USZ Universitäts Spital Zürich

Highlights 2024: Hepatologie

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Gastro Highlights 2024, Zürich – November 23, 2024

Potentielle Interessenskonflikte

Subjektive Auswahl an Publikationen aus 2024

• Consultant / Advisor: Abbvie, Advanz, Alentis, AlphaSigma, AstraZenca, Avior, Bayer, BMS, CymaBay, Escient, Falk, Gilead, GSK, Guidepoint, Intercept, Ipsen, Mirum, MSD, Novo Nordisk, Roche, Takeda

• Speaker: Abbvie, Advanz, AOP Orphan, Bayer, BMS, CymaBay, Falk, Gilead, GSK, Intercept, Ipsen, Johnson&Johnson, Medscape, Mirum, MSD, Newbridge, Novartis, Roche, Vertex Viofor.

• Unrestricted grants: Gilead, Intercept

Steatosis hepatis

KEINE NASH, NAFLD oder MALFD mehr

- Neue Klassfikation steatotischer Lebererkrankungen –

MASLD – Metabolic Dysfunction Associated Steatotic Liver Disease:

Metabolic

Dysfunction

Associated

Steatotic

Liver

Disease

Begründung für eine geänderte Nomenklatur:

- **Weniger Stigma (Alkohol, Fett…)**
- **Positive Definition der Erkrankung**
- **Möglichkeit, Mischformen (Ernährung + Alkohol) abzubilden**

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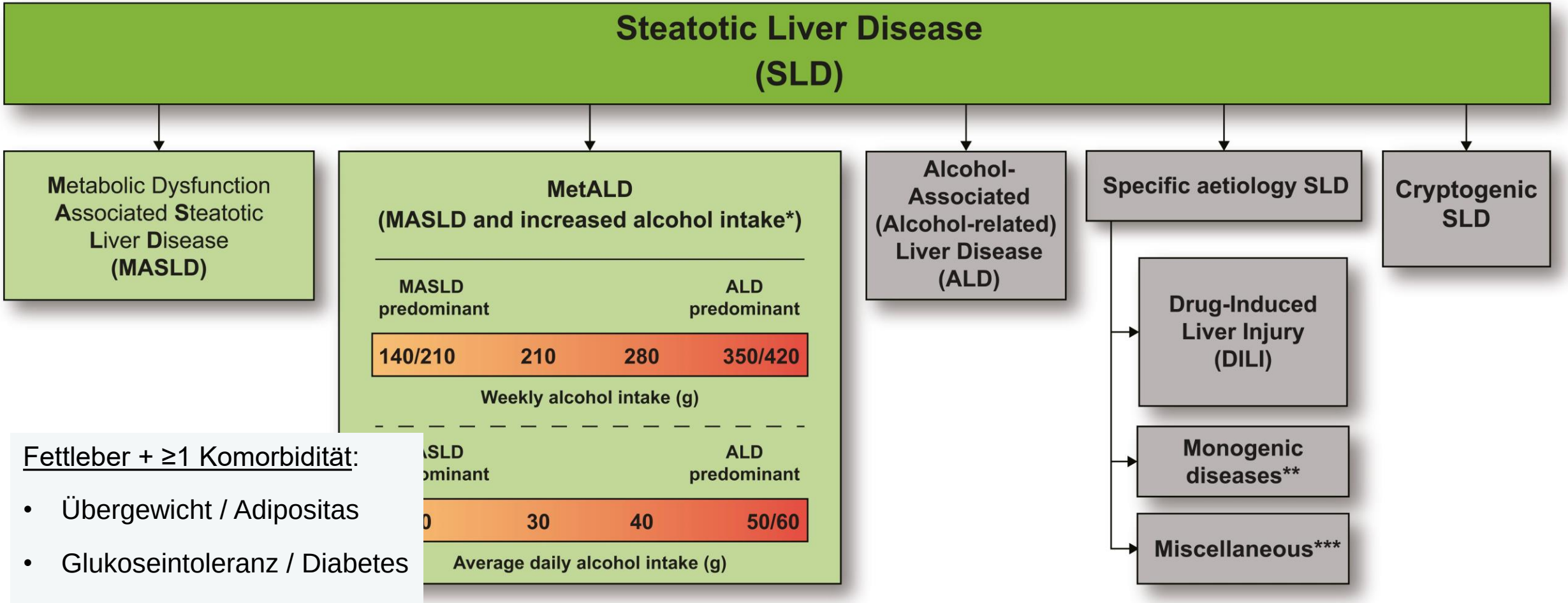
Rinella ME et al., J Hep 2023; 24: S0168



Fettleber + ≥1 Komorbidität:

- Übergewicht / Adipositas
- Glukoseintoleranz / Diabetes
- Hypertonus
- Triglyeriderhöhung
- Hypercholesterinämie

, 210-420g male (average daily 20-50g female, 30-60g male)
ficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
nalnutrition, celiac disease

