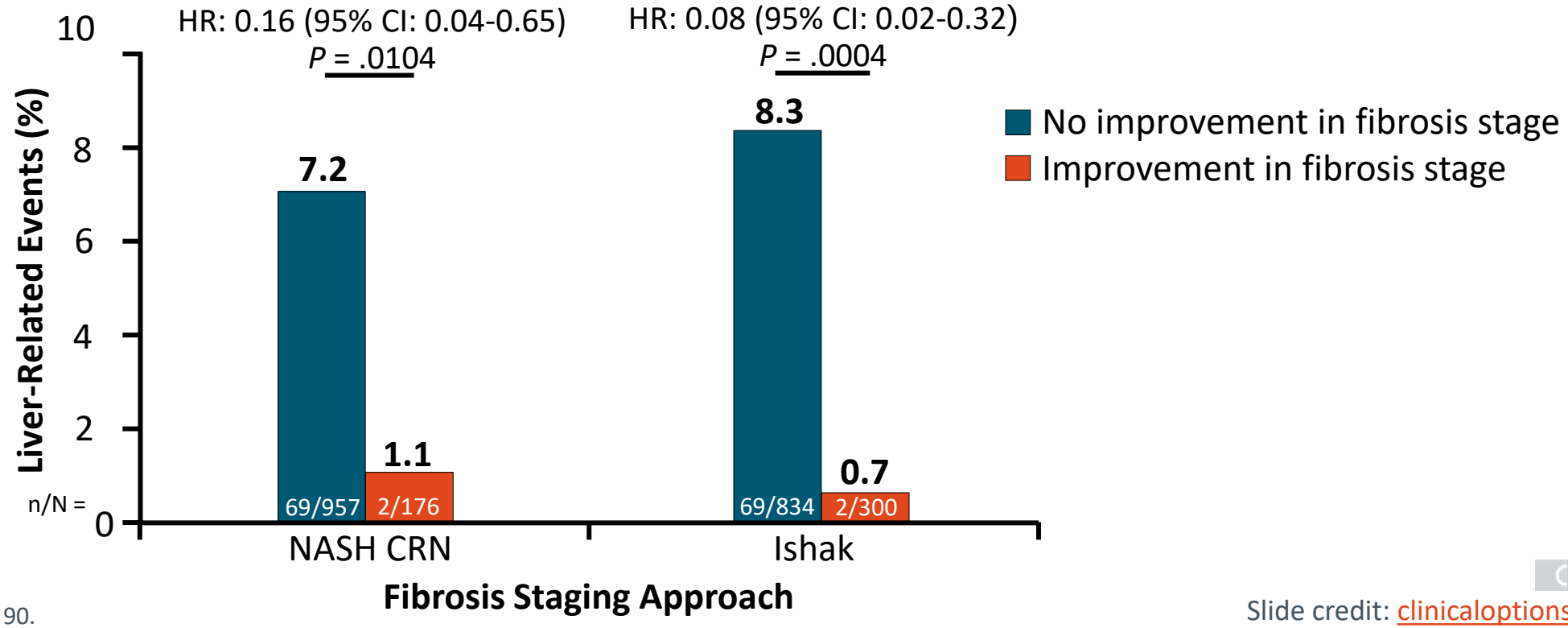
The Evidence: Regression of NASH Cirrhosis Associated With Improved Clinical Outcomes

- 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.

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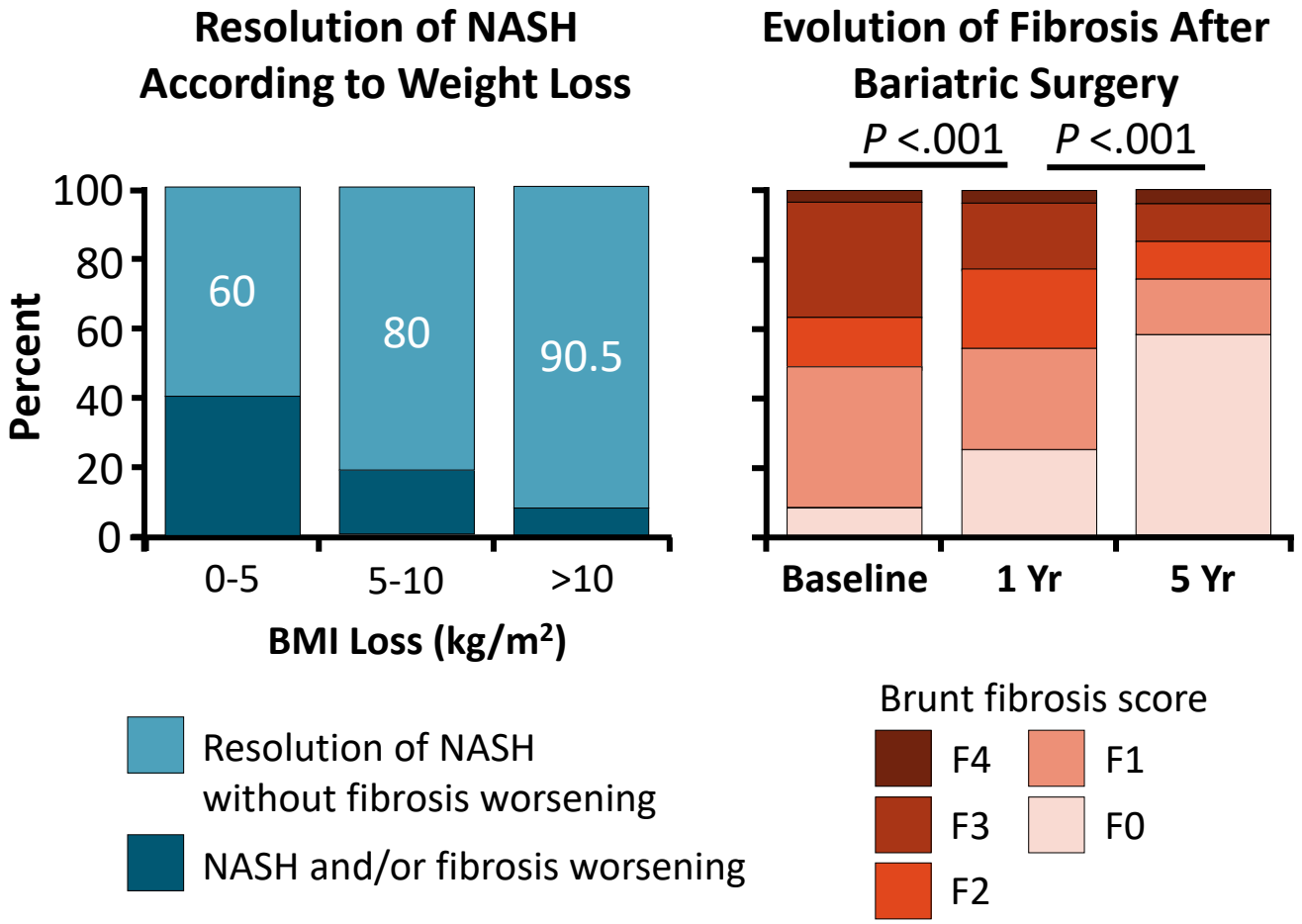
Is NASH Reversible?

