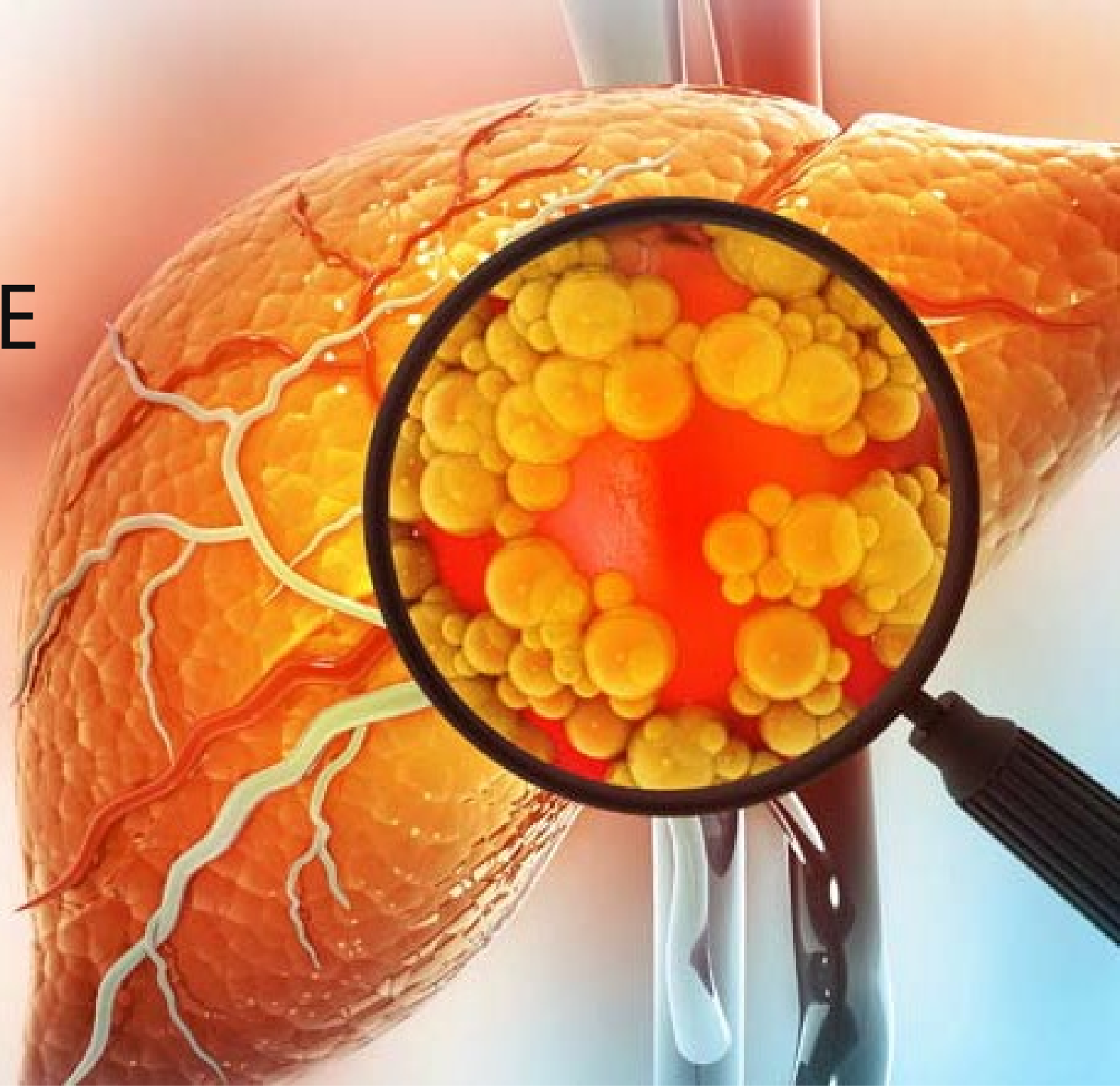
MASH IN THE INCRETIN ERA: DDW HIGHLIGHTS AND THE NEXT THERAPEUTIC TARGET

Nimish Thakral MD

Assistant Professor – Department of Digestive Diseases and Nutrition University of Kentucky



DDW REVIEW 2026

Digestive Disease Week highlights | August 2026

DISCLOSURES

Nimish Thakral, MD

Division of Digestive Diseases and Nutrition

University of Kentucky

No financial disclosures

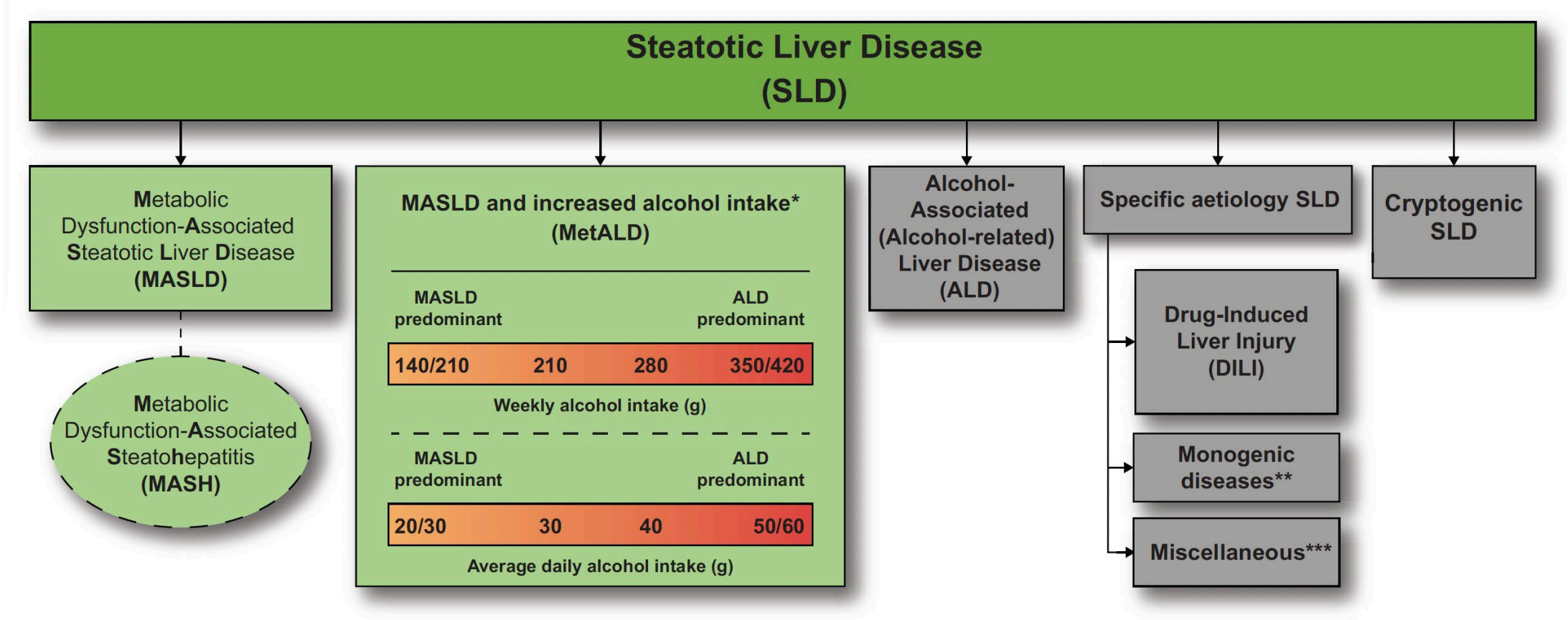
LEARNING OBJECTIVES

1. **Summarize** the key DDW 2026 findings on GLP-1 receptor agonists and related metabolic therapies in patients with MASLD and MASH.

2. **Compare** GLP-1 receptor agonists with emerging dual and triple receptor agonists, including mechanism of action, effects on weight and metabolic disease, and available liver-specific outcomes.

3. **Appraise** the strengths and limitations of the current evidence for incretin-based therapies in MASH.

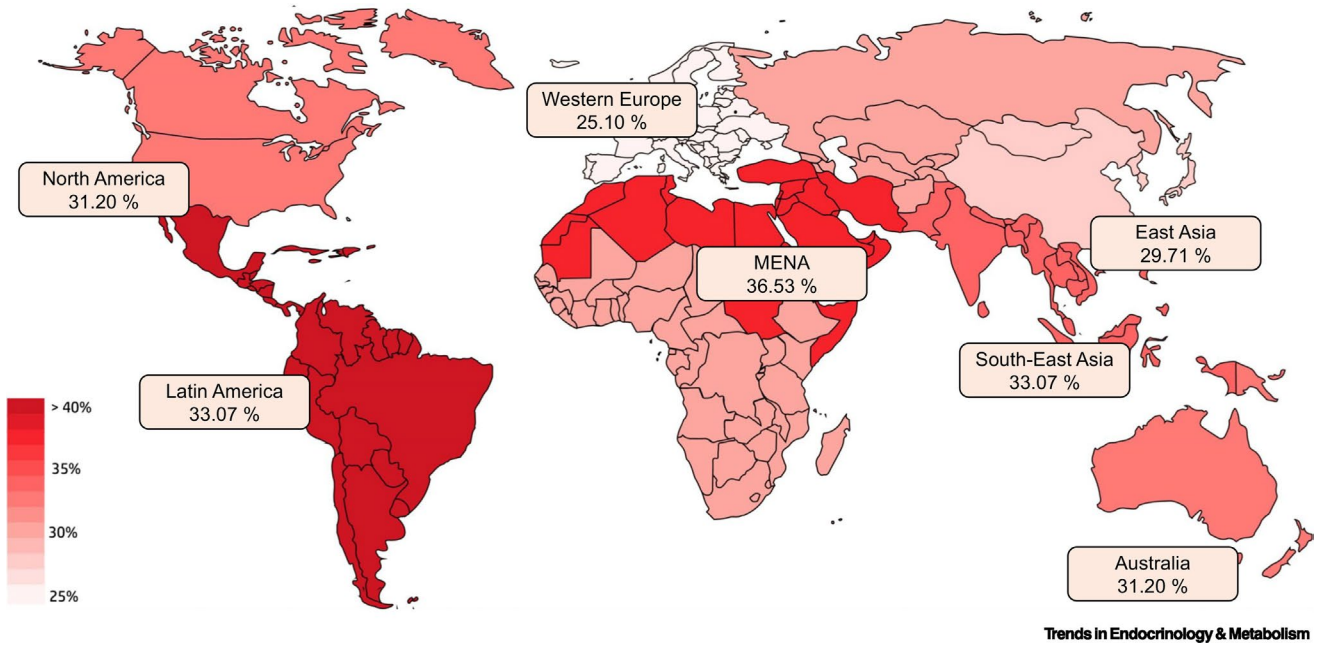
FROM NAFLD TO MASLD

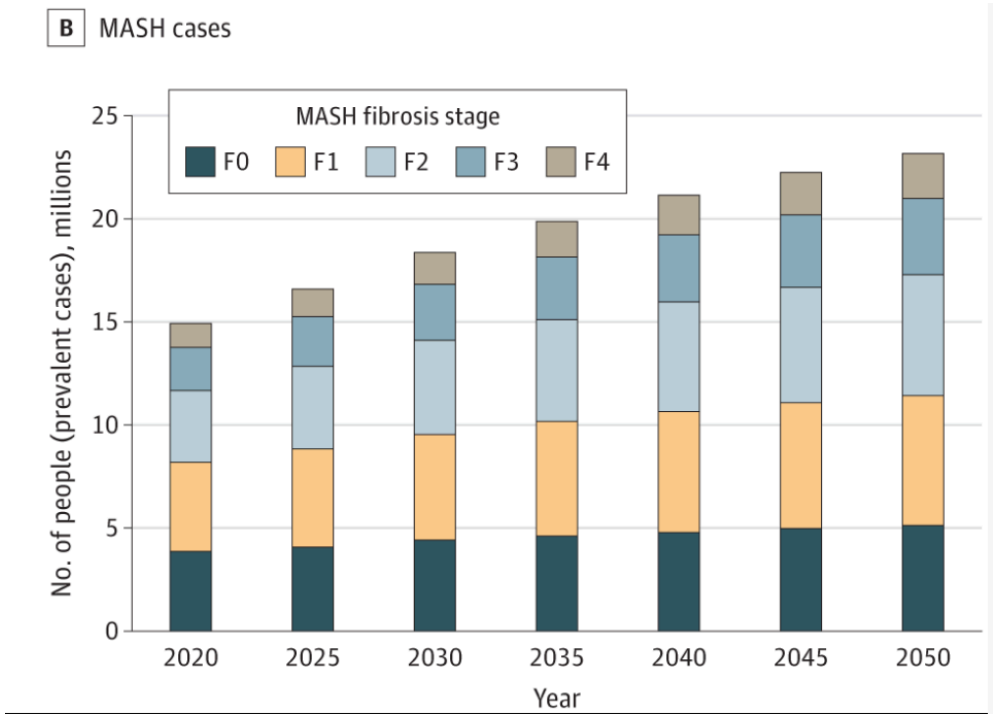


*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

Kanwal, Fasiha et al *Hepatology (Baltimore, Md.)* vol. 79,5 (2024): 1212-1219.

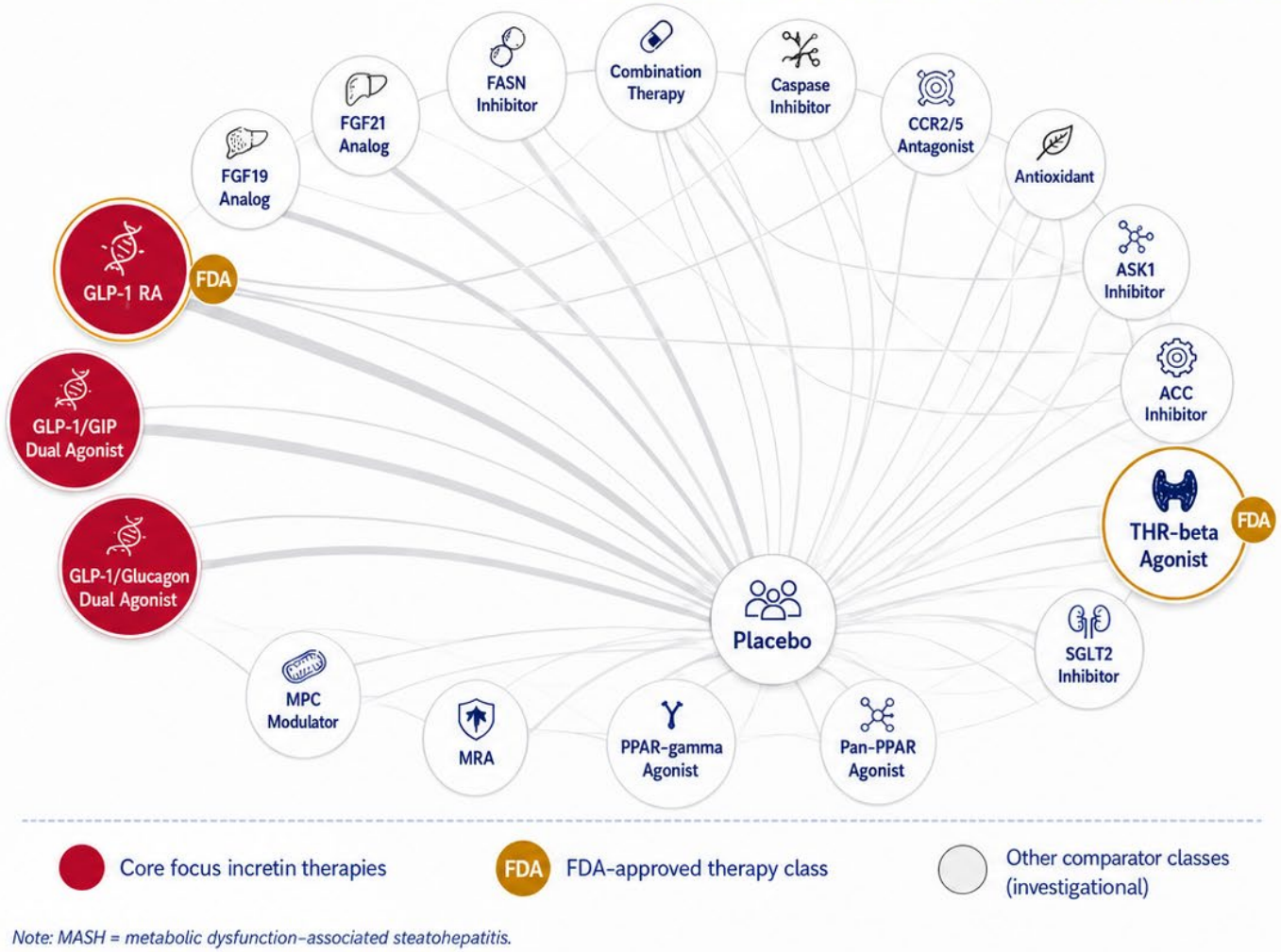
THE INCIDENCE OF MASLD IS RISING.





Treatment Landscape in MASH

Investigational classes and current FDA–approved options



Note: MASH = metabolic dysfunction–associated steatohepatitis.