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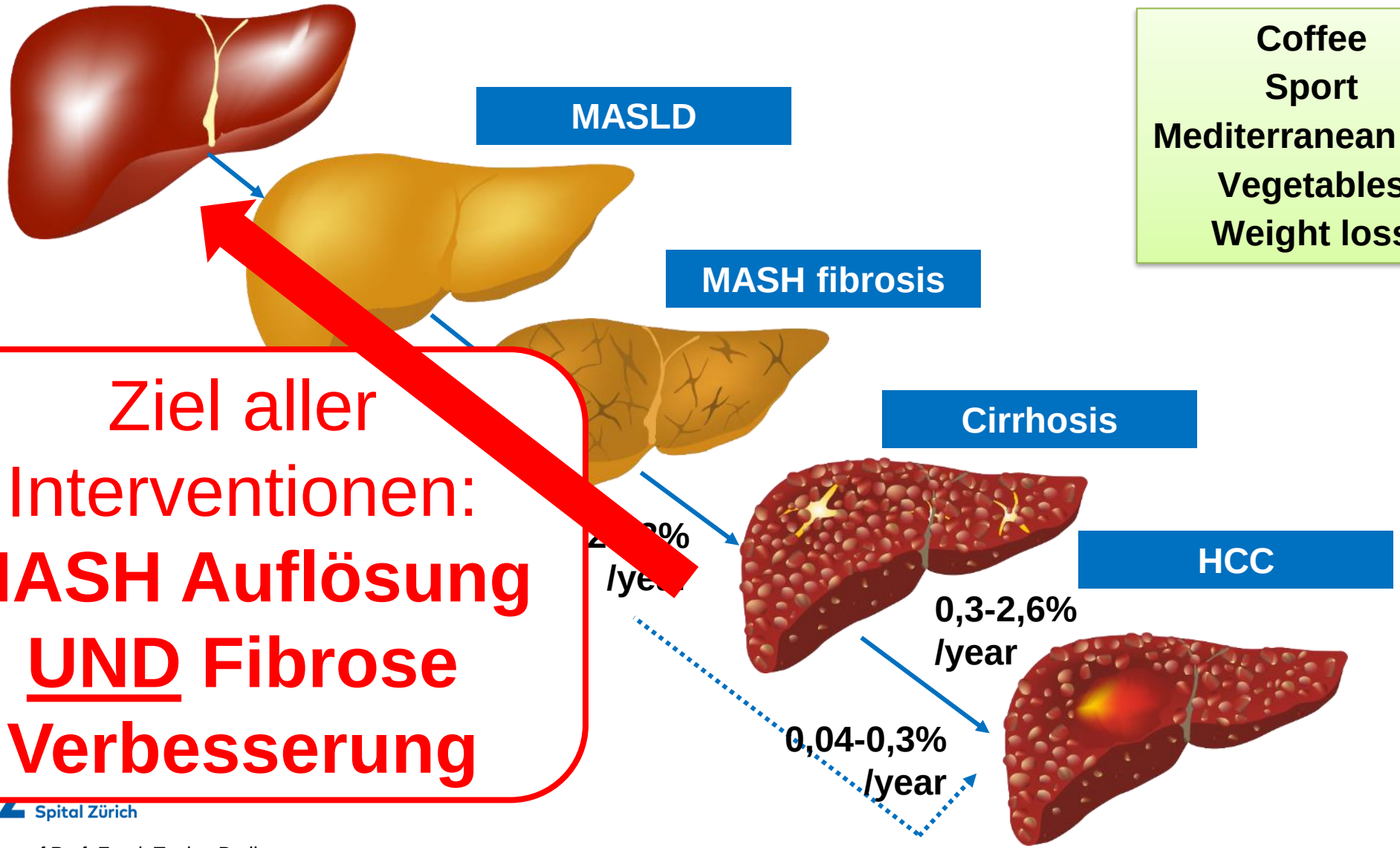
Rinella ME et al., J Hep 2023; 24: S0168

Natürlicher Verlauf der MASLD



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Courtesy of Prof. Frank Tacke, Berlin

Zentrale Frage: besteht eine fortgeschrittene Fibrose?

<u>Zweistufiges, nicht-invasives Screening:</u>

1. **Berechnung des FIB-4 Scores** (cut-off 1.3)*

2. **Leberelastographie** (VCTE, cut-off 8.0 kPa)

* FIB-4 Score cut-off über 65 Jahre: 2.0

Metabolisches Syndrom & MASLD sind pandemisch

- Obesity has **tripled since 1975**
- **>1.9 billion** adults overweight
- **>650 million** adults obese
- **>340 million** children and adolescents aged 5-19 overweight or obese

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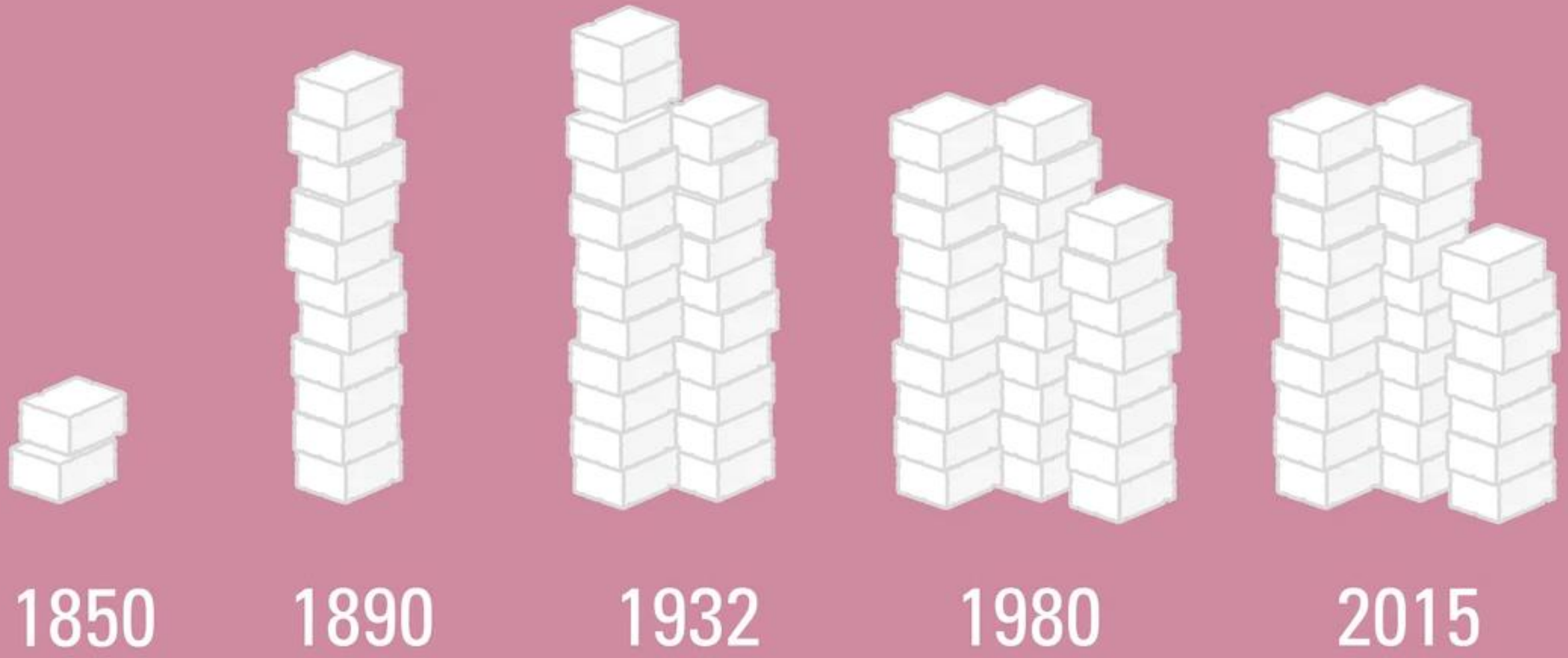
WHO & Lancet Gastroenterol Hepatol 2021