- French single-center study of **bariatric surgery** in severely obese patients with biopsy-confirmed NASH (N = 180)
- At 5 yr 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.

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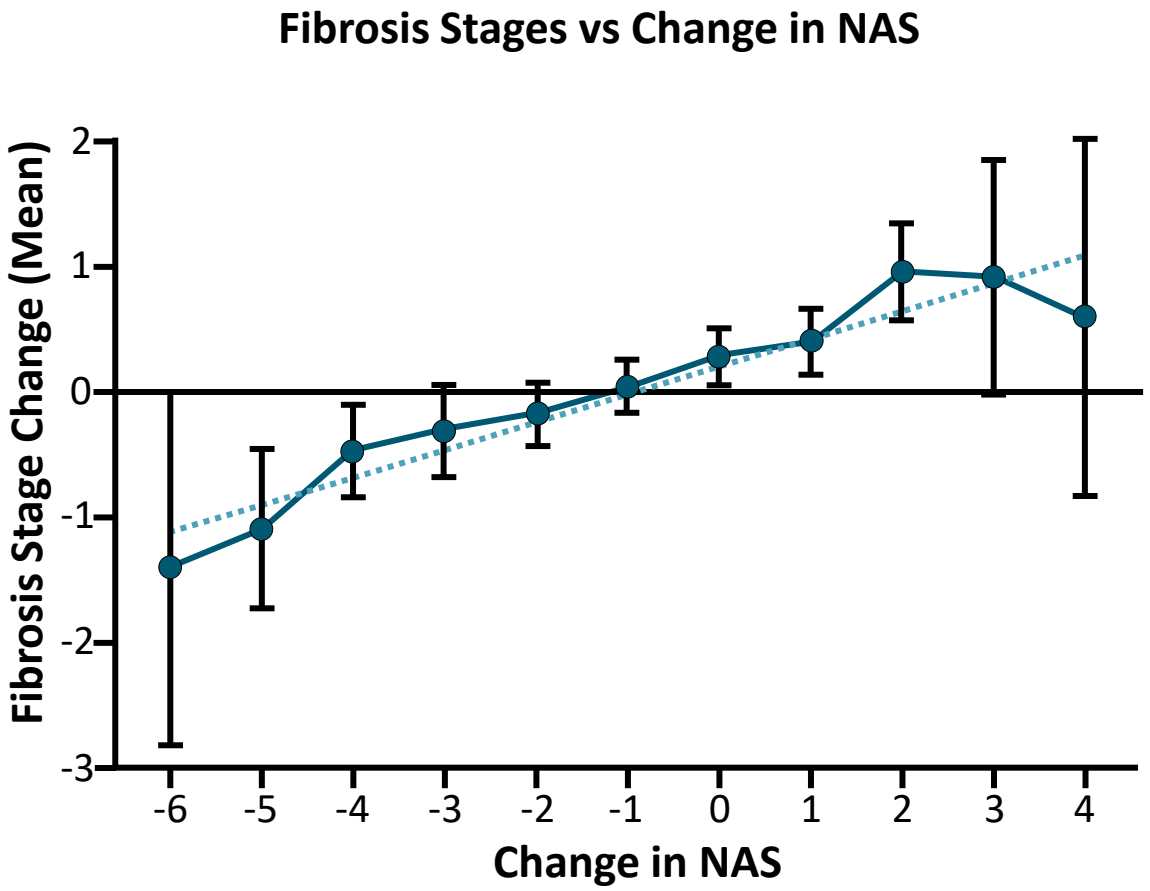
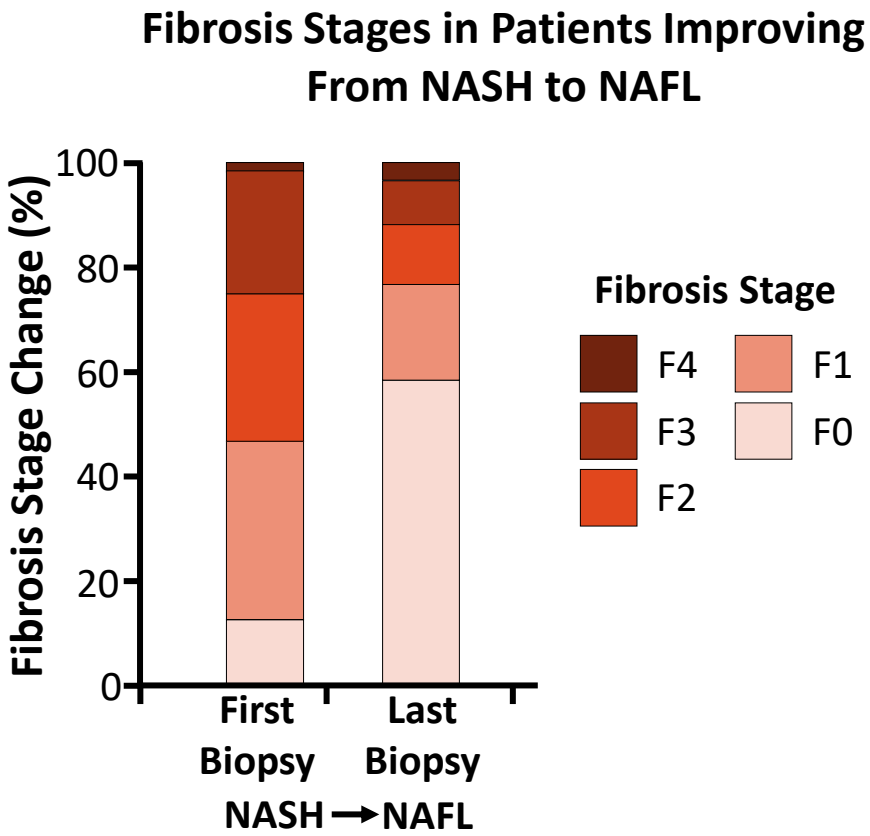
Reversal of NASH Improves Fibrosis Score





Kleiner. JAMA Network Open. 2019;2:e1912565.