FDA-Approved Therapies for MASH

Semaglutide

Class: GLP-1 RA

Status: FDA approved (accelerated approval)

Adults with MASH and moderate-to-advanced fibrosis

Resmetirom (Rezdiffra)

Class: THR-beta agonist

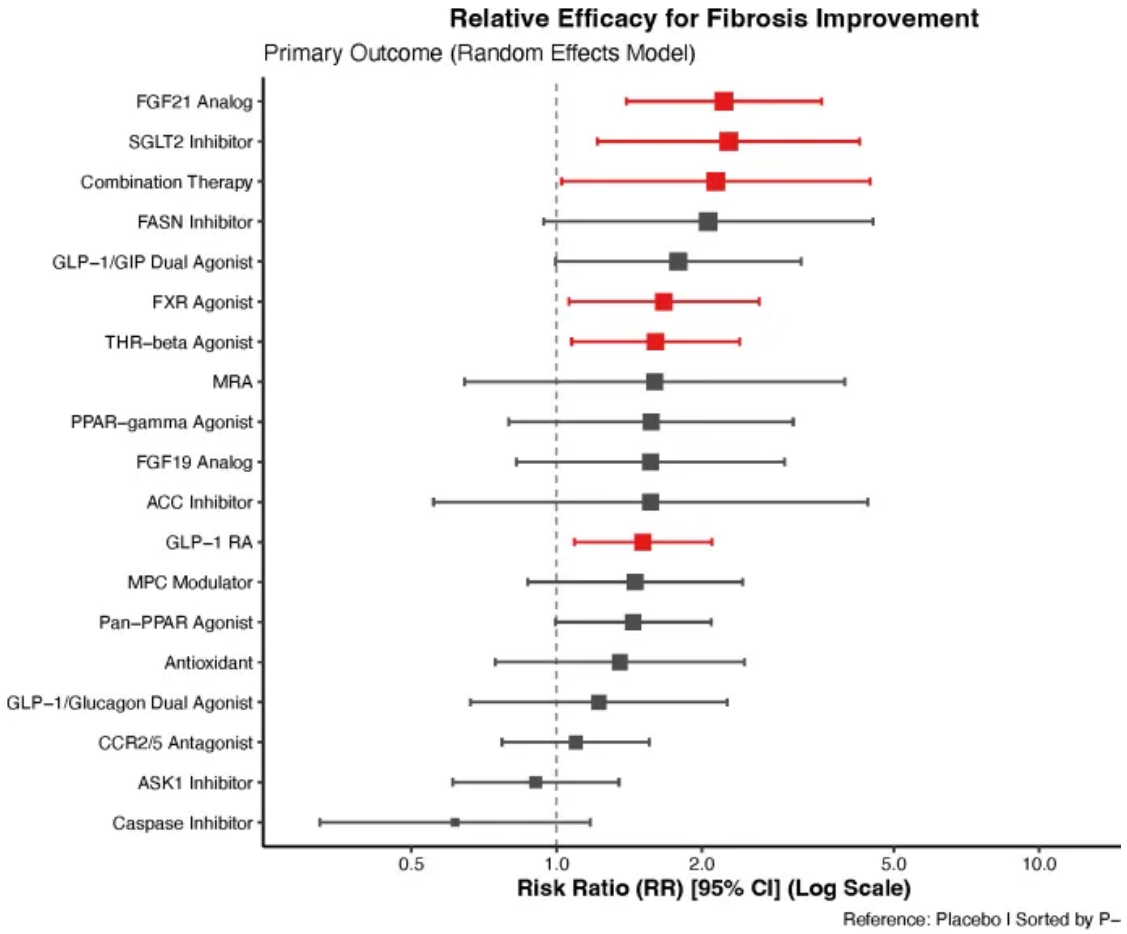
Status: FDA approved

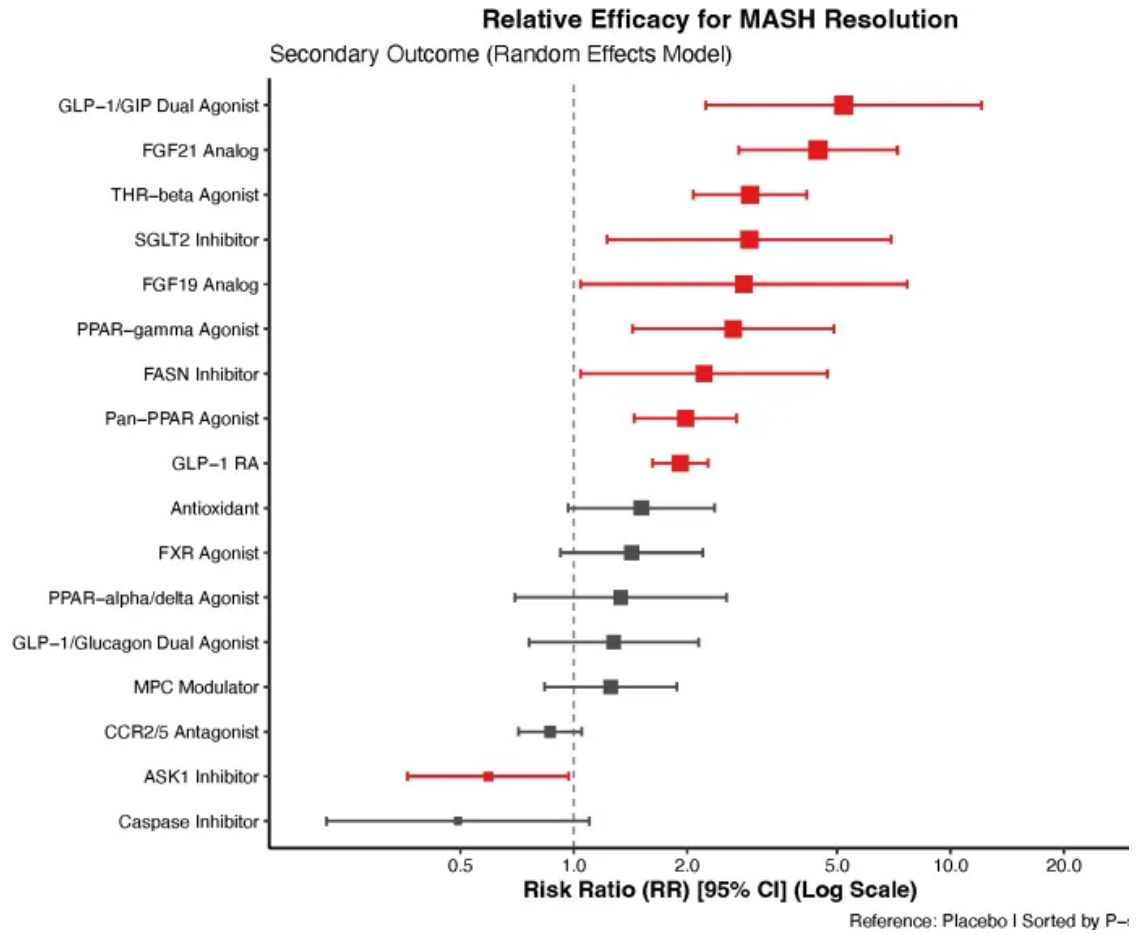
Adults with noncirrhotic MASH and moderate-to-advanced fibrosis

Most therapeutic classes remain investigational; semaglutide and resmetirom are the only FDA-approved agents for MASH.

Tang M, Ma Y and Wang Y (2026) Updating the MASH pharmacotherapy landscape: a network meta-analysis incorporating SGLT2 inhibitors and emerging combination therapies. Front. Endocrinol. 17:1829315. doi: 10.3389/fendo.2026.1829315

CURRENT LANDSCAPE FOR TREATMENT OF MASH





Tang M, Ma Y and Wang Y (2026) Updating the MASH pharmacotherapy landscape: a network meta-analysis incorporating SGLT2 inhibitors and emerging combination therapies. Front. Endocrinol. 17:1829315. doi: 10.3389/fendo.2026.1829315

Incretins: From Discovery to Mechanisms

The Foundation of Incretin Biology and Therapeutic Potential in Metabolic Disease

1 A BRIEF HISTORY

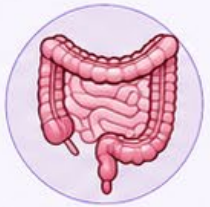
1930s Incretin concept introduced to describe intestinal factors that lower blood glucose.

1970 GIP discovered in dogs and named "gastric inhibitory polypeptide" due to inhibition of gastric acid secretion.

1973 GIP shown to stimulate insulin secretion in humans; name changed to glucose-dependent insulinotropic polypeptide.

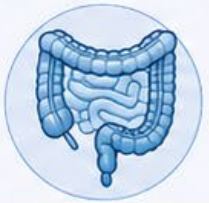
1980s GLP-1 and GLP-2 identified from glucagon precursor; GLP-1 (7–36) shown to stimulate insulin and inhibit glucagon.

2 SOURCES OF INCRETINS



GIP – Glucose-dependent Insulinotropic Polypeptide

- Secreted by K cells in the duodenum and proximal jejunum
- Also expressed in CNS (hippocampus, thalamus, cerebellum, brainstem, cortex, hypothalamus)
- Derived from pro-GIP → GIP(1–42) (primary) and GIP(1–30) (amidated)



GLP-1 – Glucagon-Like Peptide-1

- Secreted by L cells in the small and large intestine; also in CNS (brainstem)
- Derived from proglucagon by tissue-specific processing
- Two active forms: GLP-1(7–36) amide and GLP-1(7–37)

3 TISSUE-SPECIFIC PROCESSING OF PREPROGLUCAGON

Preproglucagon (160 aa) → Proglucagon (160 aa)

GRPP	Glucagon (29 aa)	IP-1	GLP-1	IP-2	GLP-2	Oxyntomodulin	Glicentin

Pancreatic α-cells (PC2 predominates)

Cleavage products

- Glucagon (29 aa)
- GRPP
- IP-1
- MPGF

Glucagon promotes hepatic glucose output and is secreted primarily during fasting.

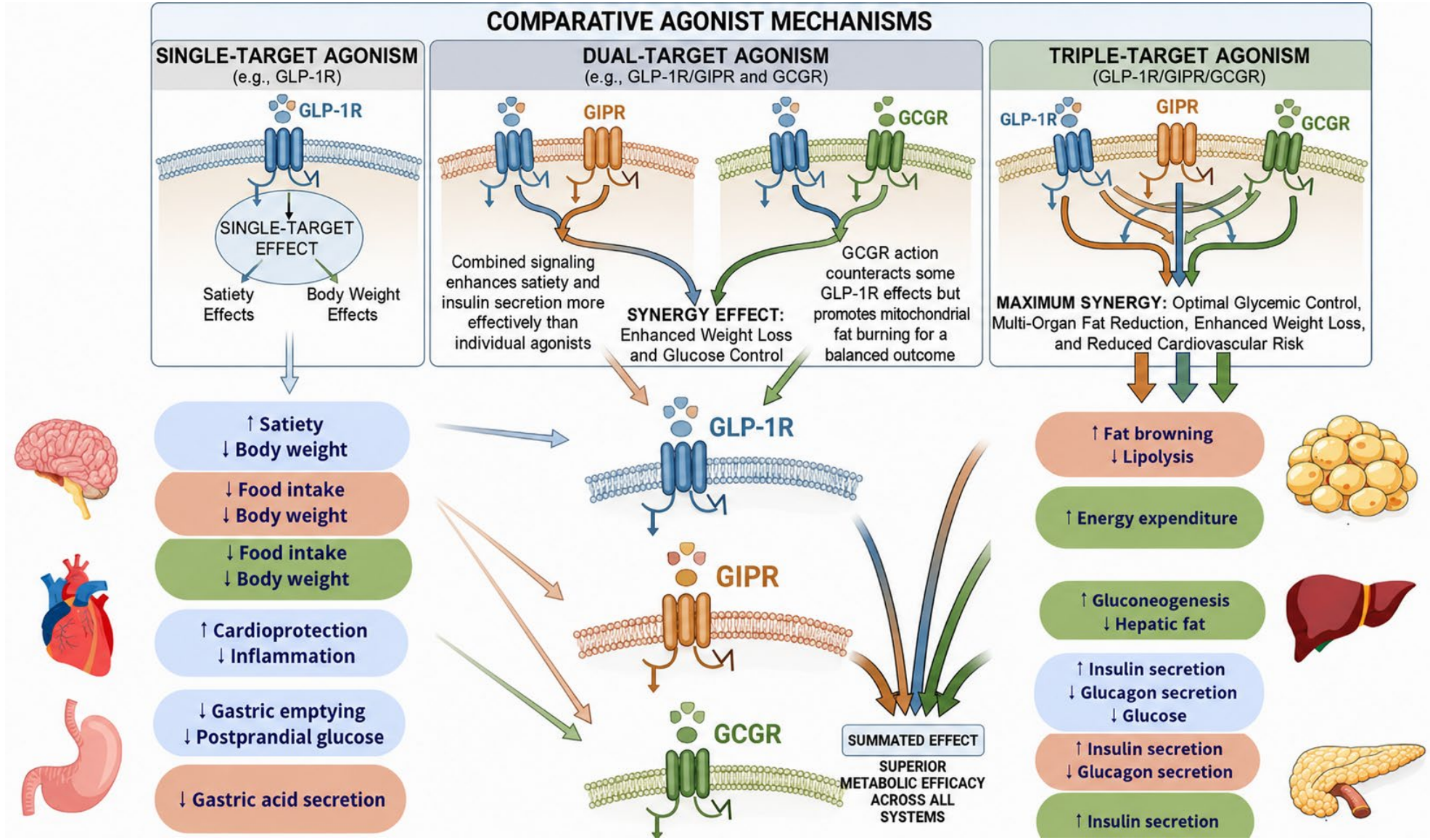
Intestinal L-cells & CNS neurons (PC1/3 predominates)

Cleavage products

- GLP-1 (7–36 amide/ 7–37)
- GLP-2
- Oxyntomodulin
- Glicentin
- IP-2

GLP-1 and GLP-2 are key incretin hormones that promote insulin secretion and nutrient homeostasis.

TAKE-HOME MESSAGE: Incretins are gut-derived hormones that coordinate glucose homeostasis and metabolic balance—laying the foundation for next-generation therapies in metabolic diseases.



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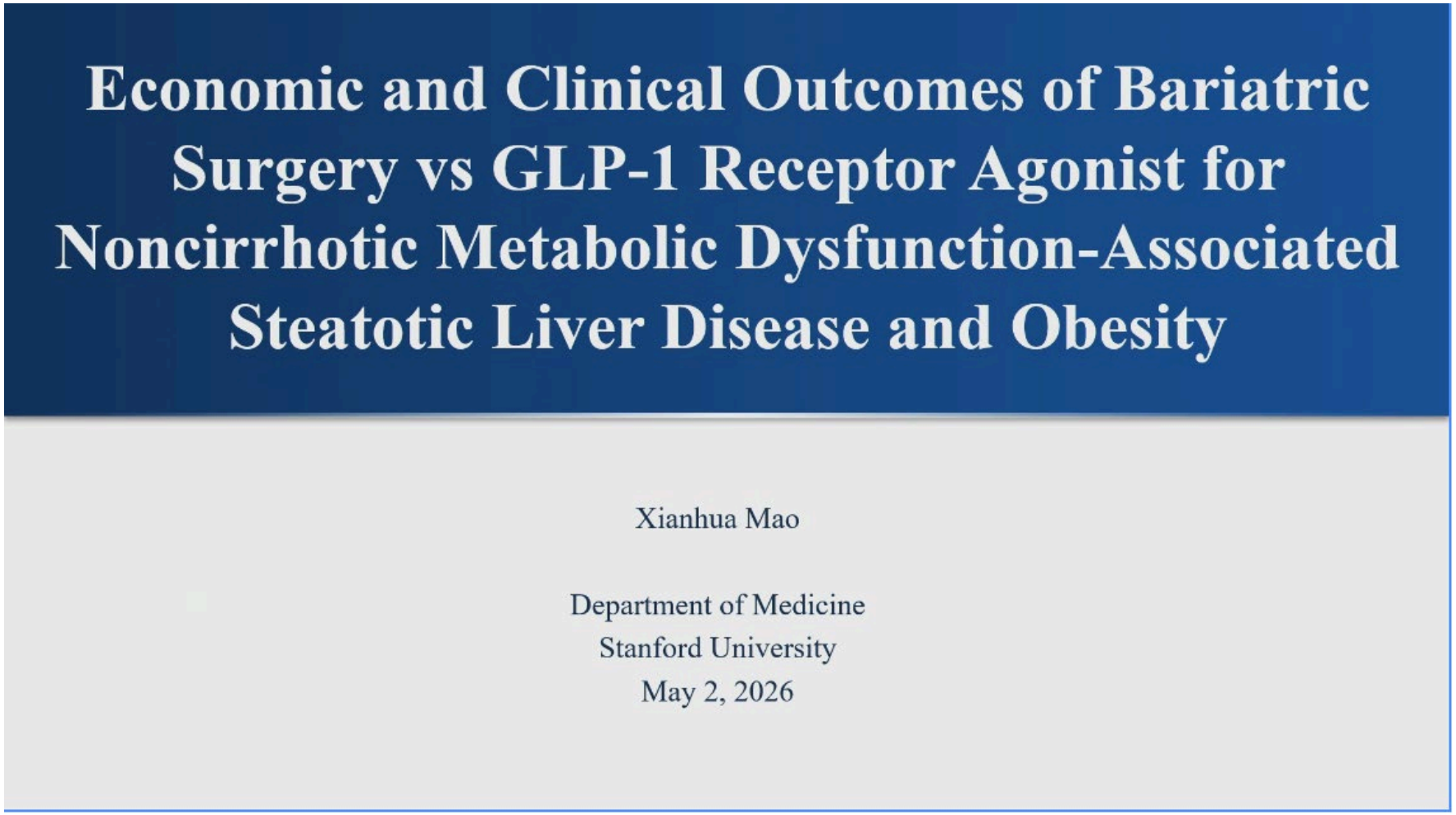
What's New at DDW?