Massive Zunahme des Zucker- und Fruktose-Konsums

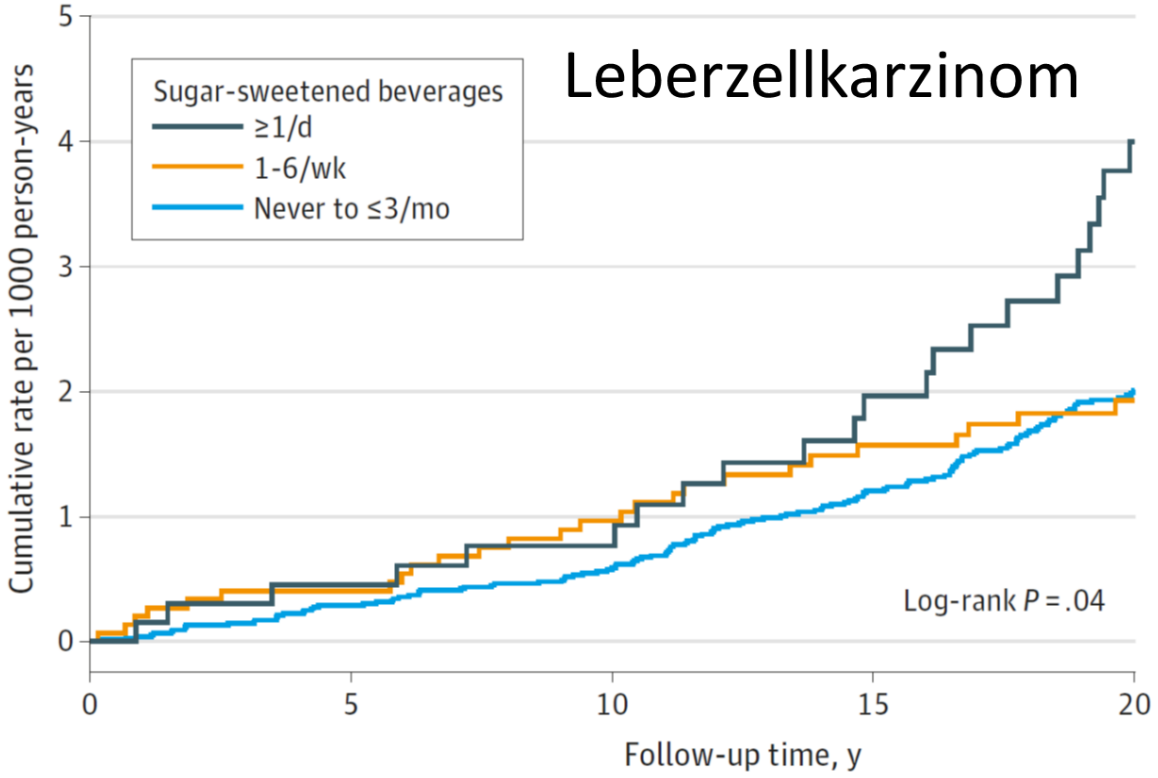


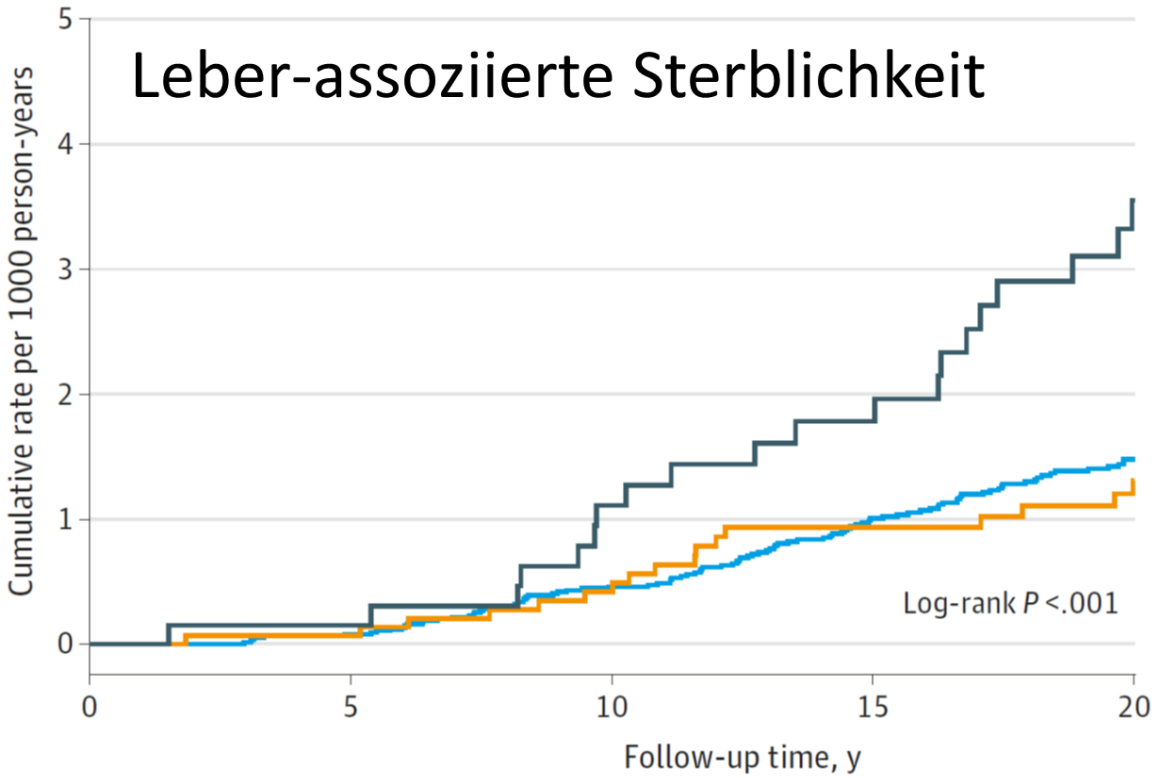
Rhyn N. Neue Zürcher Zeitung 2019

Ein Land von Schleckmäulern: Wie der Zucker in Schweizer Produkten reduziert werden soll und warum das so lange dauert

Zuckerhaltige Getränke und Leber-assoziierte Ereignisse