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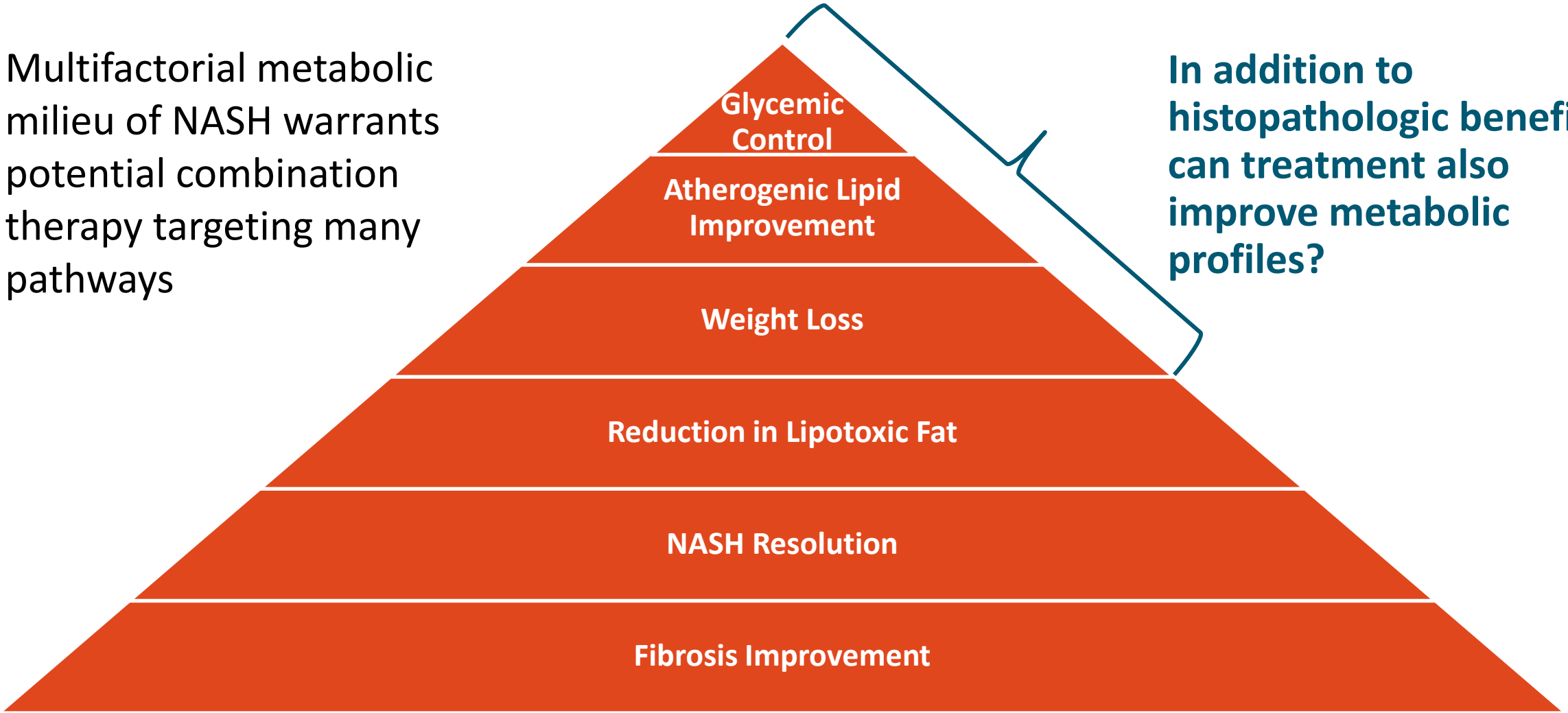
Where Are We Going?

Potential Targets for NASH Treatments

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



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

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Case Study: Steven John

- F3 hepatic fibrosis
- Biopsy-confirmed NASH
- T2D
- Obesity
- Dyslipidemia

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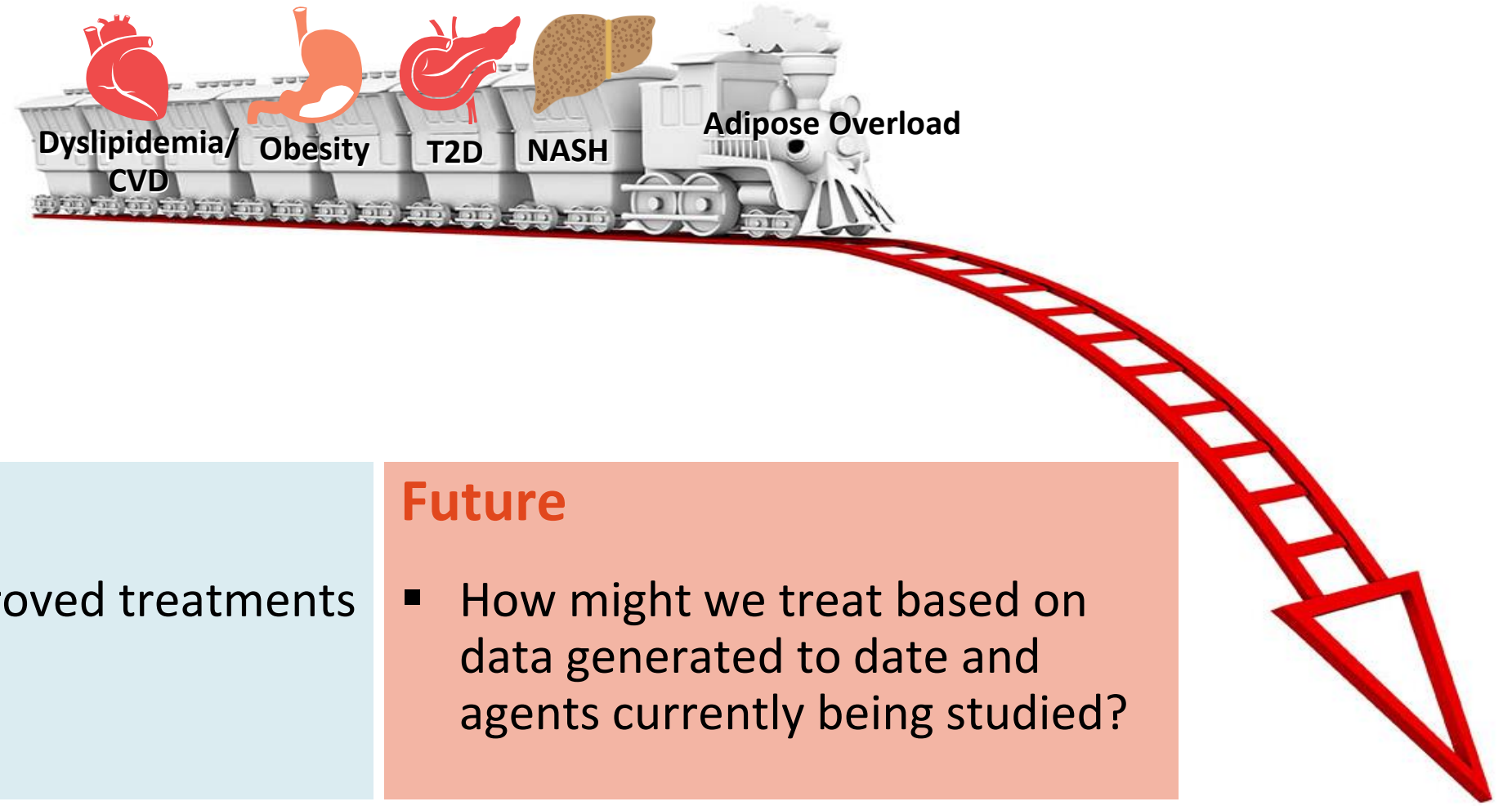
Case Study: Steven John



Current

- No FDA-approved treatments

Future

- How might we treat based on data generated to date and agents currently being studied?