Digestive Disease Week Highlights

DDW STUDY #1


Economic and Clinical Outcomes of Bariatric Surgery vs GLP-1 Receptor Agonist for Noncirrhotic Metabolic Dysfunction-Associated Steatotic Liver Disease and Obesity
Xianhua Mao
Department of Medicine
Stanford University
May 2, 2026

DDW STUDY #1

METHODS

- Population-based cohort (2008-2022); new-user design
- MASLD/obesity: ICD-9/-10 codes
- Exposure: metabolic bariatric surgery (MBS) or first prescription of GLP-1 RA
- Economic outcome: out-of-pocket costs (the sum of deductibles, copays, and coinsurances) over a 10-year horizon
- Clinical outcomes: incident major adverse liver and cardiovascular outcomes
- Other health outcomes: BMI change over time; clinical remission for diabetes, hypertension, or dyslipidemia; healthcare utilization
- Propensity score matching for balancing baseline characteristics
- Generalized linear models: 6-month landmark analyses with competing risk models

DDW STUDY #1

Results: Patient characteristics

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EXHIBIT DATES: MAY 3–5, 2026

	After propensity score matching		
Characteristics[a]	GLP-1 RA (n=4103)	MBS (n=4103)	SMD
Age, mean (SD), y	47.7 (10.3)	47.7 (10.2)	0.004
Sex			0.012
Men	1121 (27.3)	1099 (27.8)	
Women	2982 (72.7)	3004 (73.2)	
Region			0.022
Northeast	659 (16.1)	663 (16.2)	
North Central	886 (21.6)	905 (22.1)	
South	2090 (50.9)	2093 (51.0)	
West	406 (9.9)	381 (9.3)	
Unknown	62 (1.5)	61 (1.5)	
BMI[b], kg/m²			0.047
30.0-30.9	14 (0.3)	18 (0.4)	
31.0-31.9	21 (0.5)	21 (0.5)	
32.0-32.9	40 (1.0)	33 (0.8)	
33.0-33.9	62 (1.5)	60 (1.5)	
34.0-34.9	93 (2.3)	84 (2.0)	
35.0-35.9	197 (4.8)	194 (4.7)	
36.0-36.9	209 (5.1)	206 (5.0)	
37.0-37.9	204 (5.0)	228 (5.6)	
38.0-38.9	252 (6.1)	247 (6.0)	
39.0-39.9	220 (5.4)	236 (5.8)	
40.0-44.9	1332 (32.5)	1301 (31.7)	
45.0-49.9	743 (18.1)	766 (18.7)	
50.0-59.9	581 (14.2)	576 (14.0)	
60.0-69.9	111 (2.7)	108 (2.6)	
70.0 or greater	24 (0.6)	25 (0.6)	
Smoking[b,d]	909 (22.2)	927 (22.6)	0.011
Comorbidity			
Obstructive sleep apnea	2262 (55.1)	2273 (55.4)	0.005
Diabetes	2340 (57.0)	2329 (56.8)	0.005
Hyperlipidemia	3174 (77.4)	3183 (77.6)	0.005
Hypertension	3176 (77.4)	3182 (77.6)	0.004
Unstable angina	149 (3.6)	137 (3.3)	0.016
Angina pectoris	83 (2.0)	83 (2.0)	<0.001
Atrial fibrillation	187 (4.6)	185 (4.5)	0.002
Peripheral artery disease	588 (14.3)	573 (14.0)	0.010
Heart failure	237 (5.8)	228 (5.6)	0.009
Stroke	360 (8.8)	341 (8.3)	0.017
Myocardial infarction	129 (3.1)	117 (2.9)	0.017
Chronic kidney disease	211 (5.1)	214 (5.2)	0.003
Medication use[b]			
Metformin	1074 (26.2)	1038 (25.3)	0.020
Sulfonylureas	290 (7.1)	266 (6.5)	0.023
DPP-4 inhibitor	287 (7.0)	258 (6.3)	0.028
SGLT-2 inhibitor	223 (5.4)	206 (5.0)	0.019
Thiazolidinediones	89 (2.2)	81 (2.0)	0.014
Insulin	390 (9.5)	392 (9.6)	0.002
Statins	932 (22.7)	927 (22.6)	0.003
Fibrates	106 (2.6)	104 (2.5)	0.003
ACEI	891 (21.7)	909 (22.2)	0.011
CCB	447 (10.9)	422 (10.3)	0.020
Aspirin	76 (1.9)	72 (1.8)	0.007
Insurance type			0.018
CDHP	522 (12.7)	512 (12.5)	
HMO	515 (12.6)	495 (12.1)	
PPO	2140 (52.2)	2153 (52.5)	
Other/unknown	926 (22.6)	943 (23.0)	
Out-of-pocket cost, mean (SD), $[b,e]	2776 (3597)	2760 (2628)	0.005
Inpatient stay, mean (SD), day[b]	4.5 (5.5)	4.6 (6.3)	<0.001
Healthcare utilization[b]			
Hospitalization	408 (9.9)	408 (9.9)	<0.001
Inpatient surgery	164 (4.0)	169 (4.1)	0.006
Internal medicine visit	2162 (52.7)	2138 (52.1)	0.012
Gastroenterology visit	864 (21.1)	884 (21.5)	0.012
Cardiology visit	1615 (39.4)	1583 (38.6)	0.016

Table 1. Patient characteristics after propensity score matching.

ACEI, angiotensin-converting enzyme inhibitors; BMI, body mass index; CCB, calcium channel blockers; CDHP, consumer-driven health plan; DDP-4, dipeptidyl peptidase-4; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HMO, health maintenance organization; MBS, metabolic and bariatric surgery; PPO, preferred provider organization; SD, standardized deviation; SGLT-2, sodium-glucose cotransporter 2; SMD, standardized mean difference.

[a]Unless otherwise designated, figures for each characteristic are percentage (%) values.

[b]Measured within 365 days before the index intervention.

[c]Data suppressed due to privacy issues per Stanford Population Health science department policy.

[d]Smoking or smoking-related medical conditions identified before the index intervention.

[e]All costs are adjusted to 2023 U.S. dollars.

- Mean age: 47.7 years; Female: 72%
- BMI ≥40 kg/m² : 61%

DDW STUDY #1

Results: Economic outcomes

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Table 2. Out-of-pocket costs for GLP-1 RA and MBS groups after propensity score matching.

	Cost (95%CI), $			
Outcomes[a]	GLP-1 RA (n=4103)	MBS (n=4103)	Difference	P value
Mean total out-of-pocket costs per year				
Baseline[b]	2776 (2666 to 2886)	2760 (2679 to 2840)	17 (-117 to 155)	0.800
0-1 y	2789 (2719 to 2858)[c]	4833 (4727 to 4939)[d]	-2044 (-2169 to -1917)	<0.001
1-2 y	2569 (2476 to 2661)[d]	1857 (1786 to 1928)[d]	712 (599 to 828)	<0.001
2-10 y	2485 (2389 to 2580)[d]	1829 (1730 to 1928)[d]	656 (517 to 794)	<0.001
Mean pharmacy out-of-pocket costs per year				
Baseline[b]	624 (570 to 678)	470 (439 to 502)	154 (91 to 216)	<0.001
0-1 y	1095 (1070 to 1121)[d]	338 (329 to 348)[d]	757 (730 to 784)	<0.001
1-2 y	888 (863 to 914)[d]	366 (352 to 381)[d]	522 (493 to 552)	<0.001
2-10 y	915 (876 to 954)[d]	424 (401 to 447)[d]	492 (446 to 537)	<0.001
Mean medical out-of-pocket costs per year				
Baseline[b]	2152 (2058 to 2246)	2290 (2218 to 2361)	-137 (-257 to -18)	0.025
0-1 y	1700 (1645 to 1754)[d]	4509 (4402 to 4616)[d]	-2809 (-2931 to -2688)	<0.001
1-2 y	1769 (1689 to 1849)[d]	1580 (1510 to 1650)[d]	189 (81 to 295)	<0.001
2-10 y	1643 (1564 to 1721)[d]	1498 (1402 to 1595)[d]	145 (20 to 268)	0.021
Out-of-pocket costs over 10 years of follow-up				
Total costs	25237 (24463 to 26010)	21324 (20521 to 22127)	3913 (2809 to 5022)	<0.001
Pharmacy costs	9305 (8992 to 9618)	4094 (3908 to 4281)	5211 (4847 to 5575)	<0.001
Medical costs	16612 (15976 to 17247)	18075 (17292 to 18859)	-1464 (-2490 to -444)	0.003

- Total 10-year out-of-pocket costs:

  MBS < GLP-1 RA

- The main driver of the difference was lower pharmacy costs.

CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MBS, metabolic and bariatric surgery.
[a]Pharmacy costs were costs from outpatient pharmacy claims, and medical costs were costs from outpatient service claims and inpatient claims.
[b]Baseline included 12 months before the index date.
[c]P value >0.05 when compared with baseline.
[d]P value <0.05 when compared with baseline.

DDW STUDY #1

Results: Clinical outcomes

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Outcomes	Event	PYs	Incidence rate (per 1000 PYs, 95%CI)	SHR (95%CI)	P value
MALO					
GLP-1 RA	223	11535	19.3 (15.1 to 23.6)	1 (reference)	
MBS	147	11093	13.3 (9.7 to 16.8)	0.65 (0.53 to 0.81)	<0.001
MACE					
GLP-1 RA	200	11720	17.1 (13.1 to 21.1)	1 (reference)	
MBS	137	11224	12.2 (8.8 to 15.6)	0.68 (0.55 to 0.84)	<0.001
Compensated cirrhosis					
GLP-1 RA	88	11800	7.5 (4.6 to 10.1)	1 (reference)	
MBS	32	11285	2.8 (1.2 to 4.5)	0.36 (0.24 to 0.54)	<0.001
Hepatic decompensation					
GLP-1 RA	150	11678	12.8 (9.4 to 16.3)	1 (reference)	
MBS	116	11145	10.4 (7.3 to 13.5)	0.77 (0.61-0.98)	0.035
Composite liver outcomes[a]					
GLP-1 RA	<11[b]	11973	0.33 (0 to 0.90)	1 (reference)	
MBS	<11[b]	11339	0.26 (0 to 0.77)	0.75 (0.17-3.35)	0.710
Heart failure					
GLP-1 RA	113	11886	9.5 (6.5 to 12.5)	1 (reference)	
MBS	54	11352	4.8 (2.6 to 6.9)	0.47 (0.34-0.66)	<0.001
Stroke					
GLP-1 RA	128	11820	10.8 (7.6 to 14.0)	1 (reference)	
MBS	105	11249	9.3 (6.4 to 12.3)	0.82 (0.63-1.06)	0.120
Myocardial infarction					
GLP-1 RA	80	11976	6.7 (4.2 to 9.2)	1 (reference)	
MBS	54	11345	4.8 (2.6 to 6.9)	0.72 (0.51-1.02)	0.067

- Incidence of major adverse liver and cardiovascular outcomes:

  MBS < GLP-1 RA

Table 3. Incidence rates and risk of MALO and MACE for GLP-1 RA and MBS groups after propensity score matching.
CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events; MALO, major adverse liver outcomes; MBS, metabolic and bariatric surgery; PY, person-year; SHR, subdistrition hazard ratio.
[a]Composite liver outcomes included hepatocellular carcinoma, liver failure, and liver transplant.
[b]Data suppressed due to privacy issues per Stanford Population Health science department policy.

DDW STUDY #1

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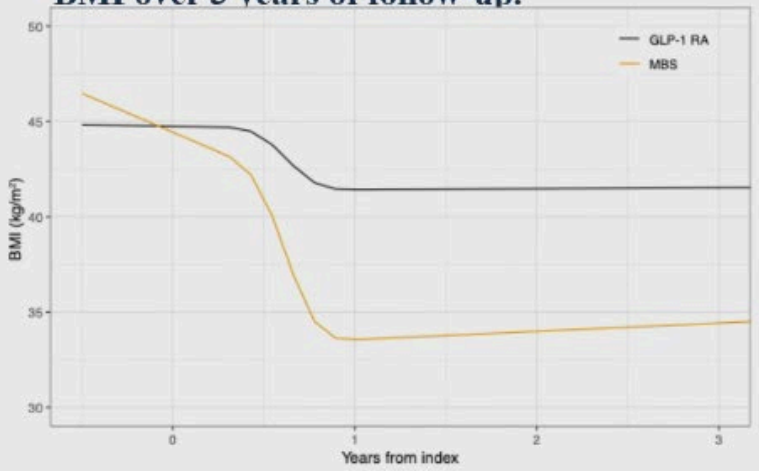
Results: Other health outcomes

eFigure. Trend curves of mean change in BMI over 3 years of follow-up.



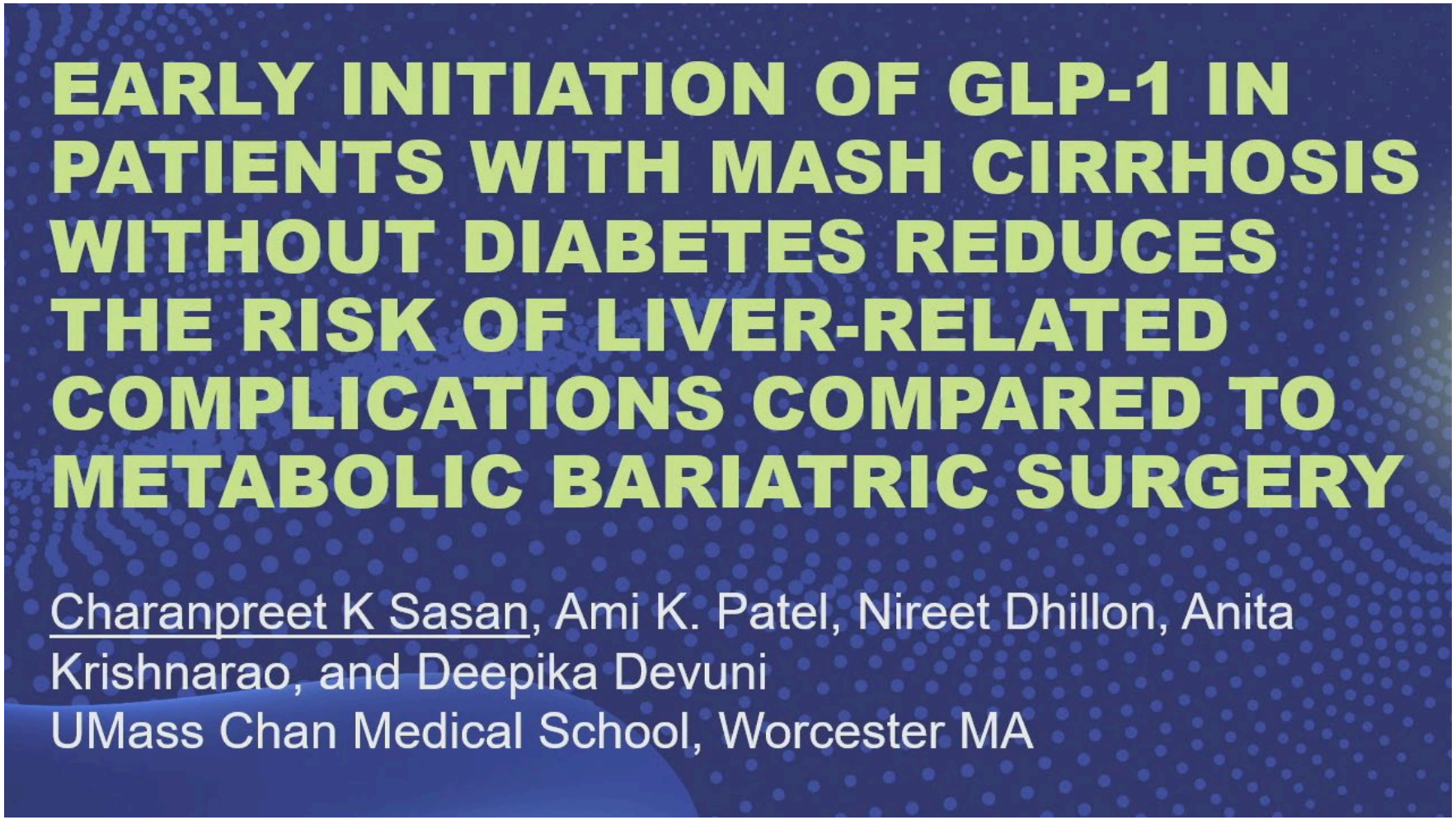
- BMI change; clinical remission; healthcare utilization:

  MBS < GLP-1 RA

Table 4. Cardiometabolic risk factors and healthcare utilization for GLP-1 RA and MBS groups.