Women's Health Initiative (98.786 postmenopausale Frauen, Alter 50–79 Jahre, 1993–1998, Beobachtung 20,9 Jahre) → 207 HCC, 148 Leber-bedingter Tod

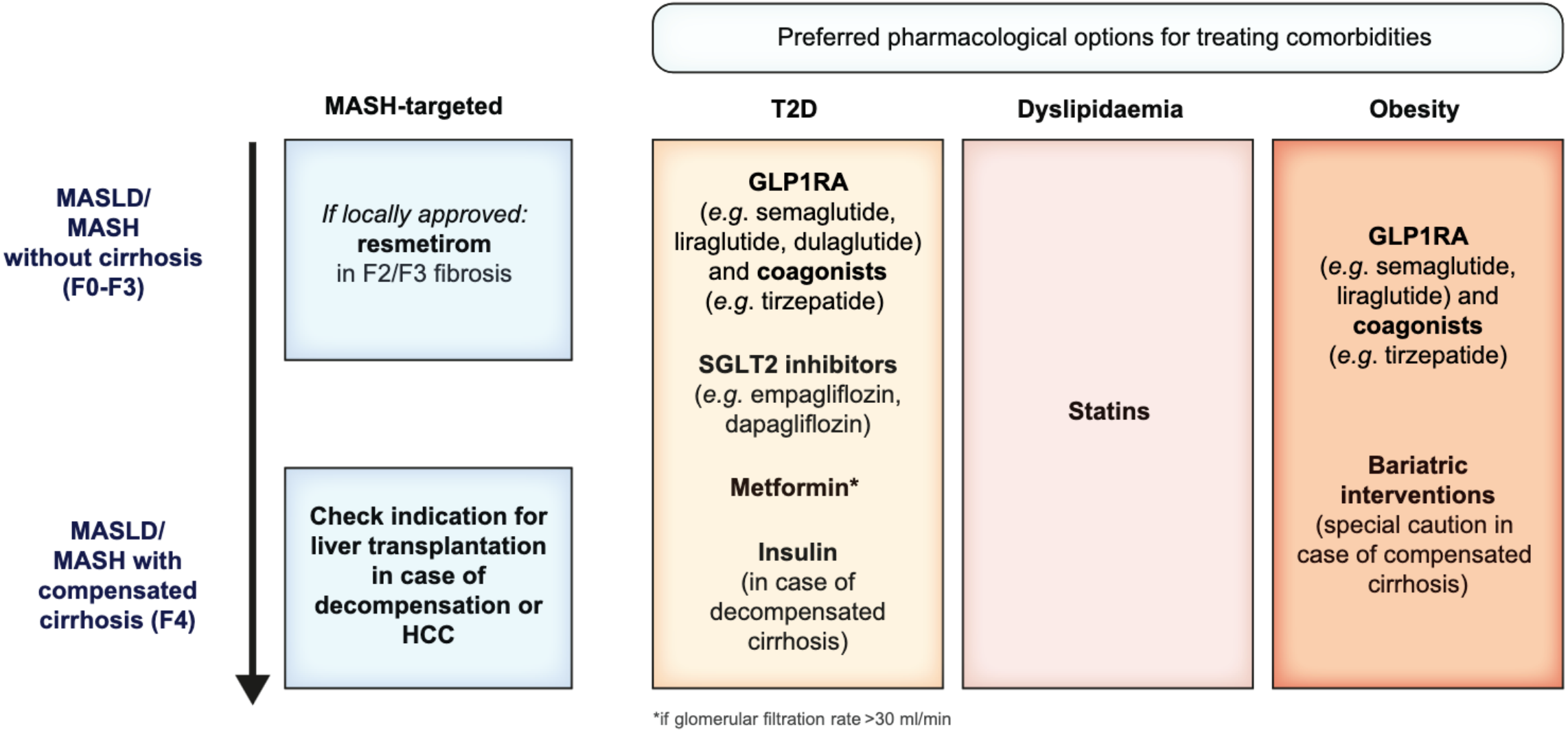




≥1 gezuckertes Getränk pro Tag: HCC-Risiko (HR 1,85), Leber-Tod (HR 1,68)
KEIN erhöhtes Risiko bei Süssgetränken mit Zucker-Austauschstoffen!