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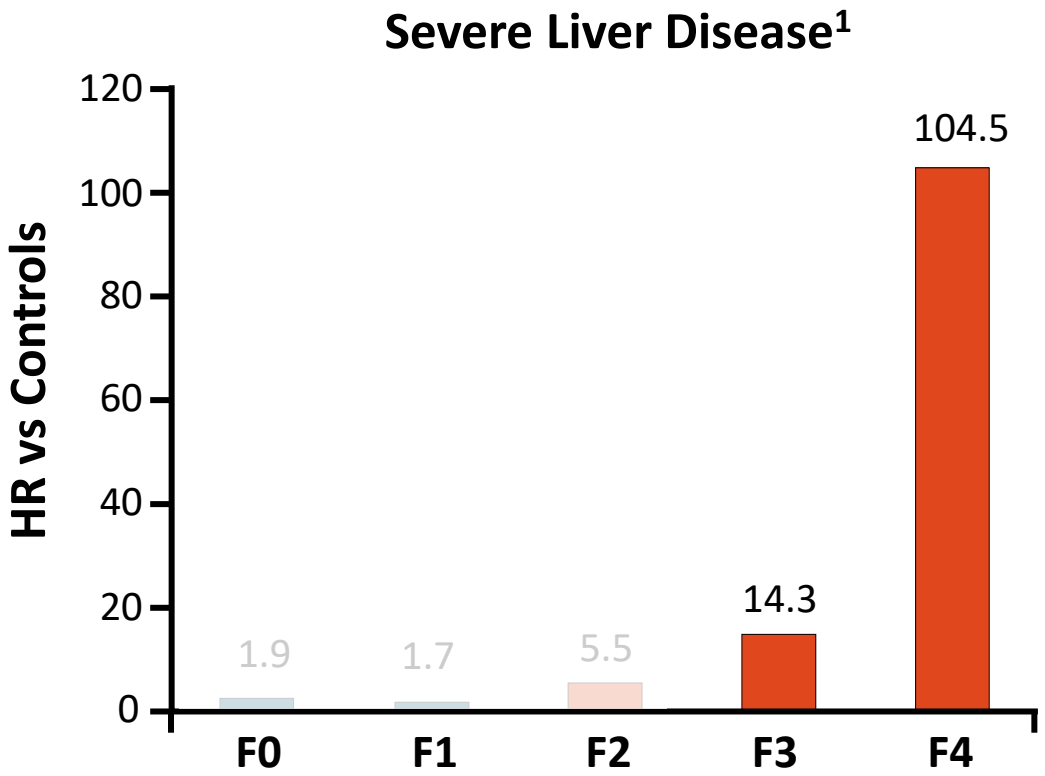
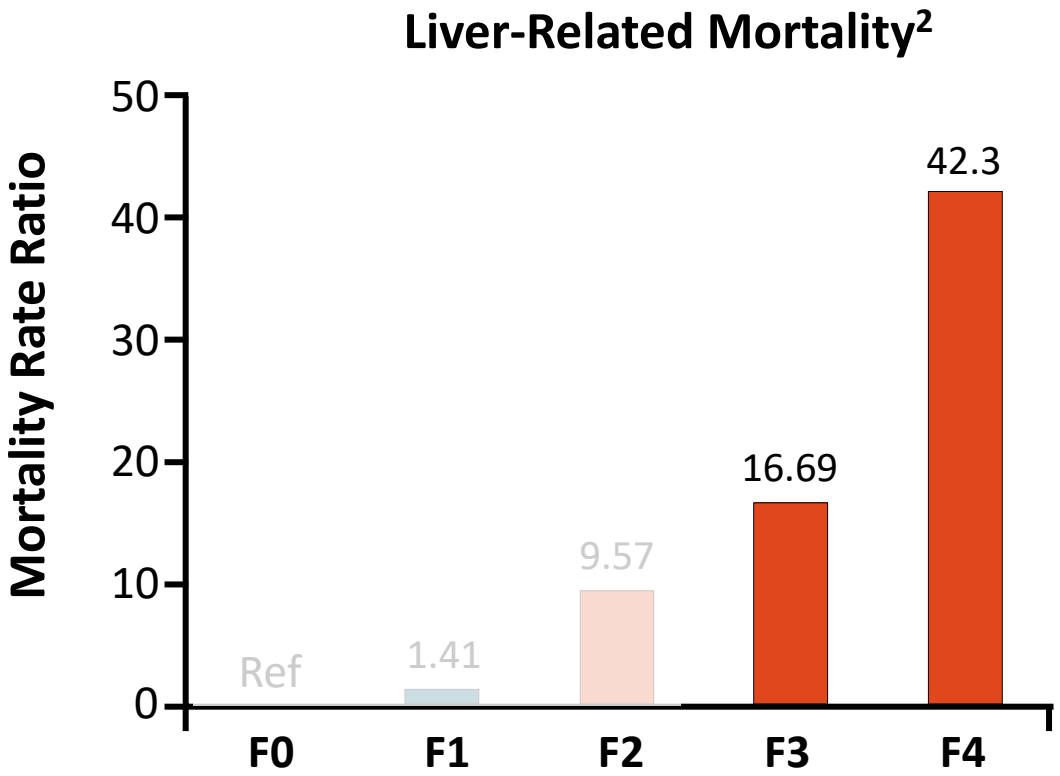
Hepatic Outcomes

Steven John's Fibrosis Puts Him at High Risk for Liver Outcomes





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

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Potential Targets:
Bringing Steven John Back From the Brink

- F3 hepatic fibrosis → Regress or prevent progression of **fibrosis**
- Biopsy-confirmed NASH → Reverse **NASH,** a driver of fibrosis

- Obesity
- T2D
- Dyslipidemia

} Improve **metabolic** state

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Multiple Agents in Development