Outcomes	GLP-1 RA	MBS	P value
BMI, mean (95%CI), kg/m² (n=1614)			
Baseline	44.7 (42.6 to 46.9)	44.4 (42.3 to 46.6)	0.841
Year 3	41.5 (40.5 to 42.6)	34.4 (33.4 to 35.5)	<0.001
Mean BMI reduction, %	7.2 (2.3 to 12.1)	22.5 (18.2 to 26.8)	<0.001
Diabetes clinical remission, No. (%) (n=778)			
0-1 y	30 (7.7)	126 (32.4)	<0.001
0-2 y	47 (12.1)	148 (38.0)	<0.001
Hypertension clinical remission, No. (%) (n=1560)			
0-1 y	27 (3.5)	110 (14.1)	<0.001
0-2 y	72 (9.2)	149 (19.1)	<0.001
Dyslipidemia clinical remission, No. (%) (n=612)			
0-1 y	20 (6.5)	61 (19.9)	<0.001
0-2 y	38 (12.4)	96 (31.4)	<0.001
Healthcare utilization, mean (95%CI), No. per patient per year (n=8206)			
Outpatient visits	13.79 (13.67 to 13.90)	10.36 (10.26 to 10.46)	<0.001
Hospitalization	0.13 (0.12 to 0.15)	0.12 (0.11 to 0.13)	0.264
Internal medicine department visits[a]	1.93 (1.89 to 1.97)	1.37 (1.34 to 1.41)	<0.001
Gastroenterology department visits[a]	0.34 (0.32 to 0.36)	0.20 (0.19 to 0.22)	<0.001
Cardiology department visits[a]	0.77 (0.75 to 0.80)	0.46 (0.44 to 0.48)	<0.001
Emergency department visits[a]	0.53 (0.51 to 0.55)	0.43 (0.41 to 0.45)	<0.001

DDW STUDY # 2


EARLY INITIATION OF GLP-1 IN PATIENTS WITH MASH CIRRHOSIS WITHOUT DIABETES REDUCES THE RISK OF LIVER-RELATED COMPLICATIONS COMPARED TO METABOLIC BARIATRIC SURGERY
Charanpreet K Sasan, Ami K. Patel, Nireet Dhillon, Anita Krishnarao, and Deepika Devuni
UMass Chan Medical School, Worcester MA

DDW STUDY # 2

- Study Design: Restrospective database study
- Data Source: Trinetx Global Collaborative Network
- Population: MASH Cirrhosis, Obesity, and no Type 2 Dm were identified by ICD-10 codes, excluding HCC and CCA between 2015 – 2025
- Exposure: Prescribed GLP-1 or undergoing MBS (metabolic bariatric surgery) within one year of cirrhosis diagnosis.
- Outcomes: Cirrhosis complications and liver transplantation

DDW STUDY # 2

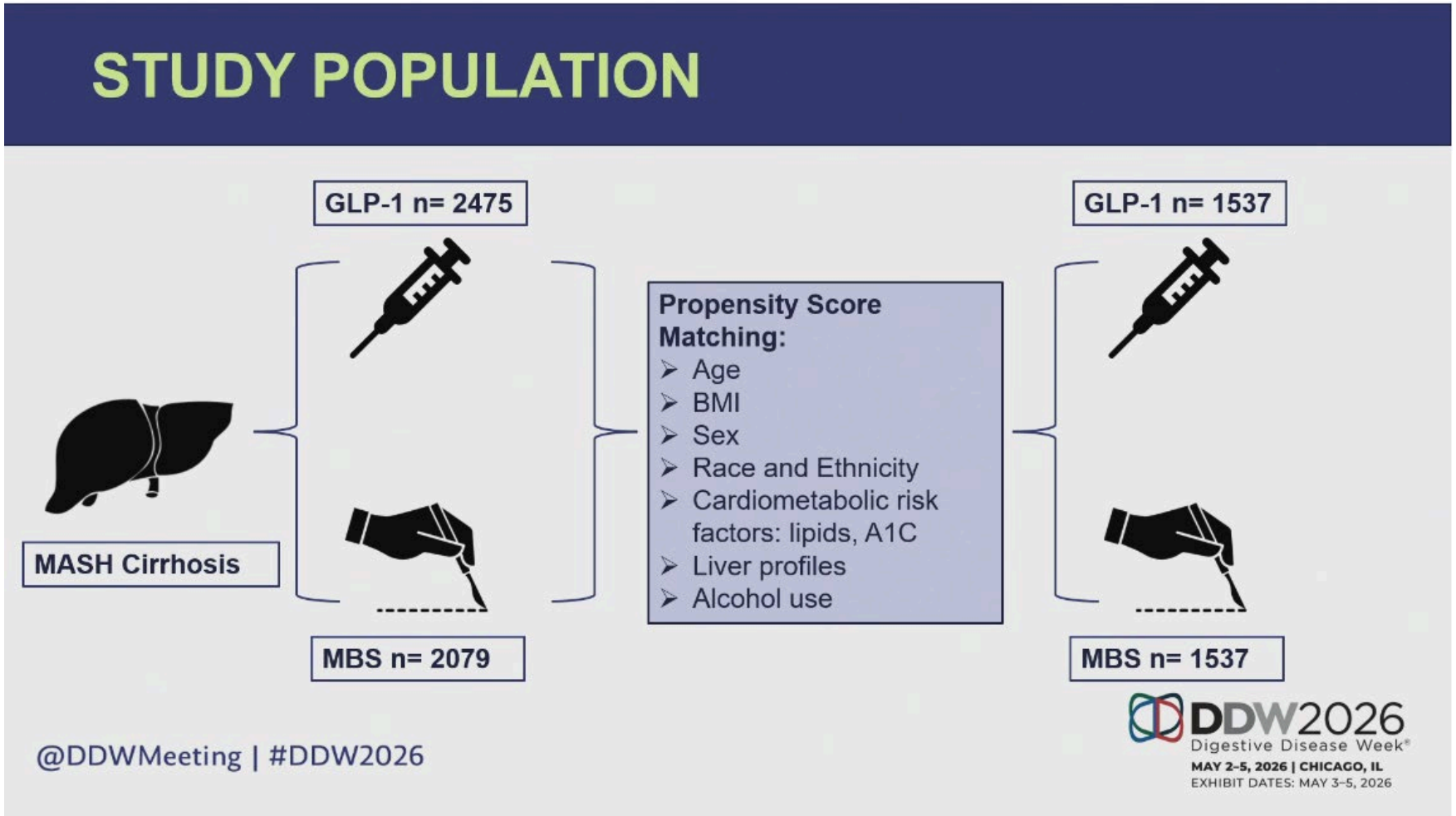

STUDY POPULATION
GLP-1 n= 2475
MASH Cirrhosis
MBS n= 2079
Propensity Score Matching:
Age
BMI
Sex
Race and Ethnicity
Cardiometabolic risk factors: lipids, A1C
Liver profiles
Alcohol use
GLP-1 n= 1537
MBS n= 1537
@DDWMeeting | #DDW2026
DDW2026
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EXHIBIT DATES: MAY 3–5, 2026

DDW STUDY # 2

Unmatched Cohort

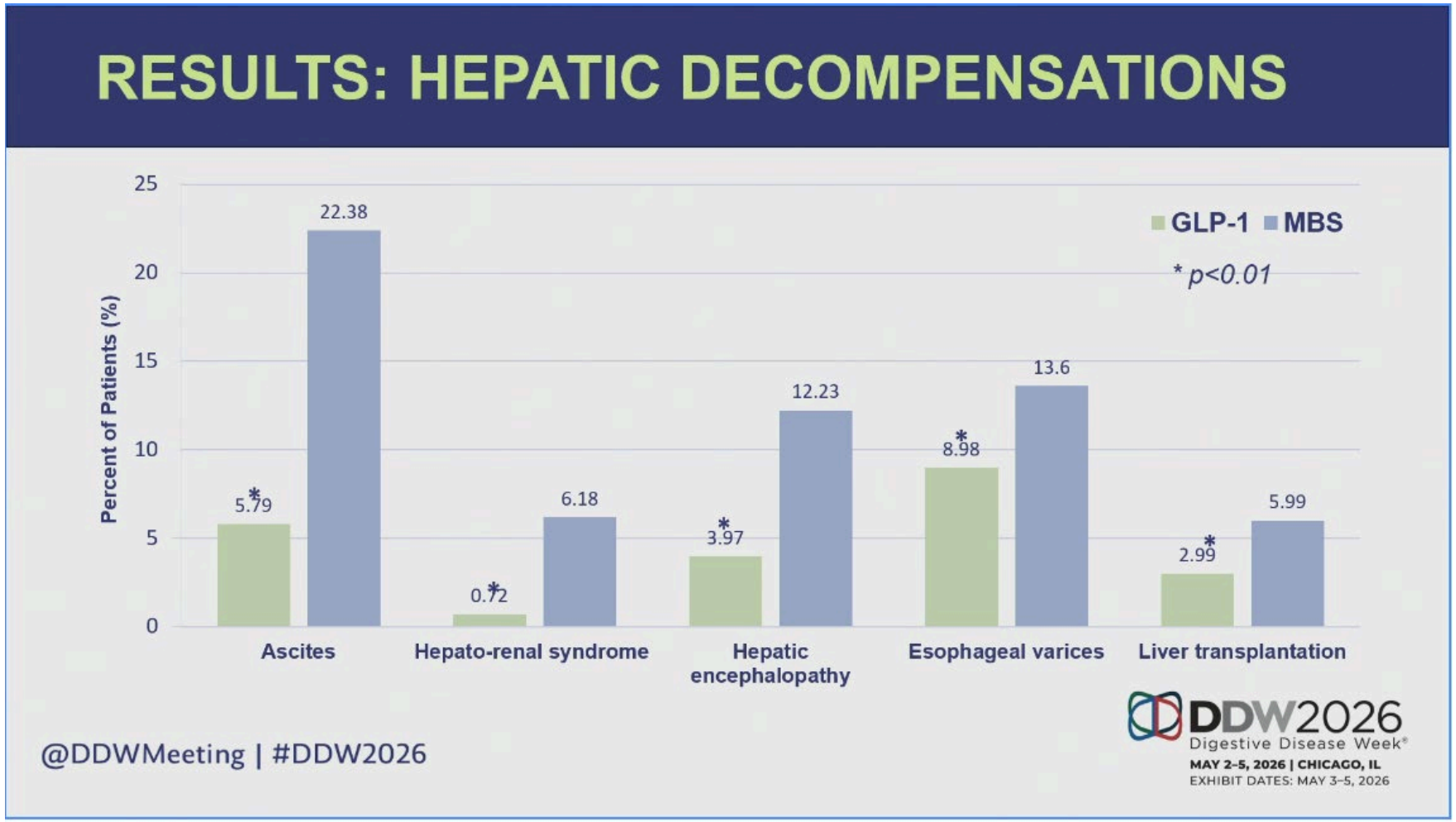
Characteristics	GLP-1 (n=2475)	MBS (n=2079)	P -value
Age, yrs	50.7 ± 11.7	48.6 ± 10.1	**< 0.001**
Race, White (%)	79.3	80.2	0.443
Sex, Female (%)	62.5	79.2	**< 0.001**
HTN, n (%)	750 (30.3)	635 (30.5)	0.005
HLD, n (%)	342 (13.8)	229 (11)	0.004
ALT, n (%)	49.1 ± 50.9 (50.1)	48.1 ± 66.1 (59.1)	0.688
BMI	38.8 ± 7.6	38.0 ± 9.7	0.017
HbA1C	5.5 ± 0.4	5.2 ± 0.7	**<0.001**

Matched Cohort

GLP-1 (n=1537)	MBS (n=1537)	P - value
49.5 ± 11.6	49.6 ± 10.1	0.741
82	82	1
73.8	74.9	0.483
438 (28.5)	445 (29.0)	0.780
174 (11.3)	186 (12.1)	0.501
46.3 ± 43.3 (47.9)	46.5 ± 58.7 (50.8)	0.968
39.2 ± 7.8	38.7 ± 9.9	0.311
5.5 ± 0.5	5.3 ± 0.6	**< 0.001**

*not all-inclusive

DDW STUDY # 2


RESULTS: HEPATIC DECOMPENSATIONS
Percent of Patients (%)
25
20
15
10
5
0
GLP-1
MBS
* p<0.01
22.38
5.79*
6.18
0.72*
12.23
3.97*
13.6
8.98*
5.99
2.99*
Ascites
Hepato-renal syndrome
Hepatic encephalopathy
Esophageal varices
Liver transplantation
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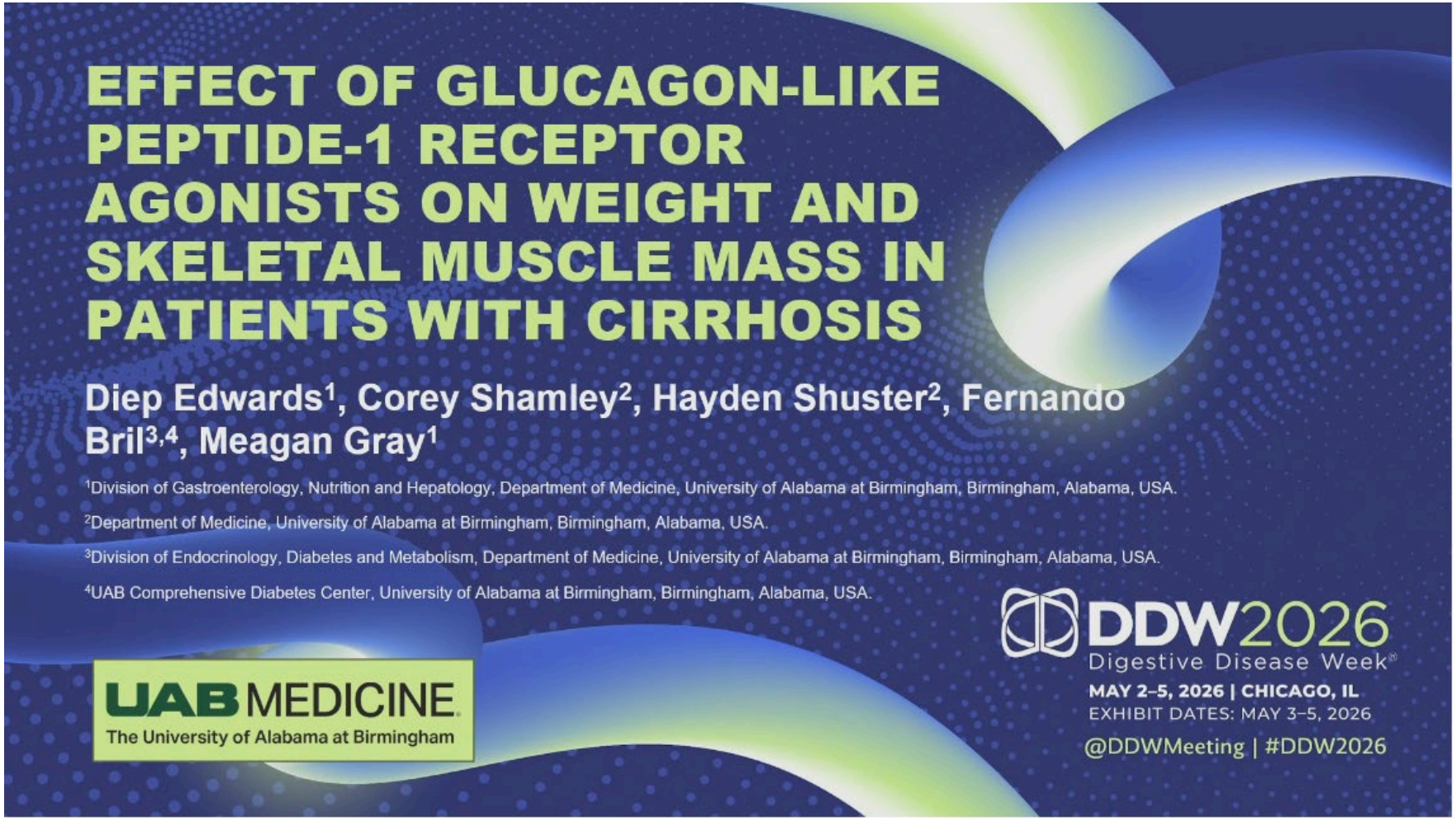
LIMITATIONS

- ICD-10 coding
  - Coding inconsistency
  - Inaccurate coding

- Inability to match for MELD/Child Pugh Score
  - Did match for liver profile (hepatic function panel?)
  - Did not match for individual components of MELD score
  - Matching details not provided & no SMD details to verify the accuracy/quality of match.