Zhao L, et al., JAMA. 2023; 330(6):537-546

Medikamentöse Behandlungsempfehlungen der MASLD
- Zusätzlich zu Lifestyle Modifikationen –



EASL EASD EASO Clinical Practice Guideline on Management of MASLD, J Hepatol 2024

MASLD Medikamente in Entwicklung (Auswahl)

Resmetirom (THR-beta Agonist) – FDA approved

Semaglutide* (GLP-1 Agonist)

Tirzepatide*, Efinopegdutide, Survodutide (Duale Inkretin Agonisten)

Efruxifermin, Pegazifermin (FGF21 Analoga)

Dapagliflozin* (SGLT2 Inhibitor)

Lanifibranor (PPAR agonists)

Aramchol (SCD-1 inhibitor)

Belpectin (Galectin 3 inhibitor)

* Bereits in der Schweiz zugelassen für Indikationen ausserhalb der MASLD/MASH

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2024 VOL. 390 NO. 6

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*

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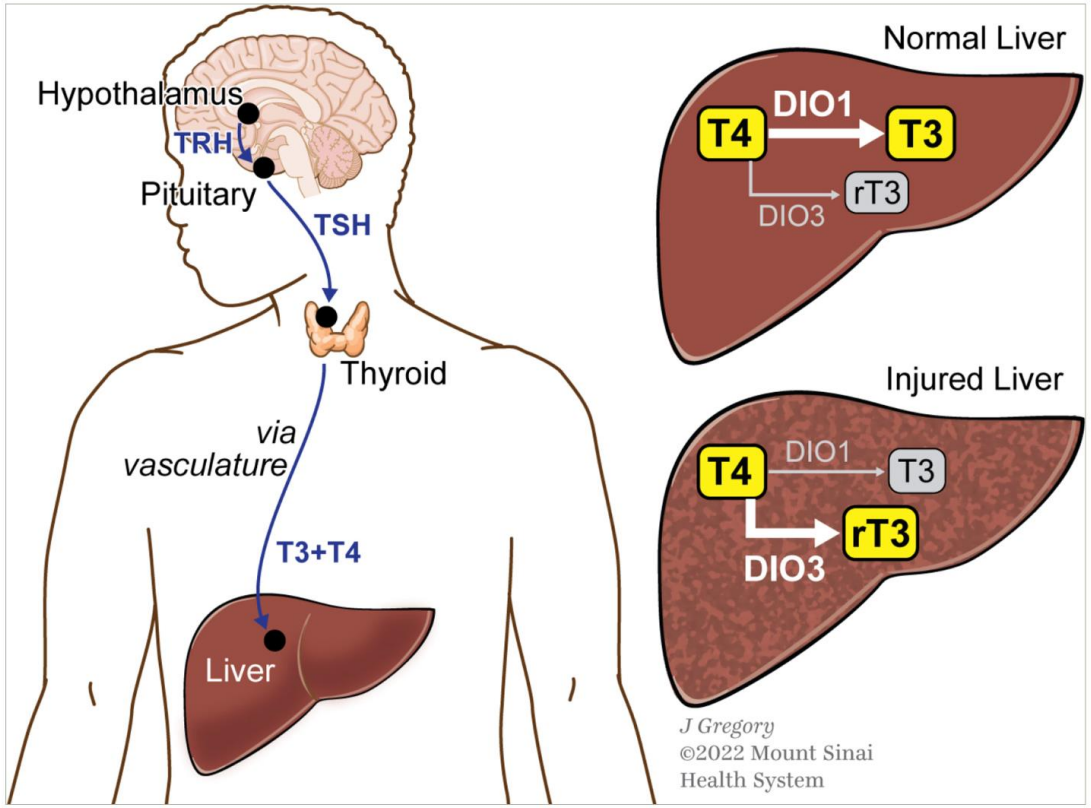
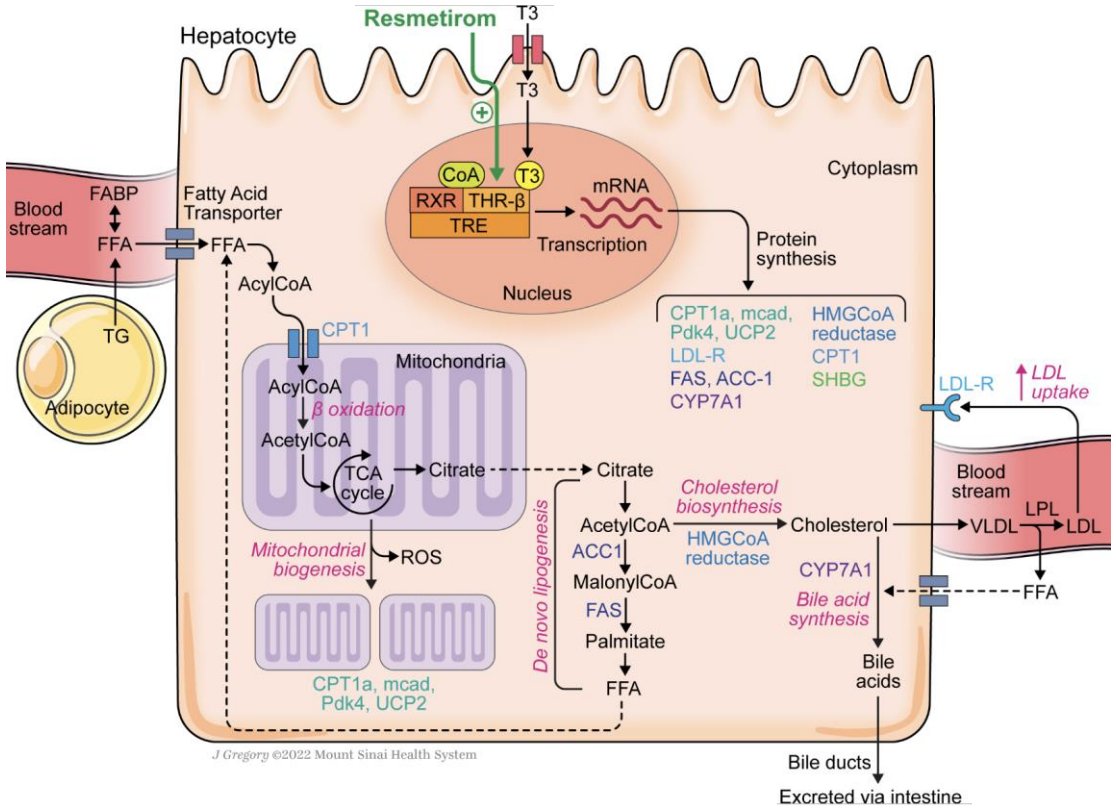
Harrison SA et al., NEJM 2024; 390: 497