Oral Agents

- FXR agonists
  - eg, obeticholic acid
- PPAR agonists
  - eg, pioglitazone, elafibranor, lanifibranor, seladelpar
- THR-beta agonists
  - eg, resmetirom
- Metabolic enzyme inhibitors
  - eg, SCD-1 inhibitor
- ACC inhibitor
- FASN inhibitor
- Mitochondrial pyruvate carrier inhibitor
- Pan-cyclophilin inhibitor
- Structurally engineered fatty acid

Injectable/Infusion

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

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Injectable/Infusion Approaches

Effects

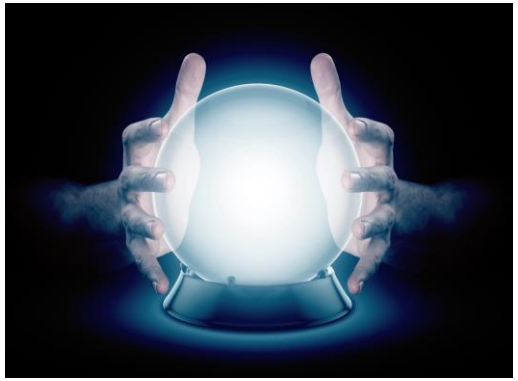
- Potentially very potent effect on **histopathology**
  - Unknown effect of GLP-1 RAs on fibrosis: potential slowing of progression of fibrosis
- Potential impact on **metabolic profiles**?

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?



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Oral Approaches

Effects

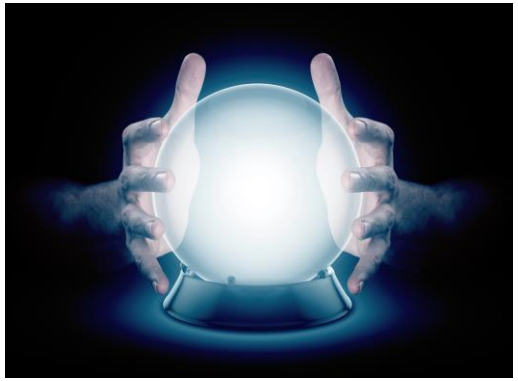
- Variable effect on **histopathology**
- Variable effects on **metabolic profiles**

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



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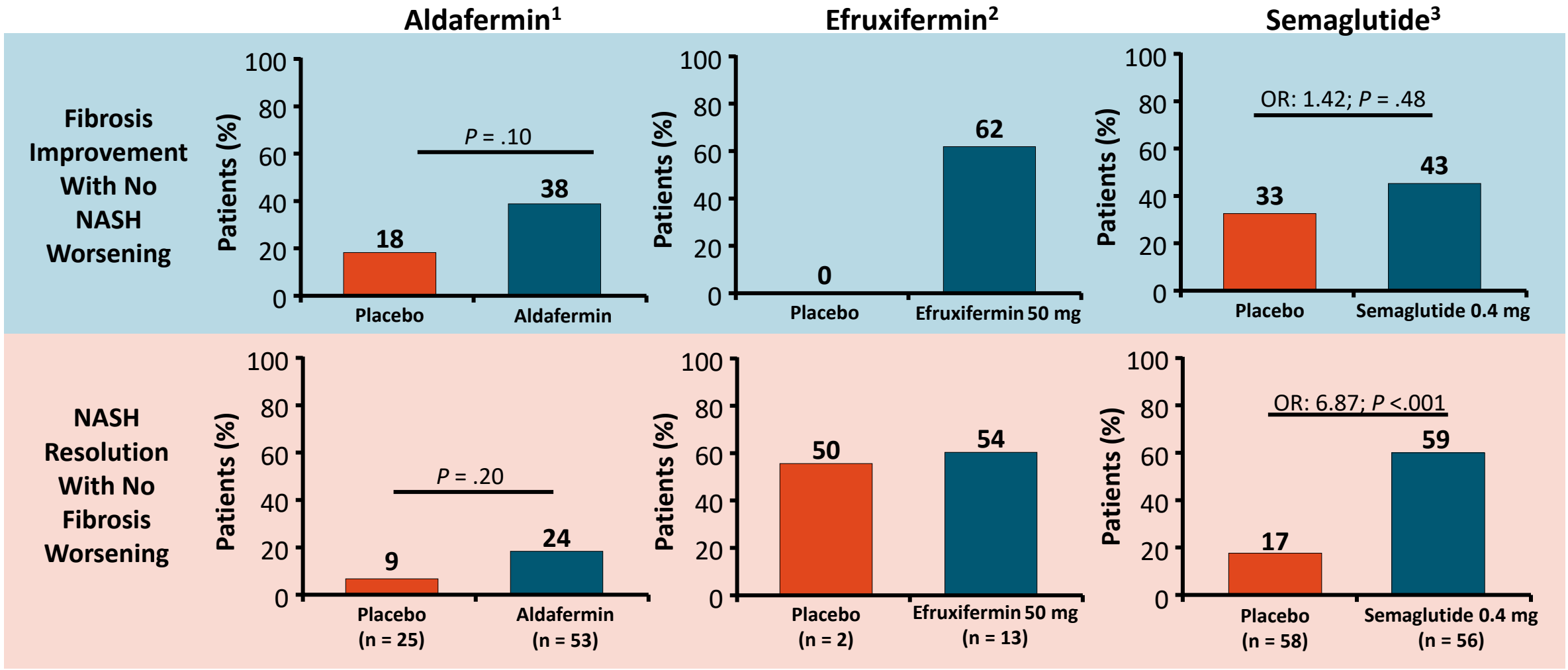
Hepatic Outcomes: Injectable Agents