- No placebo/untreated group → Study outcomes could be secondary to MBS complications

DDW STUDY # 3


EFFECT OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS ON WEIGHT AND SKELETAL MUSCLE MASS IN PATIENTS WITH CIRRHOSIS
Diep Edwards[1], Corey Shamley[2], Hayden Shuster[2], Fernando Bril[3,4], Meagan Gray[1]
[1]Division of Gastroenterology, Nutrition and Hepatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA.
[2]Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA.
[3]Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA.
[4]UAB Comprehensive Diabetes Center, University of Alabama at Birmingham, Birmingham, Alabama, USA.
UAB MEDICINE
The University of Alabama at Birmingham
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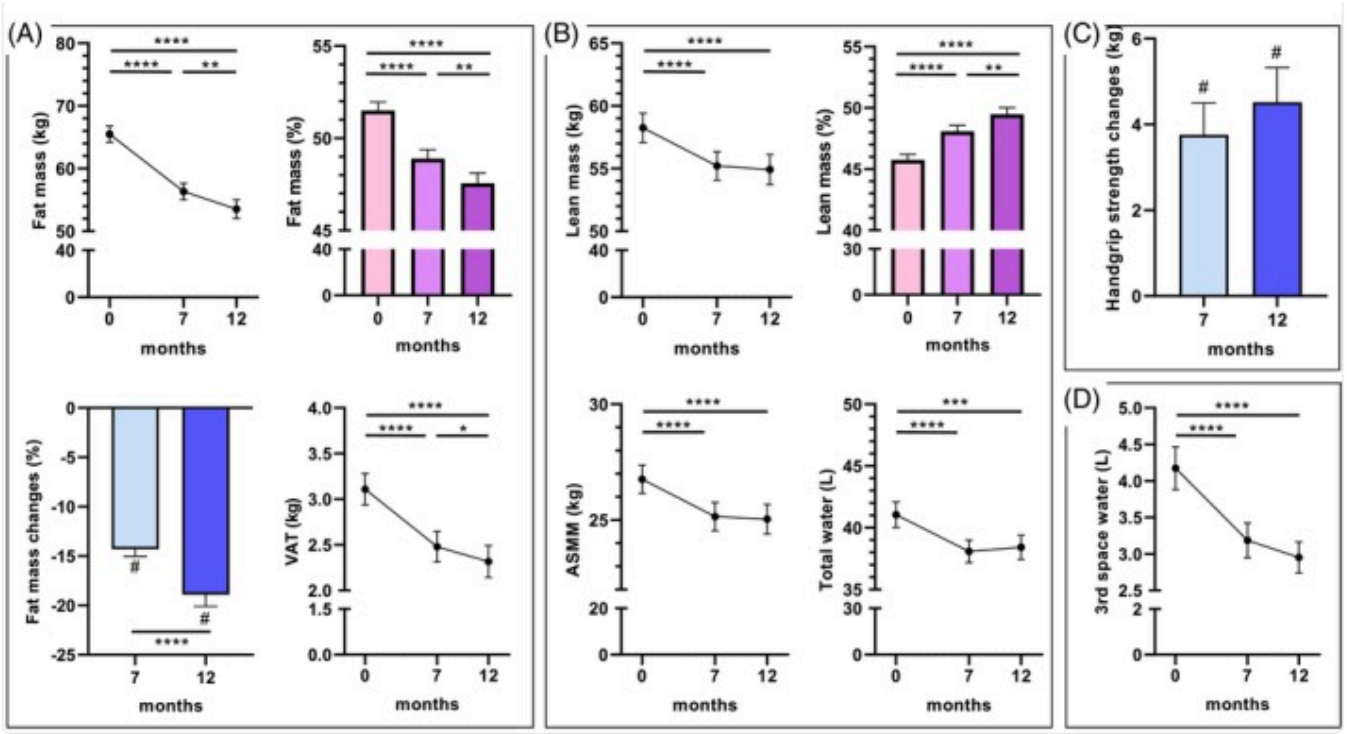
DDW STUDY # 3

- SEMALEAN study
- Design/Duration: Prospective study Feb 2022 – Nov 2024
- N= 115 w Morbid Obesity
- Inclusion criteria –
  - grade 3 obesity (BMI ≥40 kg/m^2) with at least one obesity-related comorbidity (such as OSA, HTN, HLD, CVD)

  AND

  - documented failure of lifestyle interventions (including dietary changes and increased physical activity).



* 91 % had hepatic steatosis , 38% had Type 2 DM

Alissou, Mathieu et al. “Impact of Semaglutide on fat mass, lean mass and muscle function in patients with obesity: The SEMALEAN study.” *Diabetes, obesity & metabolism* vol. 28,1 (2026): 112-121. doi:10.1111/dom.70141

DDW STUDY # 3

- AIM: To study the effect of GLP-1 RA over time on body weight and whole-body skeletal muscle mass in patients with compensated and decompensated cirrhosis.
- DESIGN: Single Center Retrospective Cohort
- Duration: October 2016 – October 2025
- Inclusion: Patients with cirrhosis (compensated and decompensated) with 2 CT scans ≥ 6 months apart
- Excluded: No valid interval CT imaging before and after GLP-1 RA use.
- Measured: Weight and muscle mass changes in patients on GLP-1 RA with non users at 2 time points.
- Skeletal muscle index (SMI cm^2/m^2) used as proxy for total muscle mass.

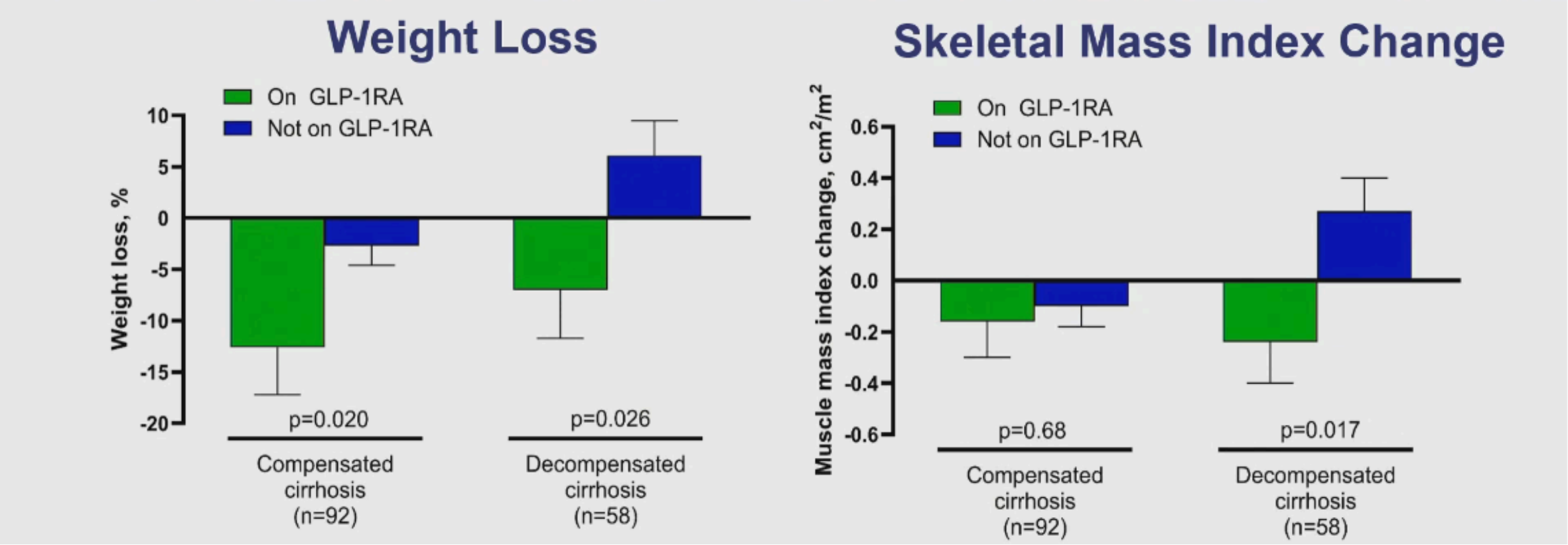
DDW STUDY # 3

150
patients

57
GLP-1RA users
38% of cohort

	Compensated Cirrhosis		Decompensated Cirrhosis	
	GLP1 RA (n=30)	No GLP1 RA (n=62)	GLP1 RA (n=27)	No GLP1 RA (n=31)
Age (years, M ± SD)	59.07 ± 11.46	58.35 ± 13.02	57.7 ± 9.91	59 ± 10.16
Sex (Female, %)	53.3	59.7	37.0	41.9
Race (%)				
Non-Hispanic White	86.7	80.7	81.5	93.6
Non-Hispanic Black	13.3	12.9	11.1	0
Other	0.0	6.4	7.4	6.4
MELD 3.0 score	9.3 ± 2.87	10.16 ± 3.5	13.9 ± 4.48	14.3 ± 5.61
T2DM (%)	83.3	37.1	88.9	32.3
BMI (kg/m^2)	35.0 ± 5.6	30.8 ± 8.4	35.2 ± 8.8	27.1 ± 7.7
Imaging interval (months, M ± SD)	23.67 ± 18.42	12.65 ± 5.72	14.37 ± 8.71	11.42 ± 2.69

DDW STUDY # 3

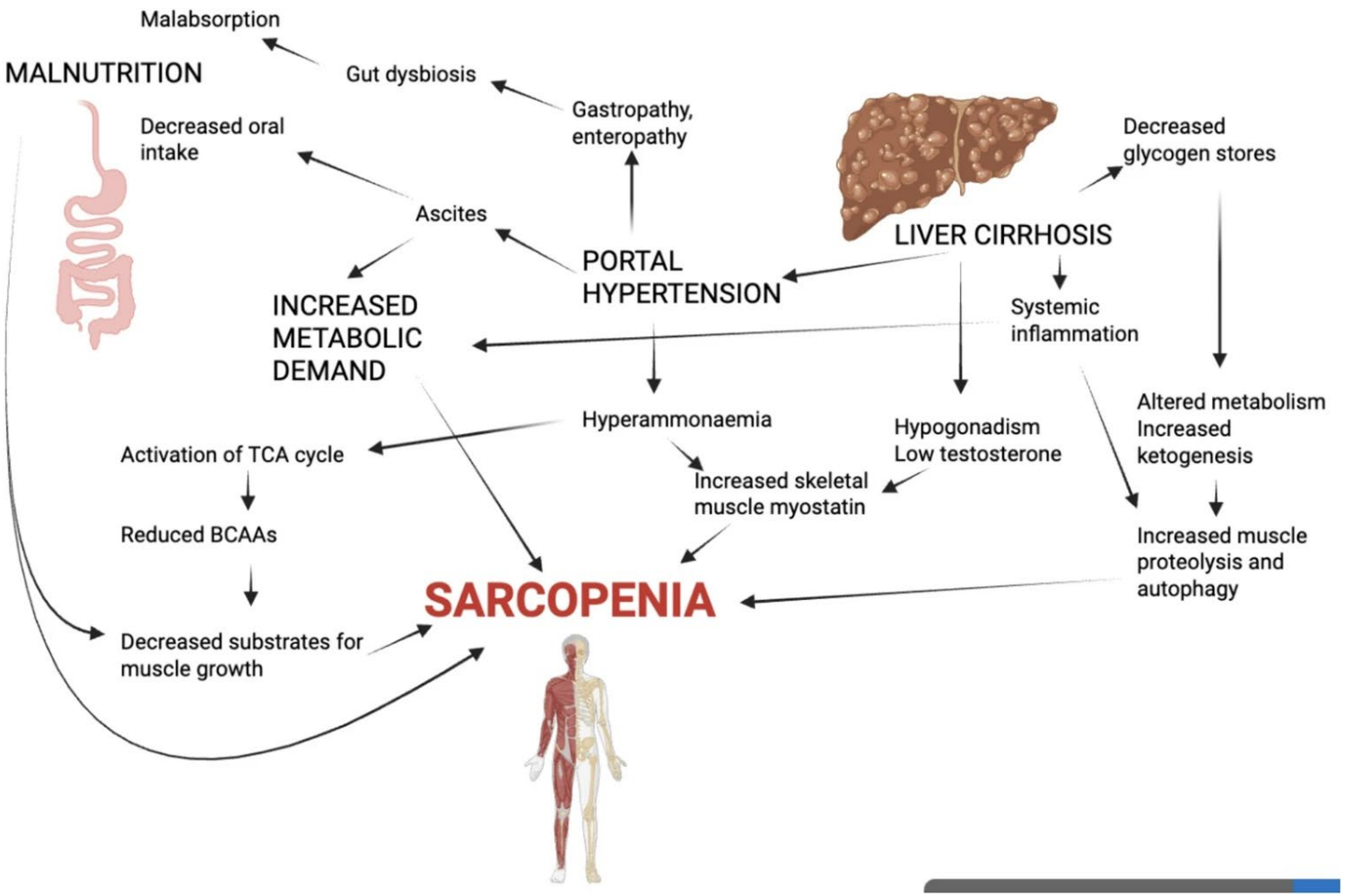

Weight Loss
On GLP-1RA
Not on GLP-1RA
Weight loss, %
10
5
0
-5
-10
-15
-20
p=0.020
p=0.026
Compensated cirrhosis (n=92)
Decompensated cirrhosis (n=58)
Skeletal Mass Index Change
On GLP-1RA
Not on GLP-1RA
Muscle mass index change, cm²/m²
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
p=0.68
p=0.017
Compensated cirrhosis (n=92)
Decompensated cirrhosis (n=58)

DDW STUDY # 3

Weight loss was associated with more pronounced muscle loss in those with decompensated cirrhosis

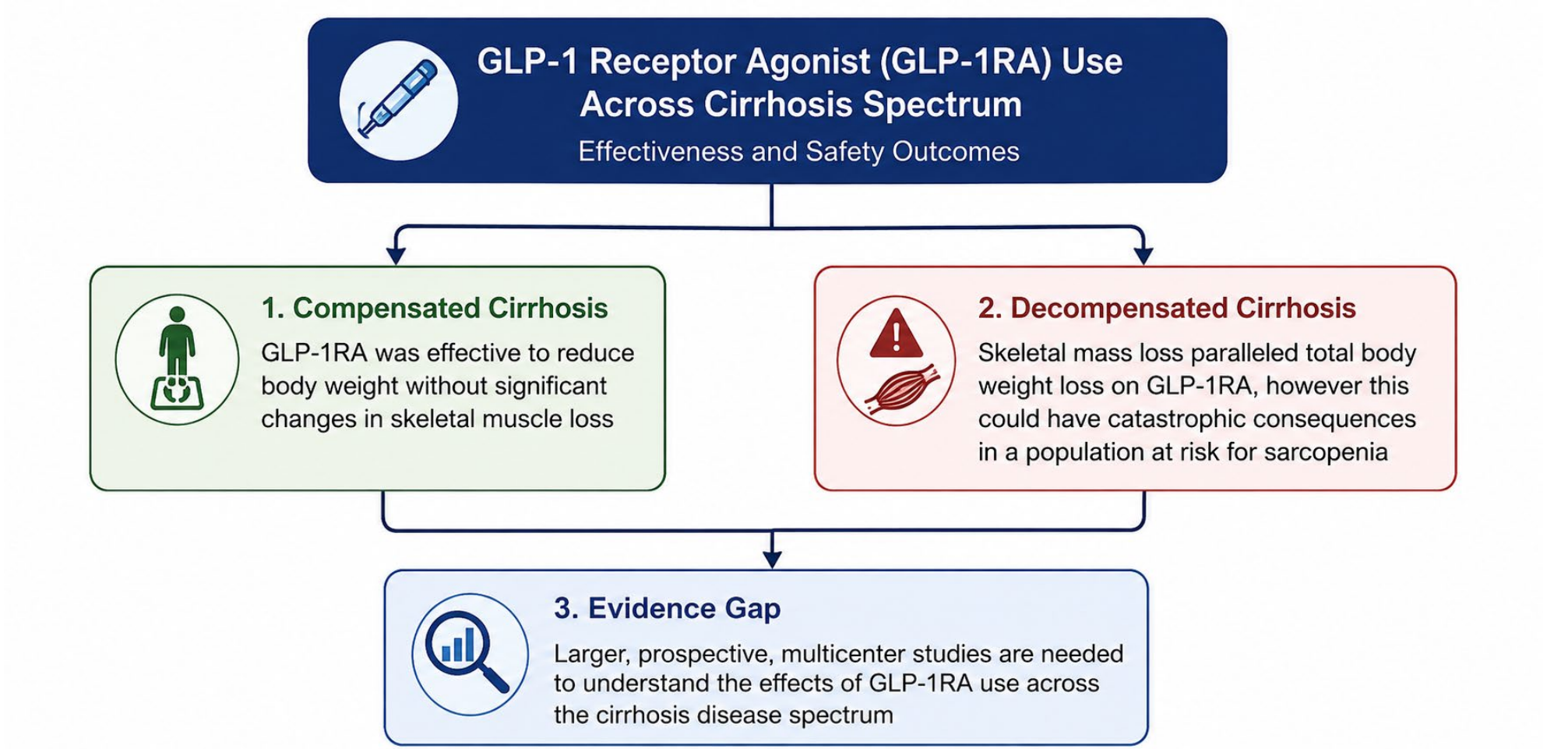
0.	β	*p*-value
Compensated Cirrhosis		
No GLP-1RA	0.0167	0.091
GLP-1RA	0.0240	0.072
Decompensated Cirrhosis		
No GLP-1RA	0.0190	0.124
GLP-1RA	0.0553	**<0.001**

DDW STUDY # 3



Tan, K., Hey, P., Vaz, K. *et al.* Testosterone Supplementation and Other Pharmacotherapy for Sarcopenia in Cirrhosis: Evaluation, Treatment and Considerations. *Curr Hepatology Rep* **25**, 7 (2026). https://doi.org/10.1007/s11901-026-00723-z

DDW STUDY # 3


GLP-1 Receptor Agonist (GLP-1RA) Use Across Cirrhosis Spectrum
Effectiveness and Safety Outcomes
1. Compensated Cirrhosis
GLP-1RA was effective to reduce body weight without significant changes in skeletal muscle loss
2. Decompensated Cirrhosis
Skeletal mass loss paralleled total body weight loss on GLP-1RA, however this could have catastrophic consequences in a population at risk for sarcopenia
3. Evidence Gap
Larger, prospective, multicenter studies are needed to understand the effects of GLP-1RA use across the cirrhosis disease spectrum

LIMITATIONS

- Single center study with modest sample size
- Etiology of cirrhosis not ascertained, perhaps MASLD. Can’t extrapolate to other etiologies
- Sub-analysis not done (Gender based, Race based etc.)
- Baseline platelet count for compensated cirrhosis not available. Did not diff between patients with Portal Hypertension and those without.
- Gold standard to assess lean mass is with DEXA, Bio-impedance, the investigators used SMI as proxy.