Thyroid Rezeptor beta-Agonist Resmetriom in MASLD
- Wirkmechanismus -

Figure 2: Changes in deiodinase type 1 and deiodinase type 3 in chronic liver injury drives intrahepatic hypothyroidism



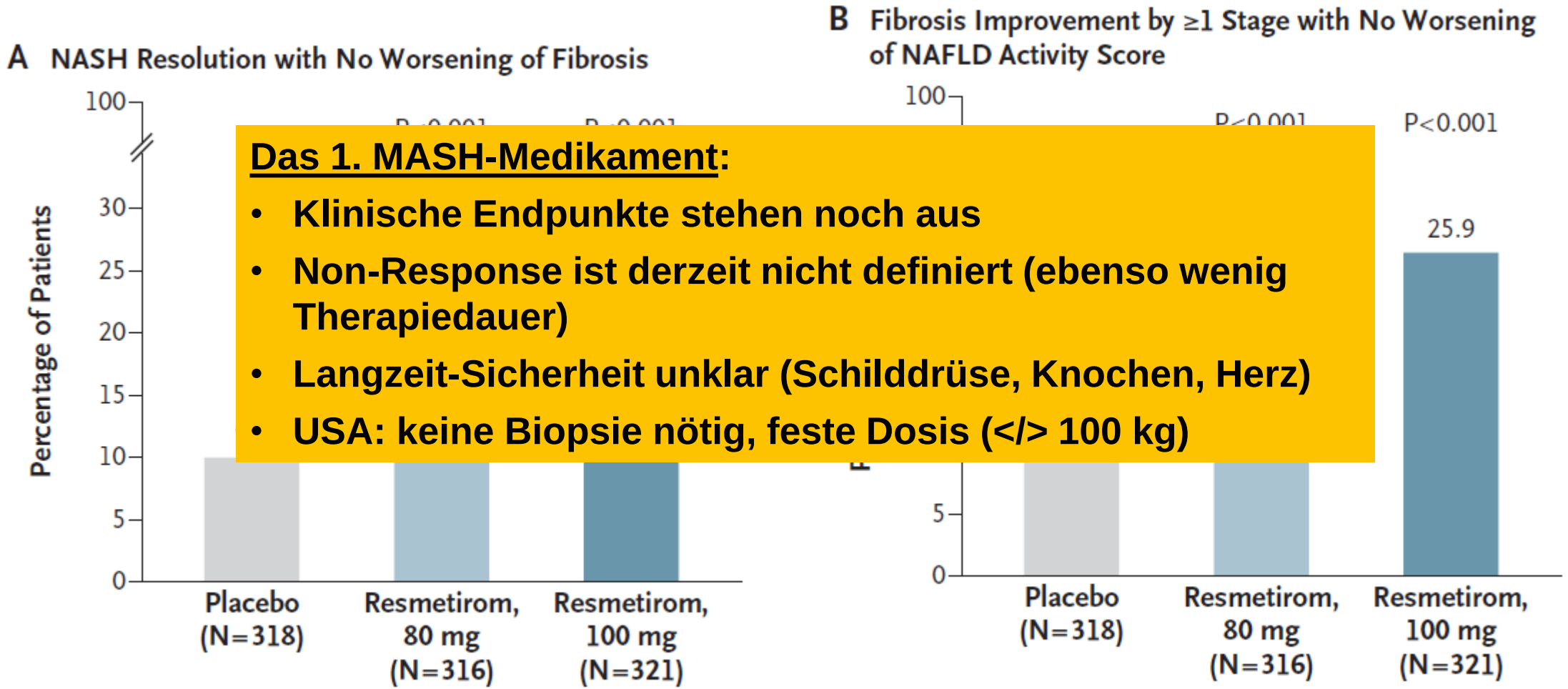
In the normal liver, DIO1 activity, an intrahepatic enzyme, drives the conversion of T4 to active T3. In chronic liver injury, a decrease in DIO1 activity coupled with an increase in DIO3 activity leads to increased conversion of T4 to inactive reverse T3, subsequently leading to accumulation of lipotoxic species, cyclic liver injury and local intrahepatic hypothyroidism. Used with permission from ©Mount Sinai Health System.
DIO1 = deiodinase type 1; DIO3 = deiodinase type 3; rT3 = reverse triiodothyronine; T3 = triiodothyronine; T4 = thyroxine; TRH = thyroid-releasing hormone; TSH = thyroid-stimulating hormone.



Karim G et al., TouchReviews Endocrinology 2023; Harrison SA et al., NEJM 2024; 390: 497

Thyroid Rezeptor beta-Agonist Resmetriom in MASLD

- Phase III-Studie (N=972), F2/F3-Fibrose; BMI: 36 kg/m^2; 66% Typ 2 DM -



<u>Das 1. MASH-Medikament</u>:

- **Klinische Endpunkte stehen noch aus**
- **Non-Response ist derzeit nicht definiert (ebenso wenig Therapiedauer)**
- **Langzeit-Sicherheit unklar (Schilddrüse, Knochen, Herz)**
- **USA: keine Biopsie nötig, feste Dosis (</> 100 kg)**

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Harrison SA et al., NEJM 2024; 390: 497

Madrigal, FDA approval in hand, outlines plan to sell MASH drug

The company expects slow initial uptake of Rezdiffra, which costs $47,400 per year, but for the launch to accelerate afterwards.