1. Harrison. Gastroenterol. 2021;160:219. 2. Harrison. Nat Med. 2021. Epub. 3. Newsome. NEJM. 2021;384:1113.

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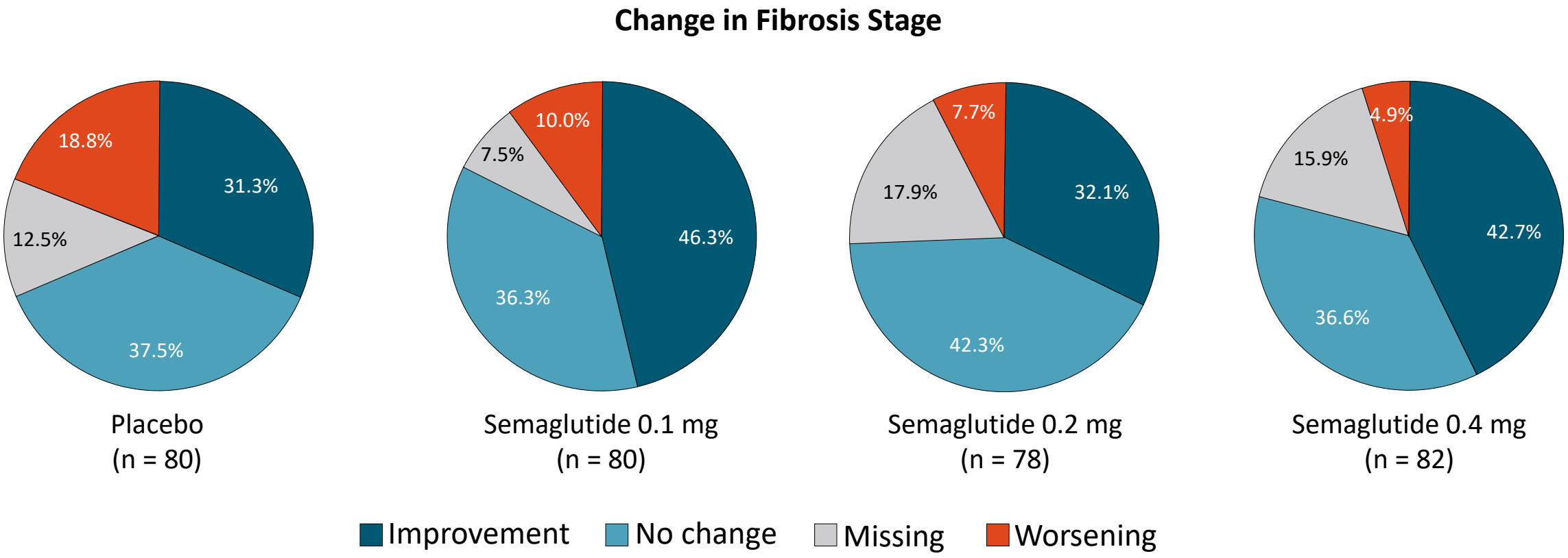
Prevention of Fibrosis Progression

- Secondary endpoint of phase II study of semaglutide in NASH



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Hepatic Outcomes: Oral Agents

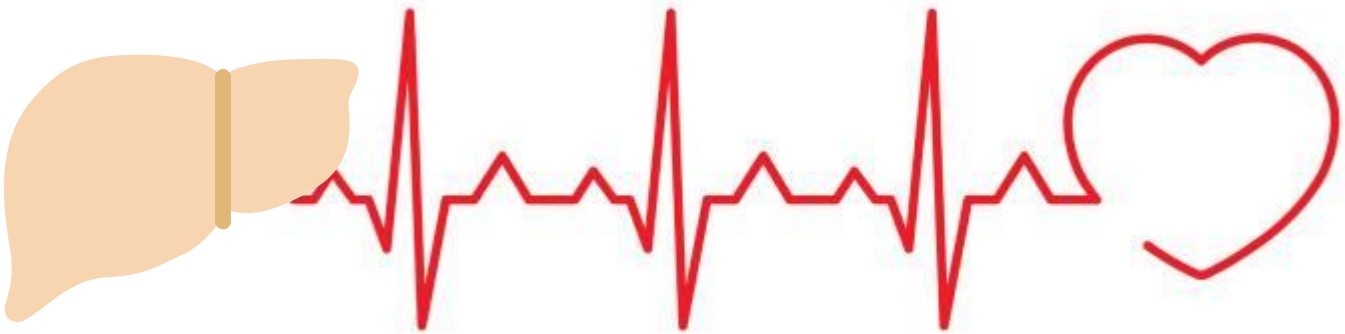
- Associated with various rates of patients with **NASH resolution**
  - eg, elafibranor,[1] lanifibranor,[2] resmetirom[3]
- Associated with various rates of patients with **fibrosis improvement**
  - eg, lanifibranor,[2] obeticholic acid,[4] resmetirom[3]

1. Ratziu. Gastroenterology. 2016;150:1147. 2. Francque. AASLD 2020. Abstr 12.
3. Harrison. Lancet. 2019;394:2012. 4. Younossi. Lancet. 2019;394:2184.

Extrahepatic Outcomes

Steven John's NASH Puts Him at High Risk for Death

- Patients with NAFLD more likely to have morbidity and mortality from **CVD** than from liver causes[1,2]
  - The ideal NASH treatment must also be **heart healthy**



1. Chalasani. Hepatology. 2018;67:328. 2. Angulo. Gastroenterology. 2015;194:389.

Slide credit: clinicaloptions.com

Potential Targets: Managing Glycemic and CV Risk

▪ F3 hepatic fibrosis	→	▪ Regress fibrosis
▪ Biopsy-confirmed NASH	→	▪ Reverse NASH, a driver of fibrosis
▪ Obesity	→	▪ Improve **metabolic state**
▪ T2D	→	▪ Address **glycemic control**
▪ Dyslipidemia	→	▪ Address—or at least do not worsen—**atherogenic risk**

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Extrahepatic Outcomes: Injectable Agents

Aldafermin[1]

Variable	Placebo (n = 25)	Aldafermin 1 mg (n = 52)	Diff Aldafermin vs Placebo (95% CI)	*P* Value
Δ Weight, kg	-0.7 (2.4)	-0.4 (3.5)	0.4 (-1.3 to 2.1)	.67
Δ A1C, %	0.5 (0.8)	0.2 (0.9)	-0.2 (-0.7 to 0.2)	.31
Δ TG, mg/dL	-28.5 (56.0)	-62.2 (136.8)	-13.1 (-36.1 to 10.0)	.26
Δ LDL-C, mg/dL	-16 (27.8)	-19.0 (30.2)	-2.3 (-16.3 to 11.6)	.74

Semaglutide[2]

Change From Baseline to Wk 72	Semaglutide 0.4 mg (n = 82)	Placebo (n = 80)
Body weight, %	-12.51	-0.61
Glycated hemoglobin level among patients with T2D, percentage points	-1.15	-0.01

Efruxifermin[3]

LS Mean Difference Vs Placebo at Wk 16 (95% CI)	Efruxifermin 28 mg (n = 19)	*P* Value	Efruxifermin 50 mg (n = 20)	*P* Value	Efruxifermin 70 mg (n = 20)	*P* Value
A1C, %	-0.2 (-0.6, 0.2)	.2969	-0.5 (-0.9, -0.1)	.0137	-0.6 (-1.0, -0.2)	.0024
TG, mg/dL	-89.1 (-120.8, -57.5)	<.0001	-107.7 (-139.4, -76.0)	<.0001	-102.5 (-133.7, -71.3)	<.0001
LDL, m/dL	-15.6 (-30.0, -1.1)	.0354	-4.3 (-18.8, 10.3)	.5592	-6.6 (-21.0, 7.9)	<.3680