DDW STUDY #4

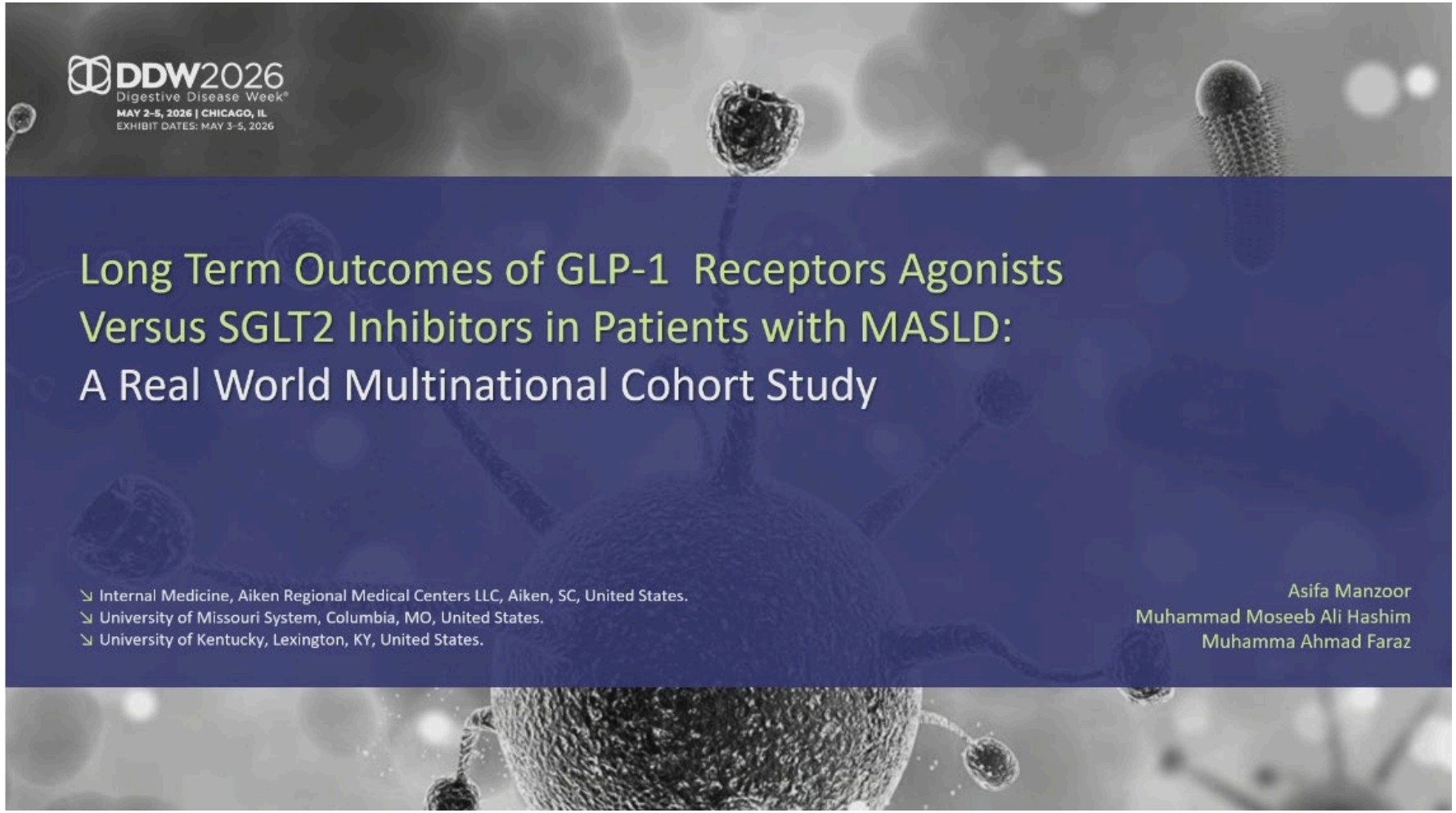

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EXHIBIT DATES: MAY 3–5, 2026
Long Term Outcomes of GLP-1 Receptors Agonists Versus SGLT2 Inhibitors in Patients with MASLD: A Real World Multinational Cohort Study
↘ Internal Medicine, Aiken Regional Medical Centers LLC, Aiken, SC, United States.
↘ University of Missouri System, Columbia, MO, United States.
↘ University of Kentucky, Lexington, KY, United States.
Asifa Manzoor
Muhammad Moseeb Ali Hashim
Muhamma Ahmad Faraz

DDW STUDY #4

- Study Design: Restrospective database study
- Data Source: Trinetx Global Collaborative Network
- Population: MASLD
- Exposure: Prescribed GLP-1 RA vs SLGT-2 inhibitors.
- Outcomes: Cirrhosis complications and liver transplantation

DDW STUDY #4


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Baseline Characteristics After Matching
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
56.3
56.6
62.30%
61.90%
68.70%
68.40%
79.70%
79.50%
76.10%
75.90%
60.00%
60.10%
11.10%
11.30%
21.80%
22.80%
Mean age
Female sex
BMI ≥30 kg/m²
Type 2 diabetes
Hypertension
Dyslipidemia
Chronic kidney disease
ASCVD
GLP-1 RA
SGLT2i

DDW STUDY #4

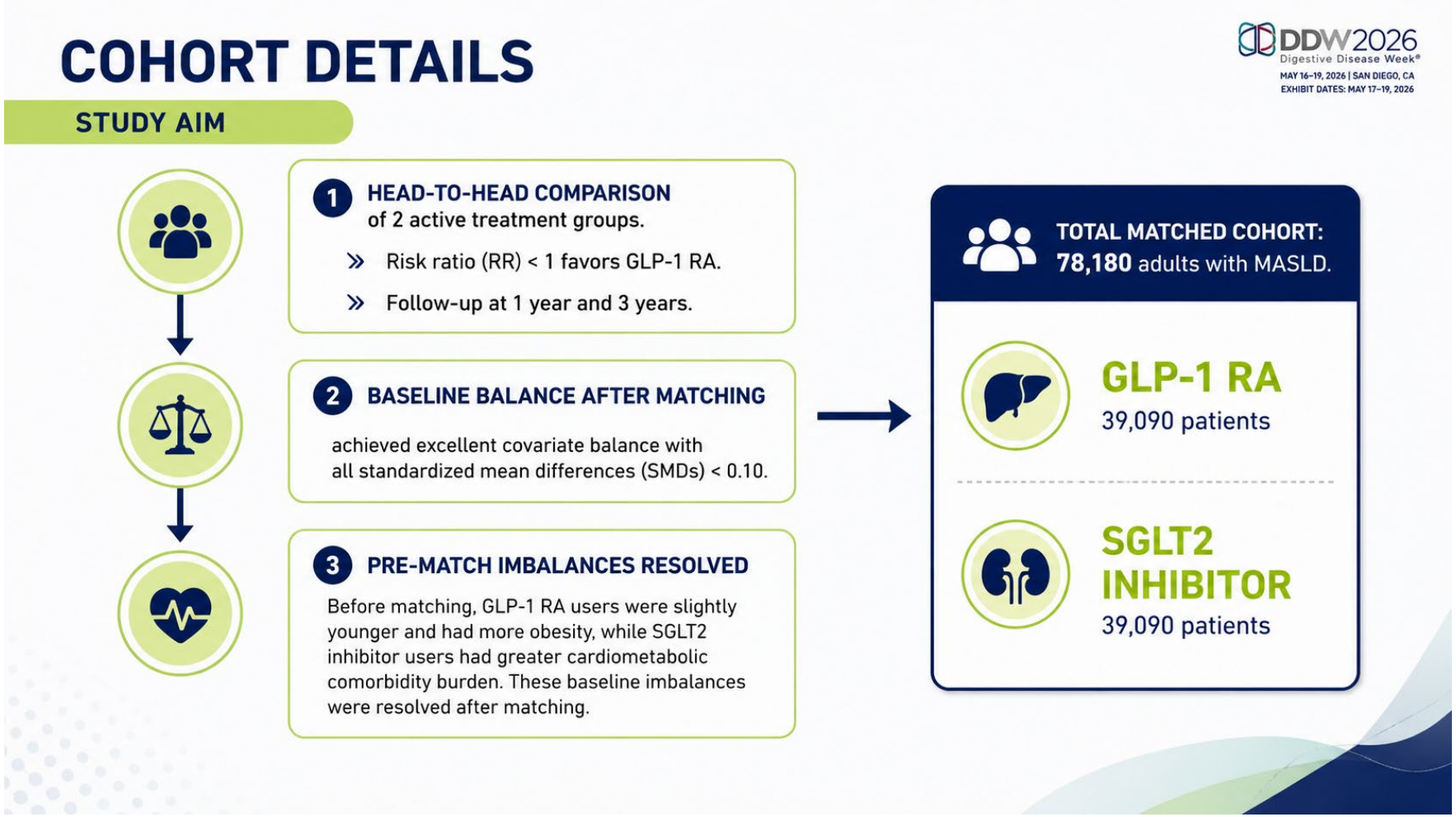
COHORT DETAILS
DDW2026
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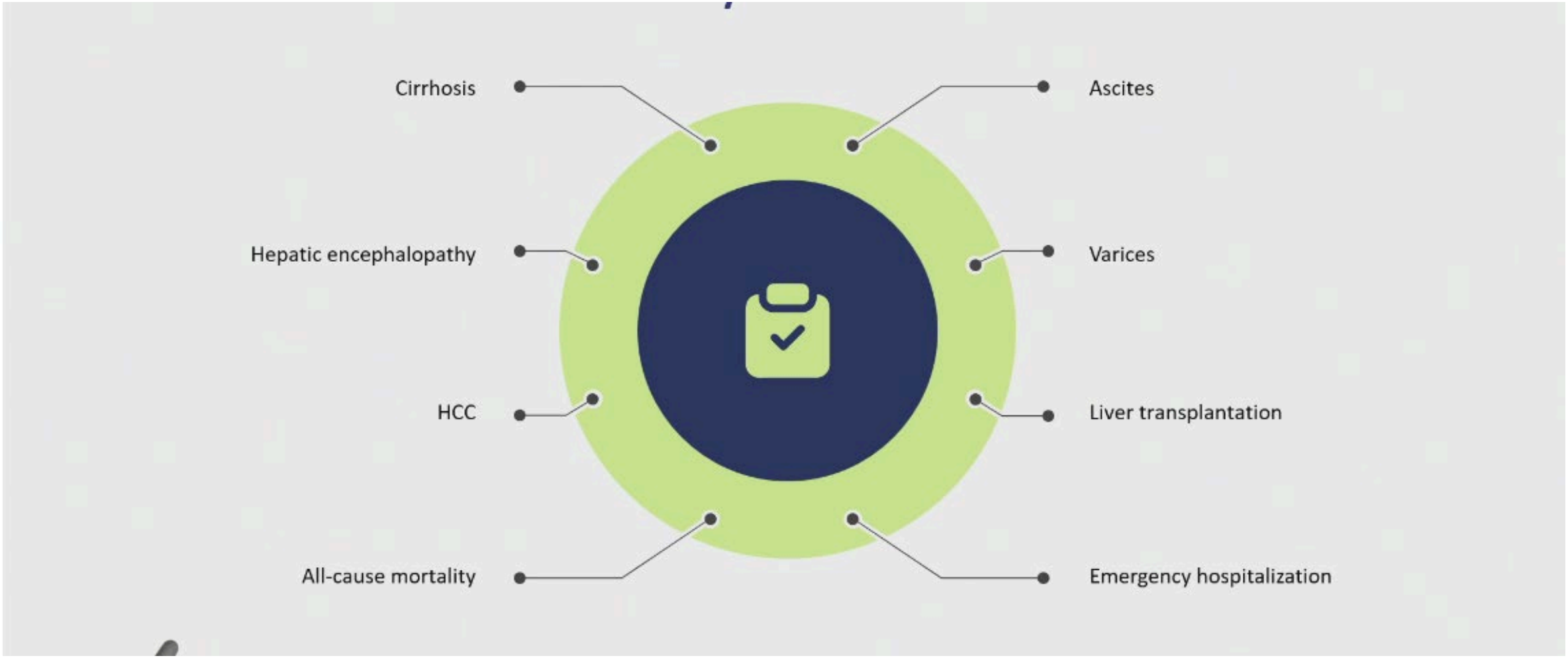
EXHIBIT DATES: MAY 17–19, 2026
STUDY AIM
1 HEAD-TO-HEAD COMPARISON
of 2 active treatment groups.
» Risk ratio (RR) < 1 favors GLP-1 RA.
» Follow-up at 1 year and 3 years.
2 BASELINE BALANCE AFTER MATCHING
achieved excellent covariate balance with all standardized mean differences (SMDs) < 0.10.
3 PRE-MATCH IMBALANCES RESOLVED
Before matching, GLP-1 RA users were slightly younger and had more obesity, while SGLT2 inhibitor users had greater cardiometabolic comorbidity burden. These baseline imbalances were resolved after matching.
TOTAL MATCHED COHORT:
78,180 adults with MASLD.
GLP-1 RA
39,090 patients
SGLT2 INHIBITOR
39,090 patients

DDW STUDY #4


Cirrhosis
Ascites
Hepatic encephalopathy
Varices
HCC
Liver transplantation
All-cause mortality
Emergency hospitalization

DDW STUDY #4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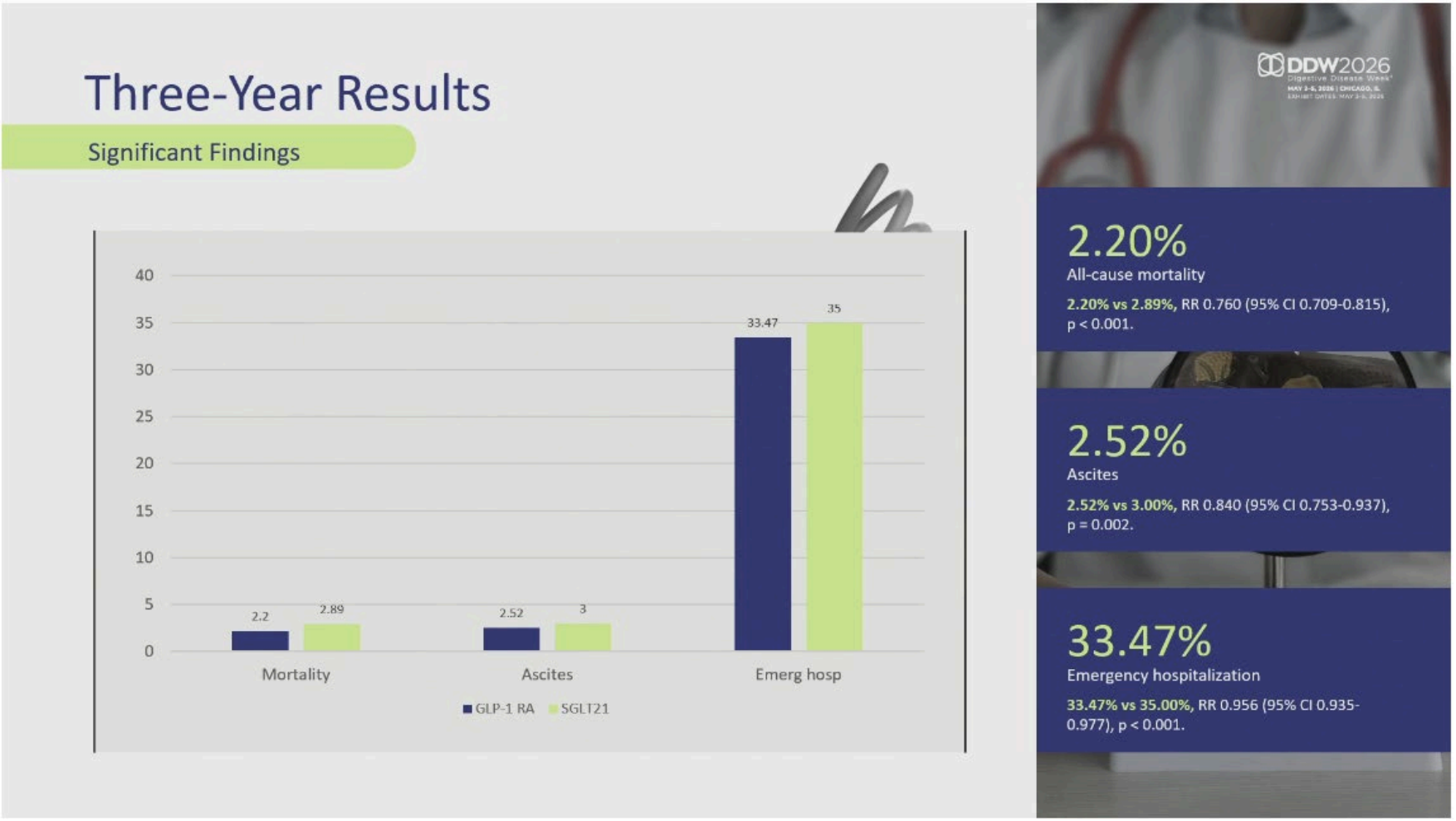
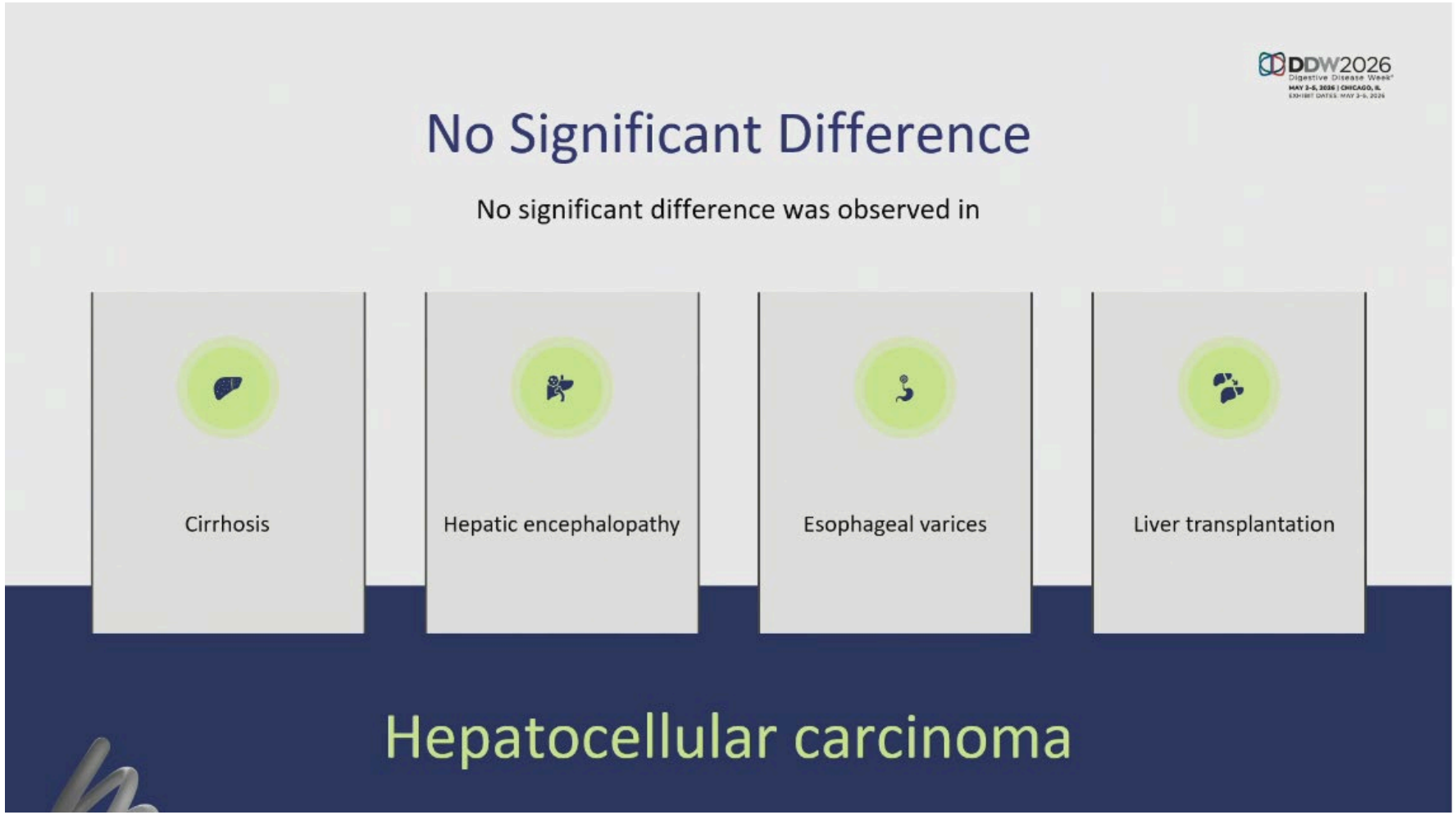
One-Year Results
Significant Findings
0.84%
All-cause mortality
0.84% vs 1.21%, RR 0.693 (95% CI 0.623-0.771), p < 0.001.
1.36%
Ascites
1.36% vs 1.79%, RR 0.758 (95% CI 0.647-0.888), p = 0.001.
13.72%
Emergency hospitalization
13.72% vs 14.91%, RR 0.920 (95% CI 0.894-0.947), p < 0.001.
1-year absolute risks (%)
16
14
12
10
8
6
4
2
0
0.84
1.21
1.36
1.79
13.72
14.91
Mortality
Ascites
Emerg hosp
GLP-1 RA
SGLT21