Published March 15, 2024

Ben Fidler
Senior Editor

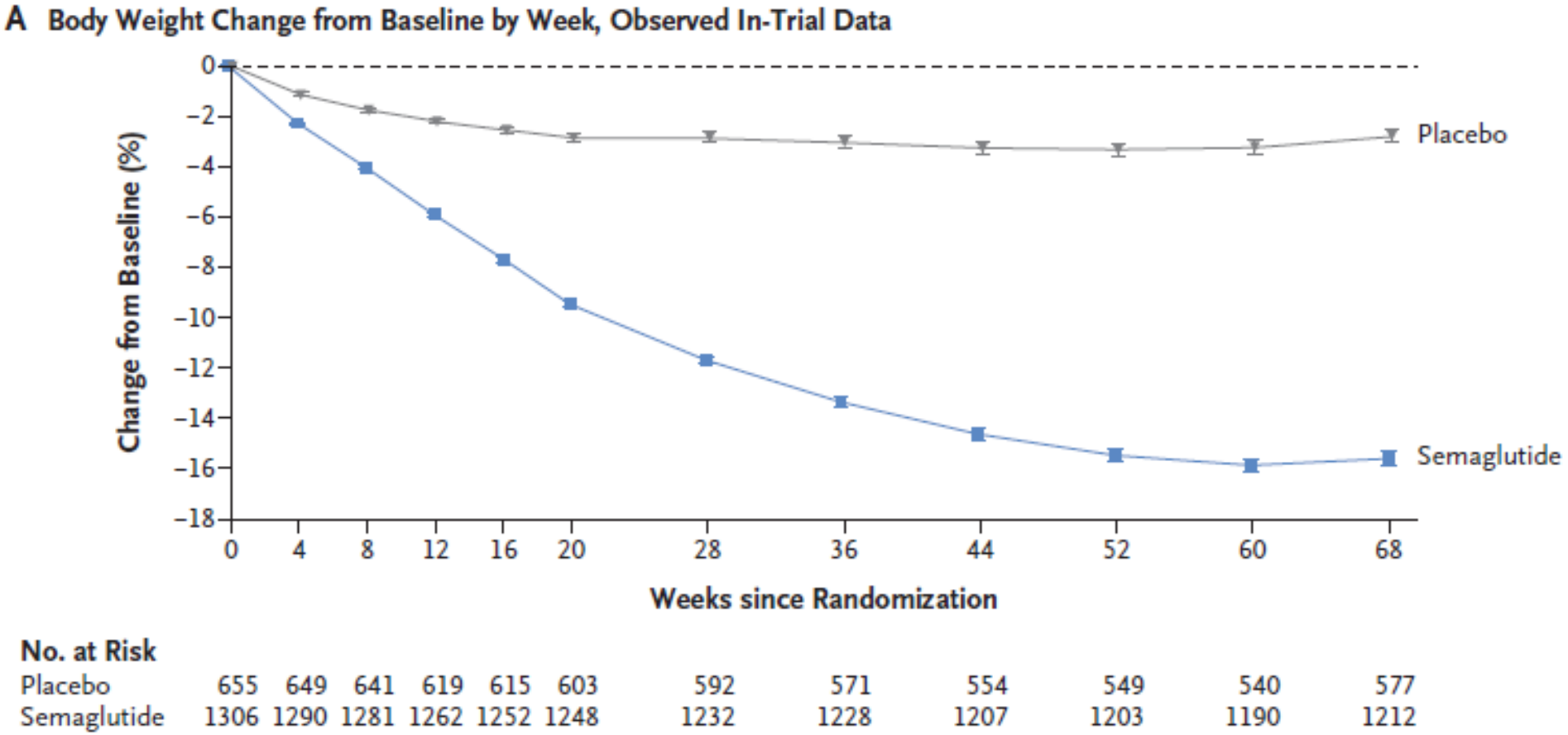
A photo of Madrigal Pharmaceuticals' Rezdiffra, the first drug approved for metabolic dysfunction-associated steatohepatitis.
Courtesy of Madrigal Pharmaceuticals

The first drug for metabolic dysfunction-associated steatohepatitis will cost $47,400 per year, its developer, Madrigal Pharmaceuticals, said Thursday.

Ozempic sheds weight, but it's not a no-brainer

https://storymd.com/story/8ojy7jOcxA-less-hype-more-facts-ozempic-s-potential-laid-bare

Semaglutid induziert starken Gewichtsverlust bei Adipositas
(N = 1961; mittlerer BMI: 37.8 kg/m^2)