1. Harrison. Gastroenterol. 2021;160:219. 2. Newsome. NEJM. 2021;384:1113. 3. Harrison. Nat Med. 2021. Epub.

Slide credit: clinicaloptions.com

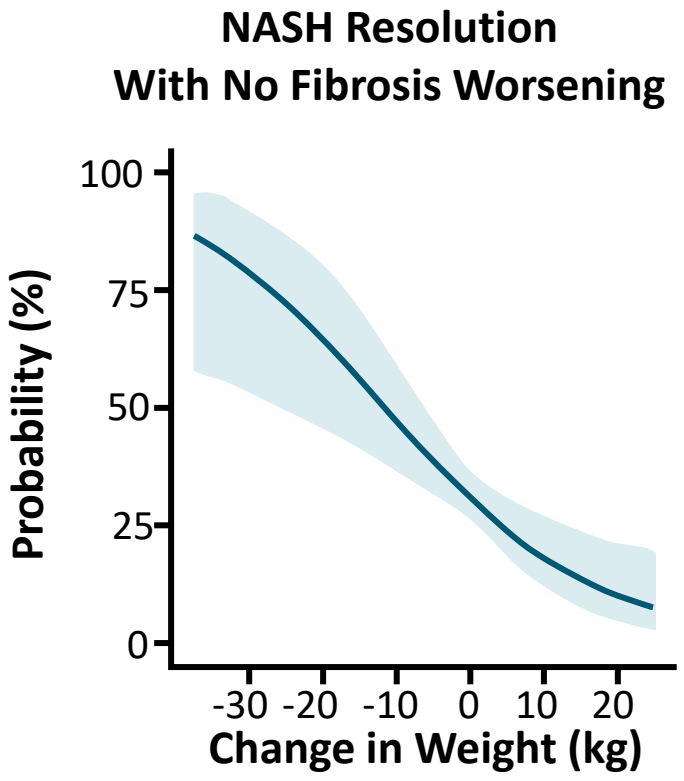
Extrahepatic Outcomes: Oral Agents

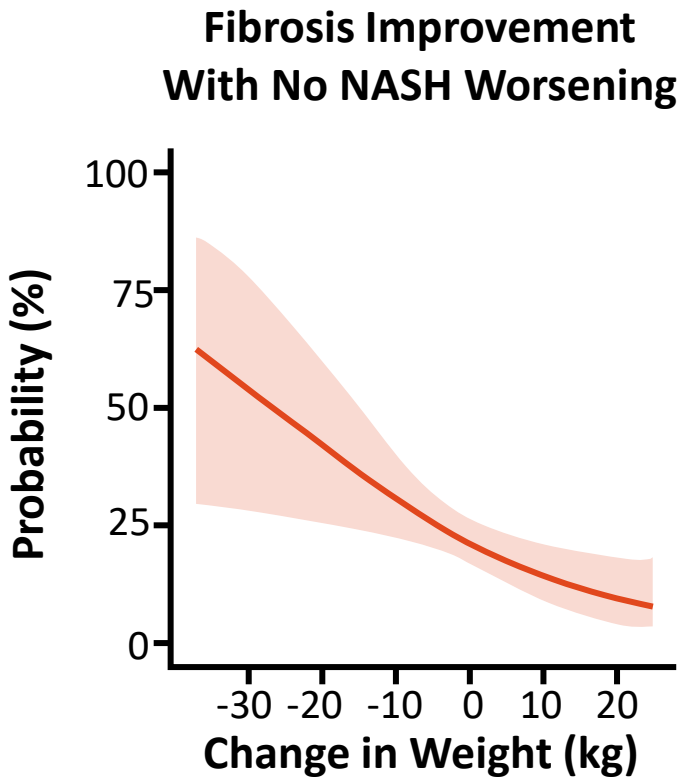
- Associated with various reductions in **TG** vs baseline
  eg, lanifibranor,[1] obeticholic acid,[2] resmetirom[3]
- Associated with various reductions in **LDL** vs baseline
  eg, elafibranor,[4] resmetirom[3]
  - By contrast, obeticholic acid associated with increased LDL[2]
- Some also associated with reductions in **A1C** and/or **body weight**
  - By contrast, lanifibranor associated with increased weight[1]

1. Francque. AASLD 2020. Abstr. 12. 2. Younossi. Lancet. 2019;394:2184.
3. Harrison. Lancet. 2019;394:2012. 4. Ratziu. Gastroenterology. 2016;150:1147.

Weight Loss Associated With Improved NASH Outcomes

- Analysis of N = 421 patients in PIVENS and FLINT studies followed for 1.5 or 2 yr





Koutoukidis. Clin Gastroenterol Hepatol. 2021;[Epub].

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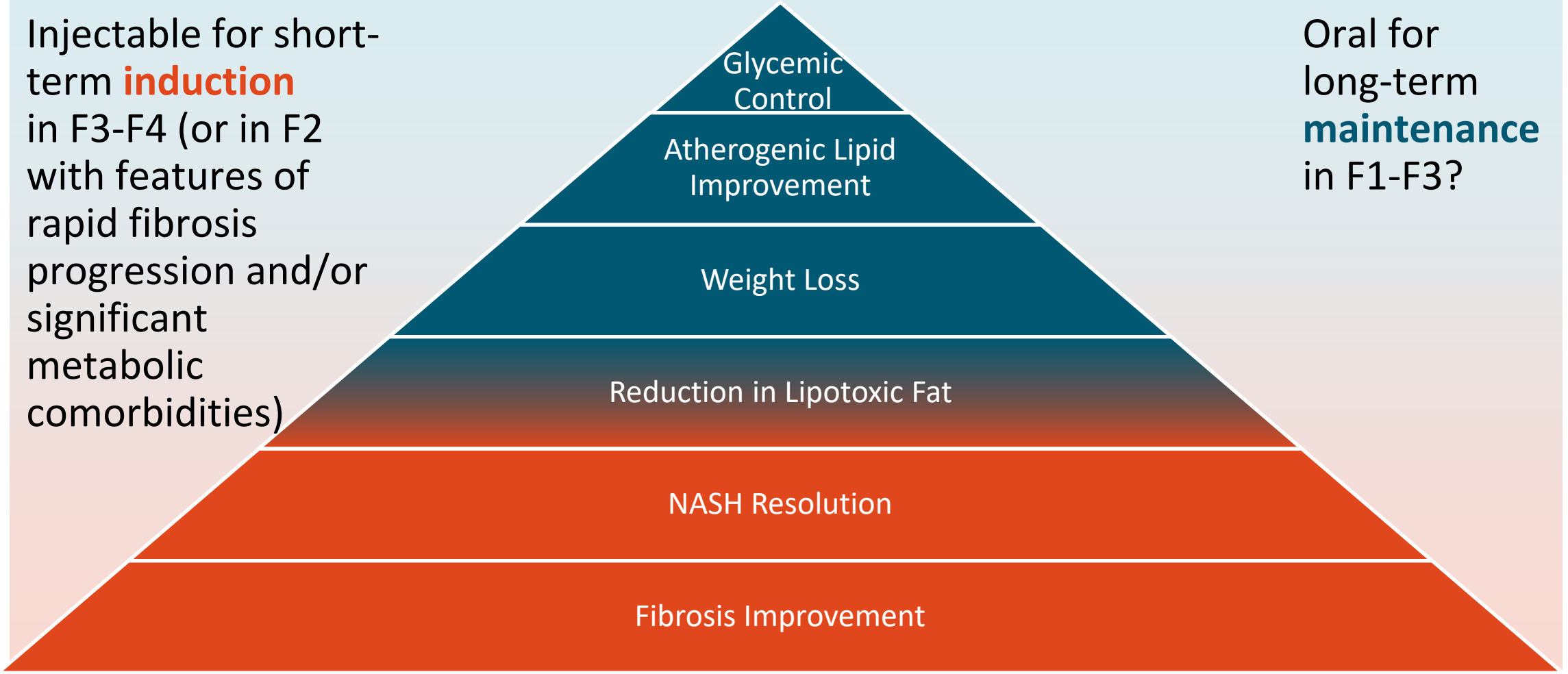
Potential Targets for NASH Treatments