DDW STUDY #4


Three-Year Results
Significant Findings
40
35
30
25
20
15
10
5
0
2.2
2.89
2.52
3
33.47
35
Mortality
Ascites
Emerg hosp
GLP-1 RA
SGLT21
DDW2026
2.20%
All-cause mortality
2.20% vs 2.89%, RR 0.760 (95% CI 0.709-0.815), p < 0.001.
2.52%
Ascites
2.52% vs 3.00%, RR 0.840 (95% CI 0.753-0.937), p = 0.002.
33.47%
Emergency hospitalization
33.47% vs 35.00%, RR 0.956 (95% CI 0.935-0.977), p < 0.001.

DDW STUDY #4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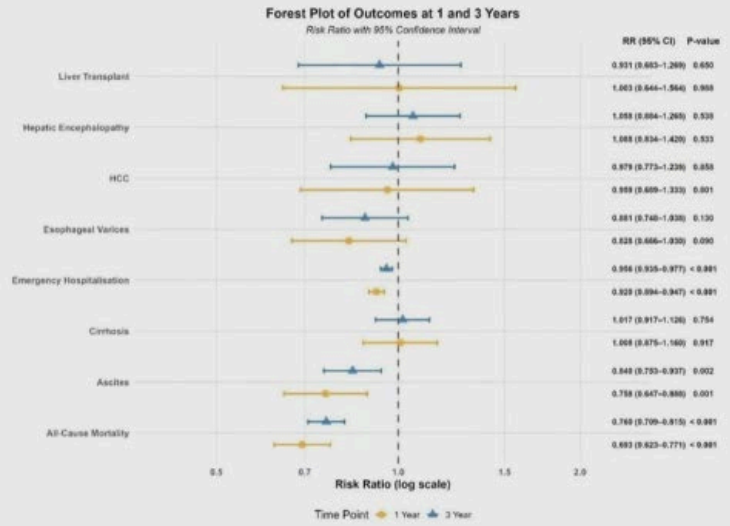
No Significant Difference
No significant difference was observed in
Cirrhosis
Hepatic encephalopathy
Esophageal varices
Liver transplantation
Hepatocellular carcinoma

DDW STUDY #4

Forest Plot Analysis

Risk Ratios At 1 And 3 Years



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01 The forest plot displayed risk ratios with 95% confidence intervals for major outcomes at 1 year and 3 years.

02 The vertical reference line at RR = 1.0 represented no difference.

03 Estimates to the left of 1 favored GLP-1 RA therapy.

At both 1 and 3 years, the forest plot showed benefit with GLP-1 RA for:

- All-cause mortality
- Ascites
- Emergency hospitalization

For cirrhosis, HCC, hepatic encephalopathy, esophageal varices, and liver transplantation, confidence intervals crossed 1.

DDW STUDY #4


DDW2026
Digestive Disease Week
Clinical Implications
GLP-1 RAs were associated with lower all-cause mortality, ascites, and emergency hospitalization.
Benefits were seen by 1 year and persisted through 3 years.
No significant difference was seen in cirrhosis, HCC, hepatic encephalopathy, and esophageal varices.
The absence of short-term differences in cirrhosis or HCC should not be interpreted as absence of disease modification.
Future studies should include longer follow-up and better fibrosis phenotyping.

LIMITATIONS

- Retrospective cohort
- Poorly defined cohorts
    - Disease not stratified by fibrosis stage or steatosis stage
    - ICD-10 code definitions not provided
    - Other liver diseases adequately excluded or not?

- Dose of medicines not defined
- Placebo comparator not present

Incretin-Based Therapies in MASLD/MASH: Key Clinical Trials

GLP-1 receptor agonists and dual/triple agonists targeting GIP and glucagon pathways

Agent	Target	Phase / Population	Duration	Key efficacy signal	Clinical takeaway
Liraglutide	GLP-1 RA	Phase 2 · MASH	48 wk	MASH resolution **39%** vs **9%** placebo; fibrosis improvement **26%** vs **14%**	First proof-of-concept for GLP-1 therapy in MASH
Semaglutide 2.4 mg	GLP-1 RA	Phase 3 · MASH with F2-F3 fibrosis	72 wk	MASH resolution **62.9%** vs **34.3%**; >=1-stage fibrosis improvement **36.8%** vs **22.4%**	Strongest late-phase GLP-1 histologic evidence
Tirzepatide	GLP-1/GIP	Phase 2 · MASH with F2-F3 fibrosis	52 wk	MASH resolution **44-62%** vs **10%** placebo; fibrosis improvement **51-55%** vs **30%**	Dual agonism shows robust MASH resolution and fibrosis benefit
Survodutide	GLP-1/Glucagon	Phase 2 · MASH with F1-F3 fibrosis	48 wk	MASH response up to **62%** vs **14%**; fibrosis improvement **34-36%** vs **22%**	Strong histologic efficacy with glucagon co-agonism
Pemvidutide	GLP-1/Glucagon	Phase 2b · MASH with F2-F3 fibrosis	24 wk	MASH resolution **52-58%** vs **20%**; fibrosis improvement **33-36%** vs **28%**	Promising early histologic response
Efinopegdutide	GLP-1/Glucagon	Phase 2a · MASLD	24 wk	Liver fat reduction **72.7%** vs **42.3%** with semaglutide	Potent hepatic fat reduction; histologic confirmation needed
Retatrutide	GLP-1/GIP/Glucagon	Phase 2 · Obesity + MASLD	48 wk	Liver fat reduction **81-82%** at higher doses	Triple agonism shows profound hepatic fat reduction; histology pending

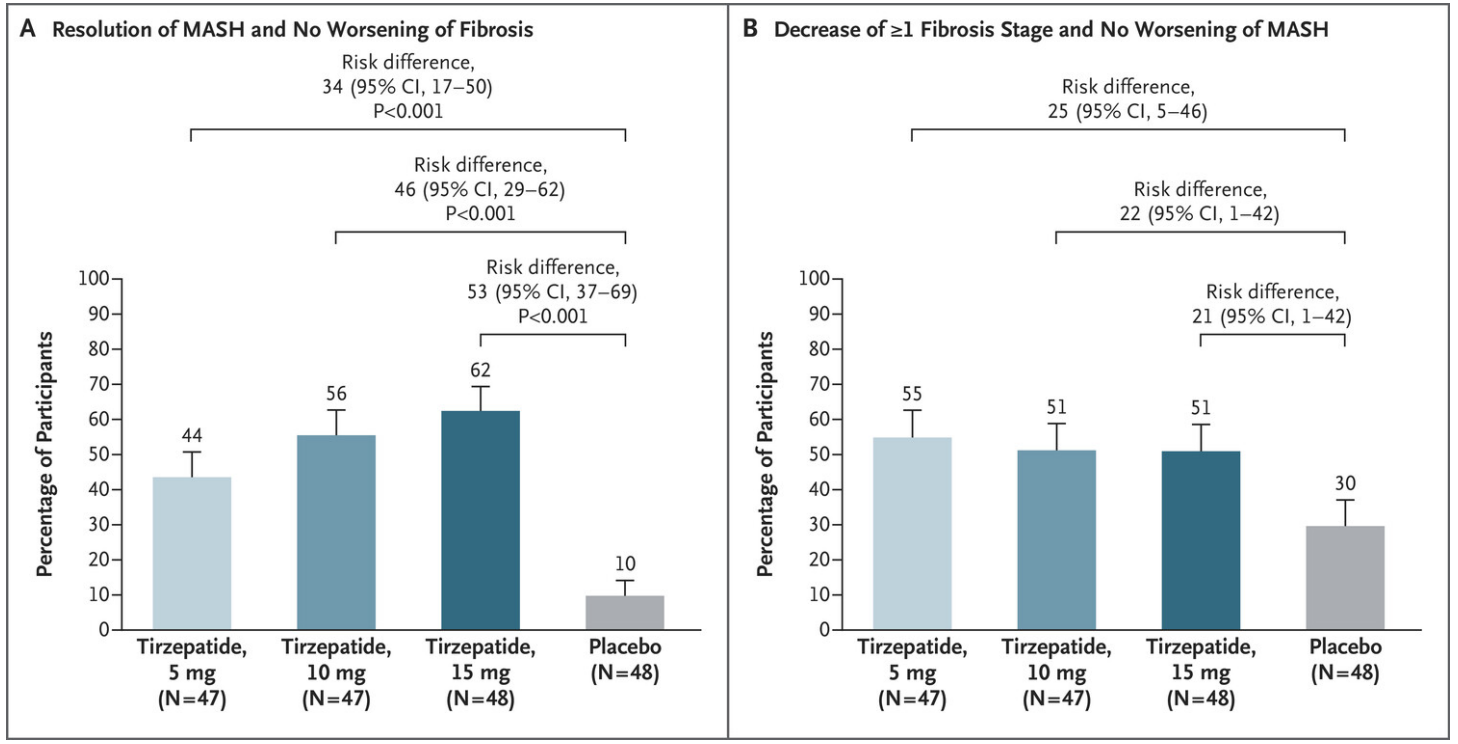
Visual message: GLP-1 proof-of-concept -> dual agonist histologic efficacy -> triple agonist metabolic potency.

Class-wide tolerability: GI adverse effects predominate (nausea, diarrhea, constipation).

TIRZEPETIDE – SYNERGY NASH

- Phase 2 study in adults with biopsy proven MASH with stage 2/3 fibrosis
- 196 adults with overweight/obesity (157 patients with biopsy proved MASH)
- Hepatic steatosis reduction showed direct correlation with higher doses of Tirzepetide at 52 weeks.

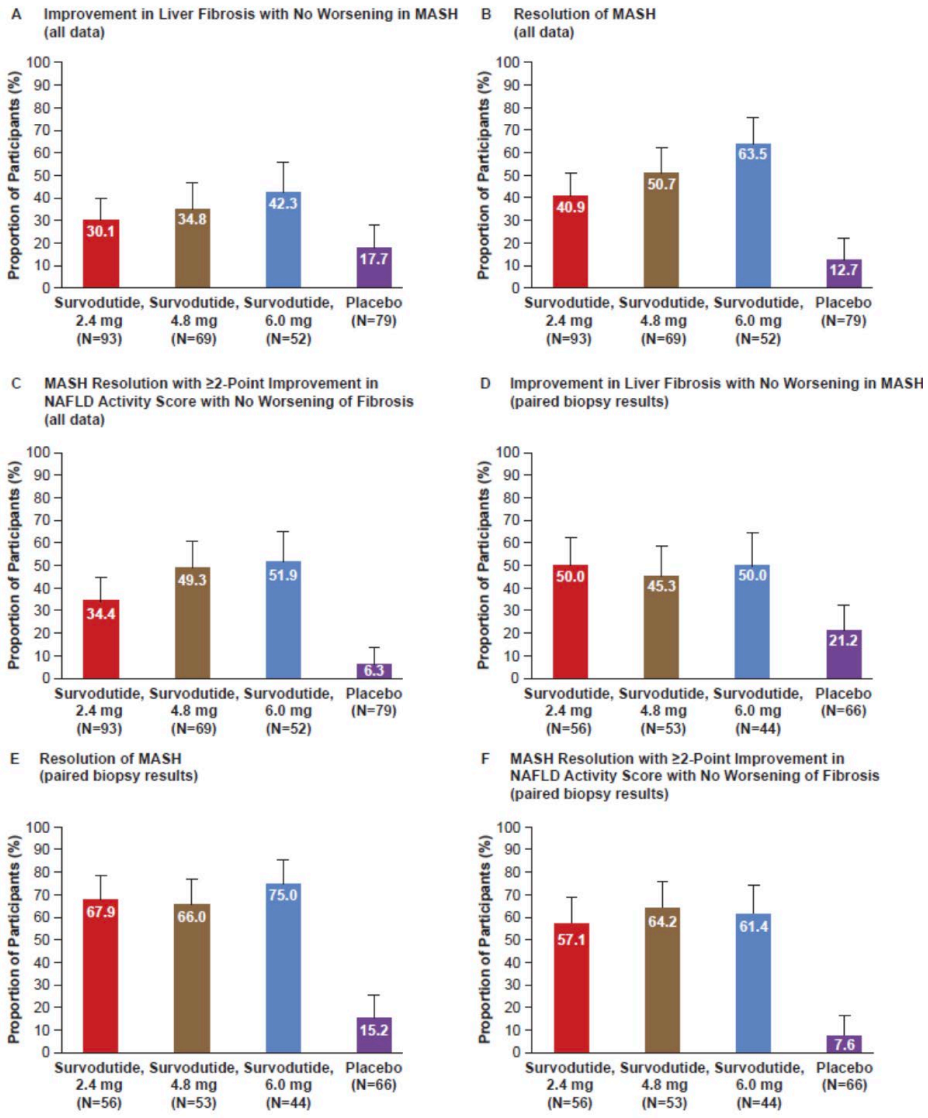
AE in >15%	Placebo (%) n=48	5 mg (%) n=47	10 mg (%) n=47	15 mg (%) n=48
Nausea	12	36	34	44
Diarrhea	23	32	36	27
Decreased Appetite	2	19	21	23
Constipation	6	23	19	15
COVID-19	8	11	13	19
AE related discontinuation	4	4	0	8



Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis. *N Engl J Med*. 2024;391(4):299-310. doi:10.1056/NEJMoa2401943

SURVODUTIDE IN MASH – PHASE IIB STUDY

- Key findings
- Glucagon/GLP-1 dual agonist, once weekly for 48 weeks
- Liver fat reduction ≥30%: 63% (2.4 mg), 67% (4.8 mg), 57% (6.0 mg) vs 14% placebo
- Gastrointestinal events were the most common adverse events and increased with dose



A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

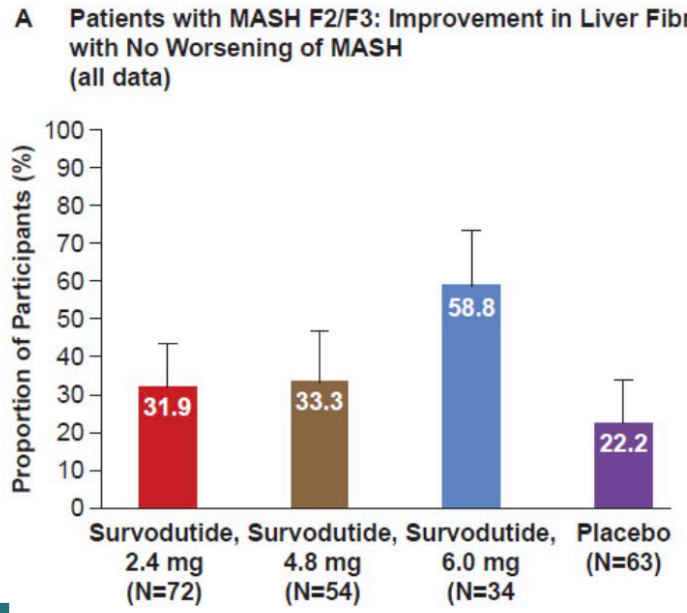
Authors: Arun J. Sanyal, M.D., Pierre Bedossa, M.D., Ph.D., Mandy Fraessdorf, Ph.D., Guy W. Neff, M.D., Eric Lawitz, M.D., Elisabetta Bugianesi, M.D., Quentin M. Anstee, Ph.D., F.R.C.P., +8 , for the 1404-0043 Trial Investigators* Author Info & Affiliations

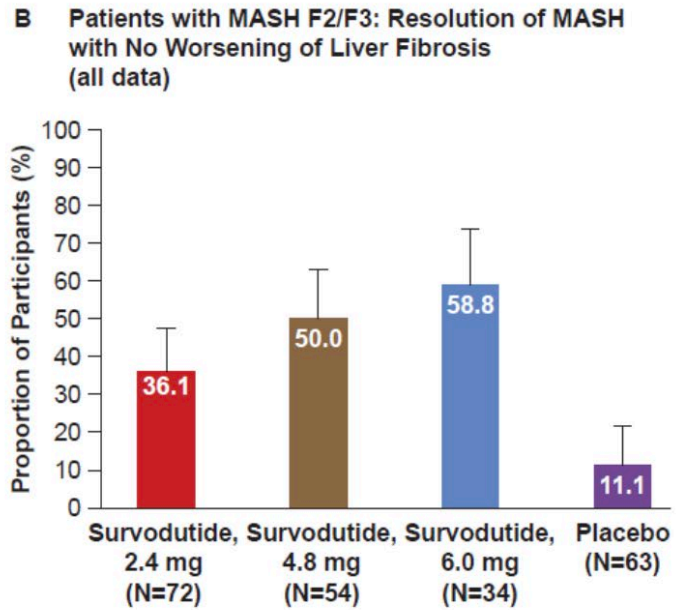
SURVODUTIDE IN MASH – PHASE IIB STUDY

Post hoc analysis – hepatic fat response and safety

Key findings

- Glucagon/GLP-1 dual agonist, once weekly for 48 weeks
- Liver fat reduction ≥30%: 63% (2.4 mg), 67% (4.8 mg), 57% (6.0 mg) vs 14% placebo
- Gastrointestinal events were the most common adverse events and increased with dose





Adverse Events 15%+	Survodutide (total)	Placebo	Adverse Events 15%+
Nausea	66	23	Nausea
Diarrhea	49	23	Diarrhea
Vomiting	41	4	Vomiting
Decreased Appetite	17	9	Decreased Appetite
Fatigue	17	8	Fatigue
Treatment Discontinuation due to AE	20	3	Treatment Discontinuation due to AE

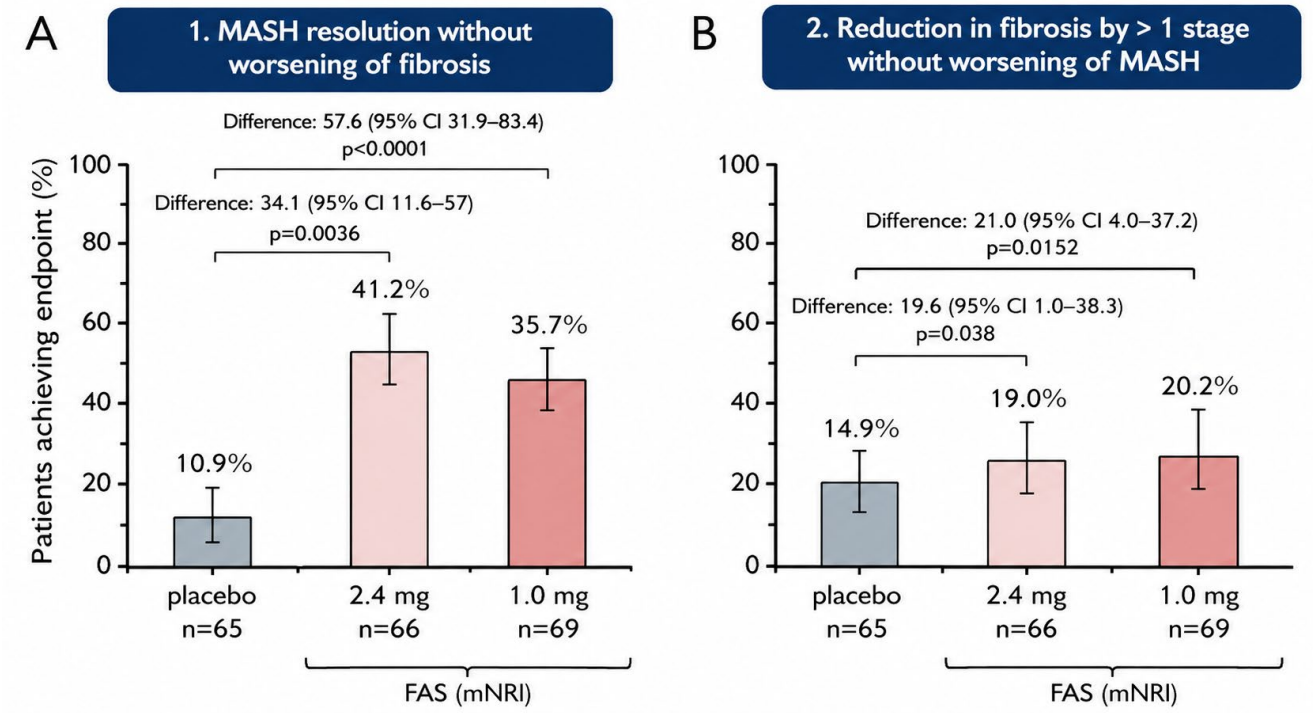
Adverse event rates to be completed from the trial safety table.

A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

Authors: Arun J. Sanyal, M.D., Pierre Bedossa, M.D., Ph.D., Mandy Fraessdorf, Ph.D., Guy W. Neff, M.D., Eric Lawitz, M.D., Elisabetta Bugianesi, M.D., Quentin M. Anstee, Ph.D., F.R.C.P., +8 , for the 1404-0043 Trial Investigators* Author Info & Affiliations

PEMVIDUTIDE FOR F2/F3 MASH – PHASE IIB STUDY

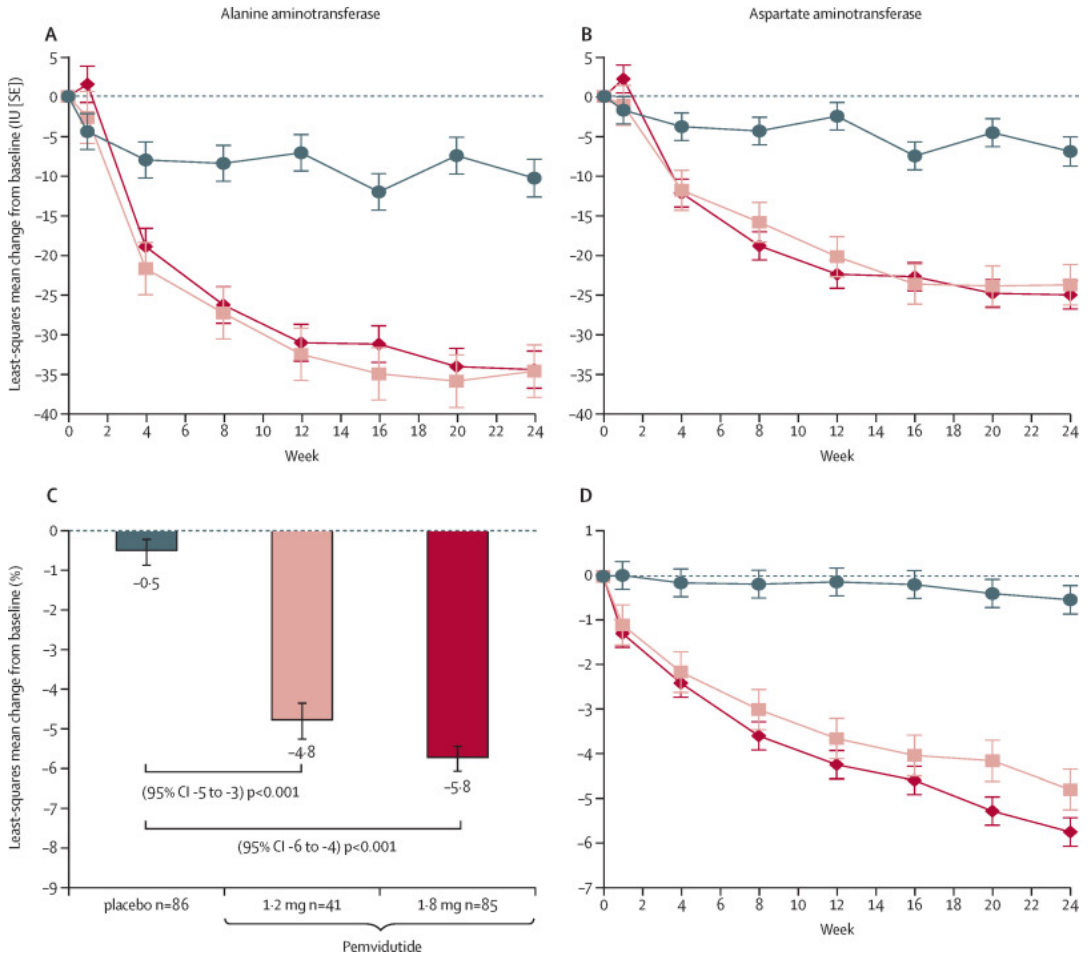
- Phase 2 study in adults with biopsy proven MASH with stage 2/3 fibrosis
- Mechanism: Dual GLP/Glucagon agonist
- 1557 patients screened → 212 randomly assigned
  - Placebo: 86%
  - Pemvidutide 1.2 mg: 48
  - Pemvidutide 1.8 mg: 85
- Duration: 24 weeks
- Endpoint
  - Primary:
    - Biopsy proven MASH resolution with no worsening fibrosis; and
    - Fibrosis reduction > 1 stage without worsening of MASH (Not met)
  - Secondary: achieving both MASH resolution and at least a one-stage improvement in liver fibrosis, relative change from baseline in liver fat by MRI-PDFF, the proportion of patients achieving 30%, 40%, or 50% reduction in liver fat content from baseline per MRI-PDFF, and normalization of liver fat content (≤5%) per MRI-PDFF



PEMVIDUTIDE FOR F2/F3 MASH – PHASE IIB STUDY

Secondary endpoint	Placebo	Pemvidutide 1.2 mg	Pemvidutide 1.8 mg
NAS change	−1.3	−2.9*	−2.6*
Liver fat, relative change	−11.4%	−52.0%*	−57.7%*
≥50% liver fat reduction	11%	62%*	72%*
ALT change	−10.3 IU/L	−34.6*	−34.4*
ELF score change	+0.03	−0.6*	−0.5*
Liver stiffness change	−0.7 kPa	−3.7*	−2.2†
FIB-4 change	−0.06	−0.34*	−0.31*
Body weight change	−0.5%	−4.8%*	−5.8%*

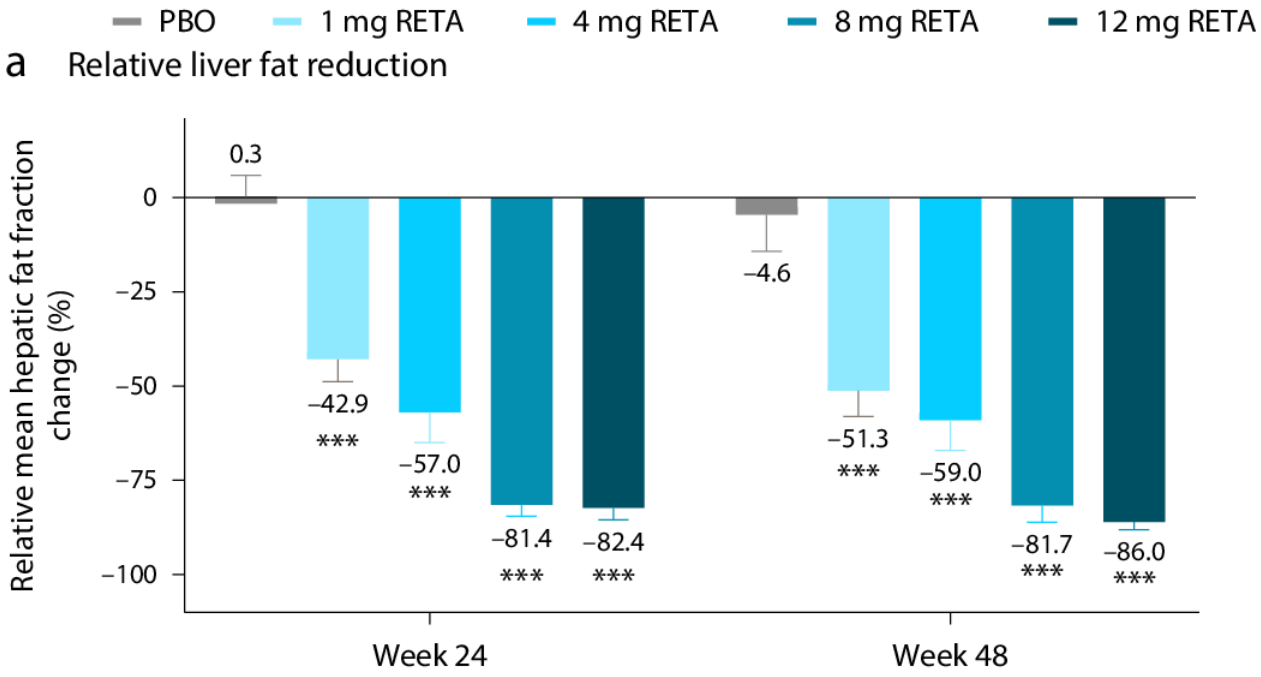
% of patients	PBO (n=86)	1.2 mg (n=41)	1.8mg (n=85)
Weight Loss (mean TBWL)	0.5	4.8	5.8
Discontinuation due to AE	2	0	1



RETRATRUTIDE IN MASLD

- GLP-1/GIP/Glucagon agonist
- Obesity data with 338 patients treated for 48 weeks from 2023 study.
- Phase 2 study (subset) evaluated 98 patients.
- MRI-PDFF to evaluate Hepatic fat reduction
  - 70% patients → Hepatic fat reduction 30%, 40% patients → Hepatic fat reduction 50%.

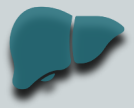
No changes in fibrosis based biomarkers were noted



Sanyal, Arun J et al. "Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial." *Nature medicine* vol. 30,7 (2024): 2037-2048. doi:10.1038/s41591-024-03018-2

WHAT DID DDW 2026 TEACH US?

GLP-1 therapy is associated with favorable real world outcomes in MASLD populations.



Benefits might extend into compensated cirrhosis, but evidence in decompensated cirrhosis remains questionable.

Weight loss in decompensated cirrhosis → sarcopenia concern.

The Incretin Arms Race

More receptors → more metabolic power? The antifibrotic answer is still evolving.

GLP-1 → GLP-1/GIP → GLP-1/GCG → GLP-1/GIP/GCG

Strategy	Agent	Target	Key liver signal	Clinical readout
Single agonist	**Semaglutide**	GLP-1	MASH resolution + fibrosis benefit; FDA-approved class signal	Benchmark liver-directed incretin
Dual incretin	**Tirzepatide**	GLP-1 + GIP	MASH resolution 44–62%; fibrosis improvement 51–55%	Strongest biopsy-based dual incretin signal
Dual incretin–glucagon	**Survodutide**	GLP-1 + GCG	MASH resolution up to 63.5%; fibrosis improvement up to 42.3%	Adds hepatic lipid oxidation / energy expenditure
Dual incretin–glucagon	**Pemvidutide**	GLP-1 + GCG	Marked liver-fat reduction; fibrosis endpoint less convincing	Potent hepatic-fat signal; longer data needed
Triple agonist	**Retatrutide**	GLP-1 + GIP + GCG	Liver-fat reduction >80% at higher doses; histology pending	Maximum metabolic potency; MASH outcomes pending

Key message

Increasing metabolic potency does not guarantee incremental antifibrotic efficacy.

MASH IN THE INCRETIN ERA – TAKE HOME MESSAGES

01

GLP-1 has crossed over

From metabolic treatment to liver-directed therapy in MASH.

02

DDW 2026 broadened the signal

Real-world data suggest benefits may extend to clinical outcomes — not just histology.

03

Cirrhosis requires nuance

Compensated disease may benefit, but decompensated cirrhosis raises sarcopenia and safety concerns.

04

The next proof is durability

Dual and triple agonists are potent; the field still needs durable fibrosis and outcomes data.

Bottom line

Incretin therapy is reshaping MASH care — but the next frontier is proving antifibrotic durability, clinical outcome benefit, and muscle-preserving safety.