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?

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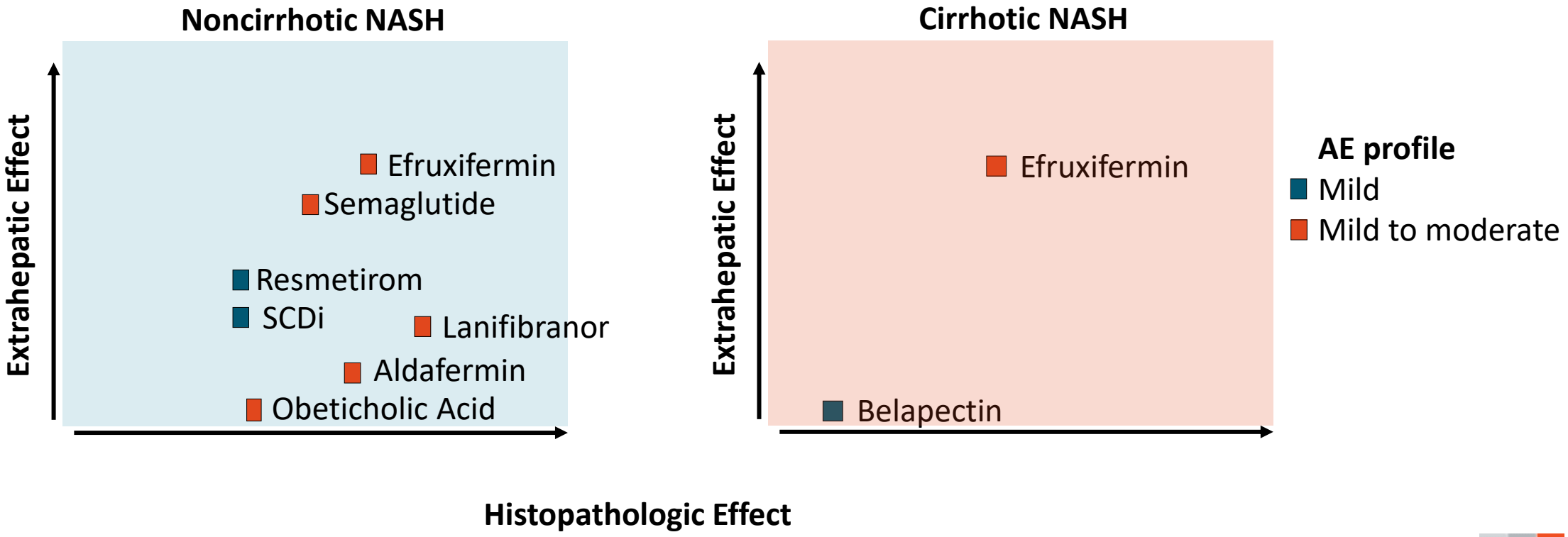
My Perspective: Histopathologic and Extrahepatic Profiles

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



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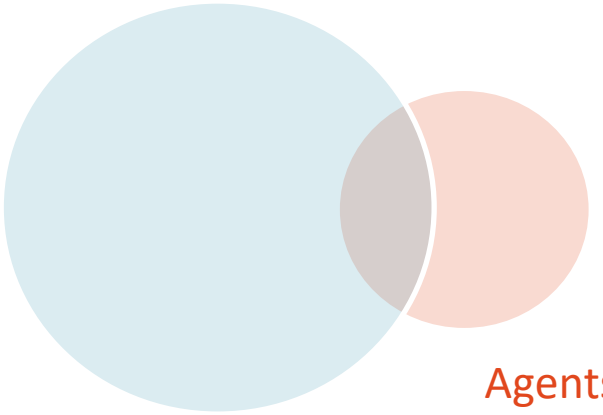
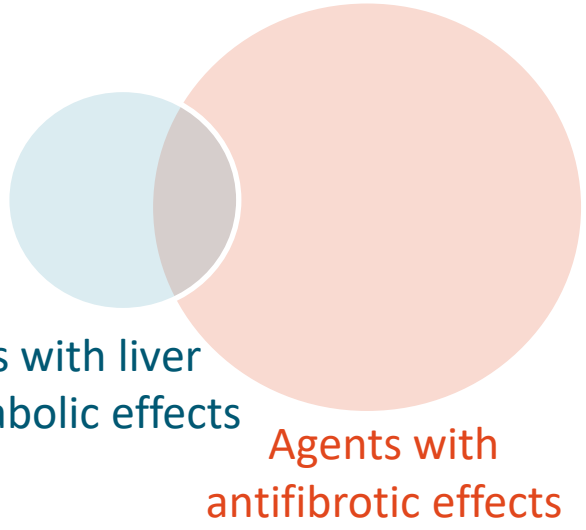
Combination Therapy

- Synergizing/optimizing histopathologic benefit
  - eg, phase IIb study of **GLP-1 RA** semaglutide in combination with **FXR agonist** cilofexor and **ACC inhibitor** firsocostat
- Different MoAs to lower atherogenic risk

Combination Therapy for Noncirrhotic NASH



Combination Therapy for Cirrhotic NASH



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Summary

- **Histologic** liver endpoints are currently accepted FDA endpoints for NASH treatments
  - Reversal of NASH or fibrosis without worsening of the other
- **Extrahepatic** endpoints may have a role
  - Glycemic control
  - Atherogenic risk

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