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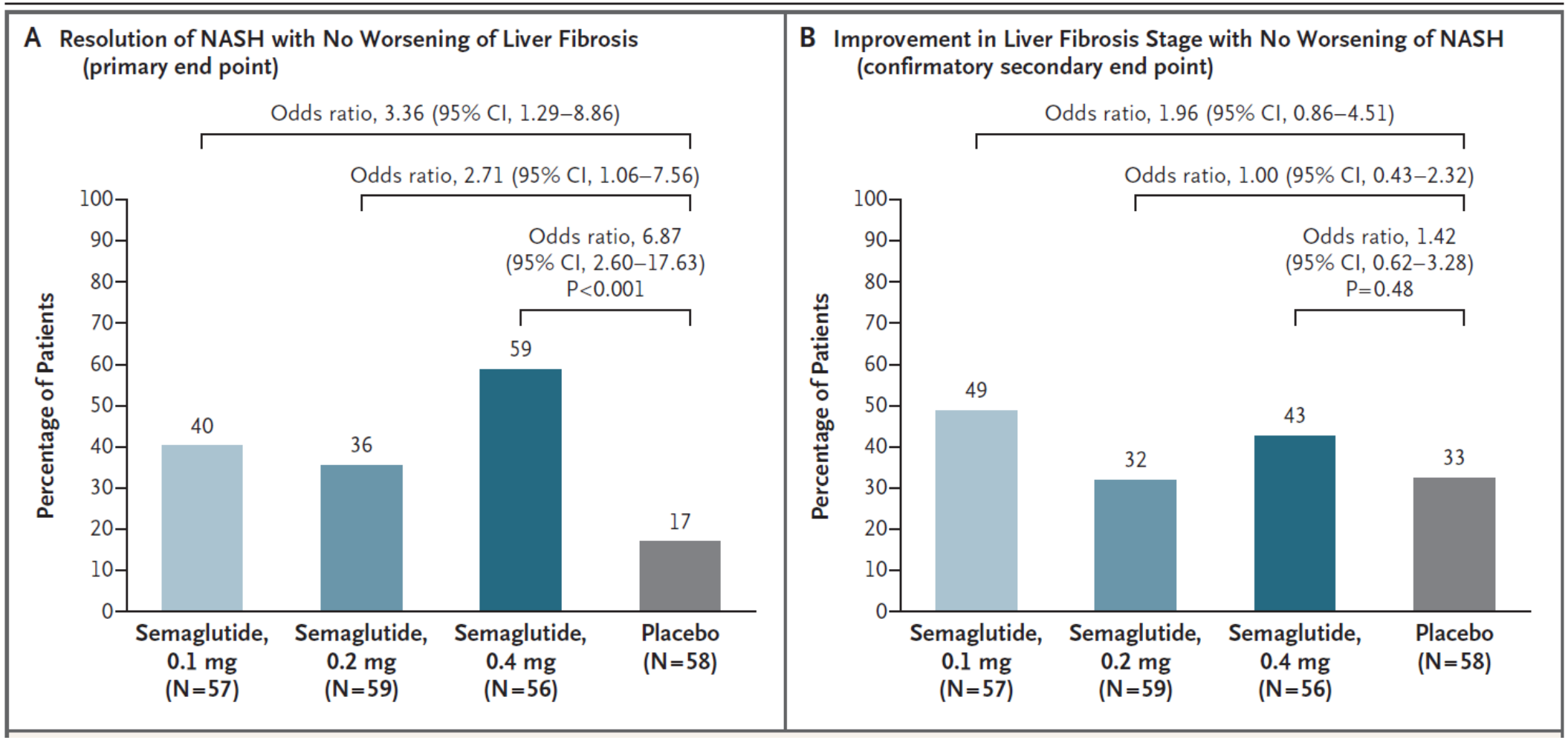
Wilding JP et al., New Engl J Med 2021; 384:989

Semaglutid in MASH mit F2/F3-Fibrose

- Phase II-Studie (N=320), BMI: 35.1 kg/m^2; 62% Typ 2 DM -



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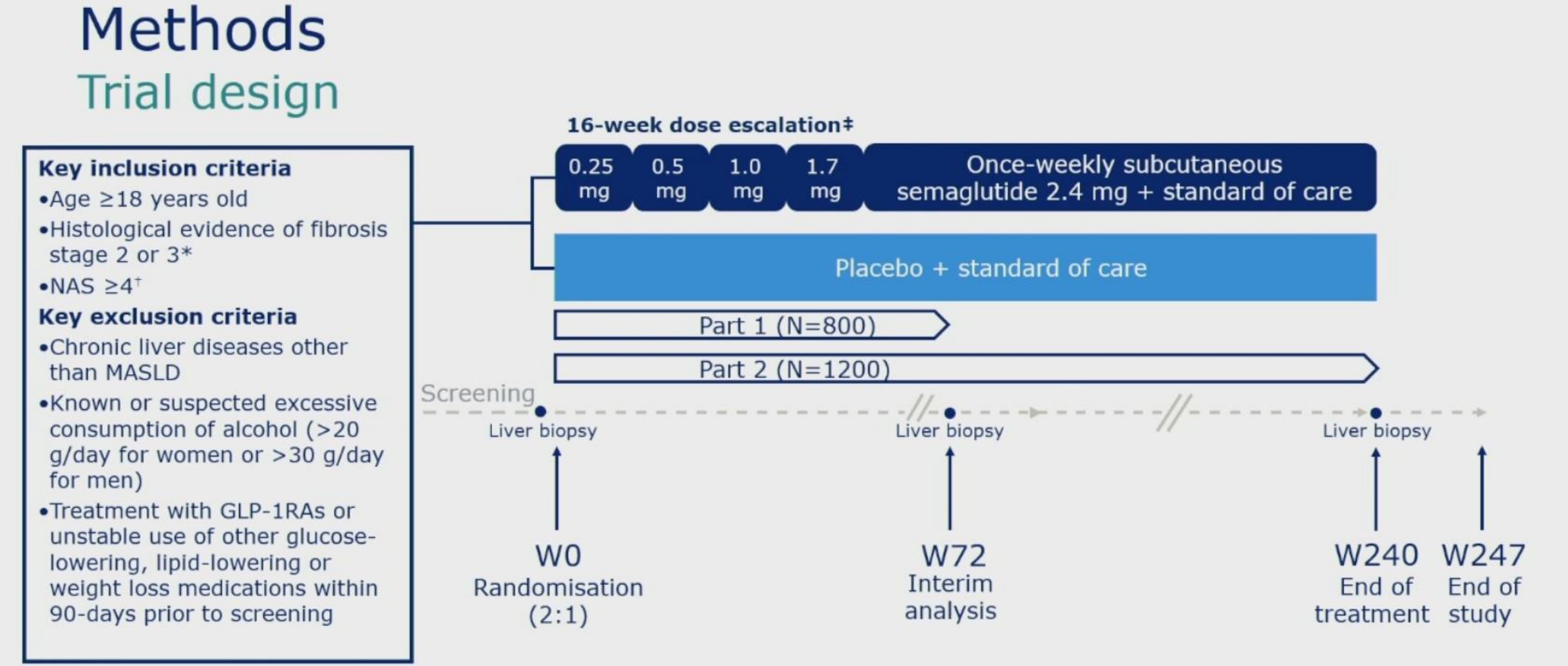
Newsome PN et al., NEJM 2021;384:1113

Semaglutid in MASH mit F2/F3 Fibrose

- Phase III-Studie (N=800), BMI: 34.3 kg/m^2; 56% Typ 2 DM -



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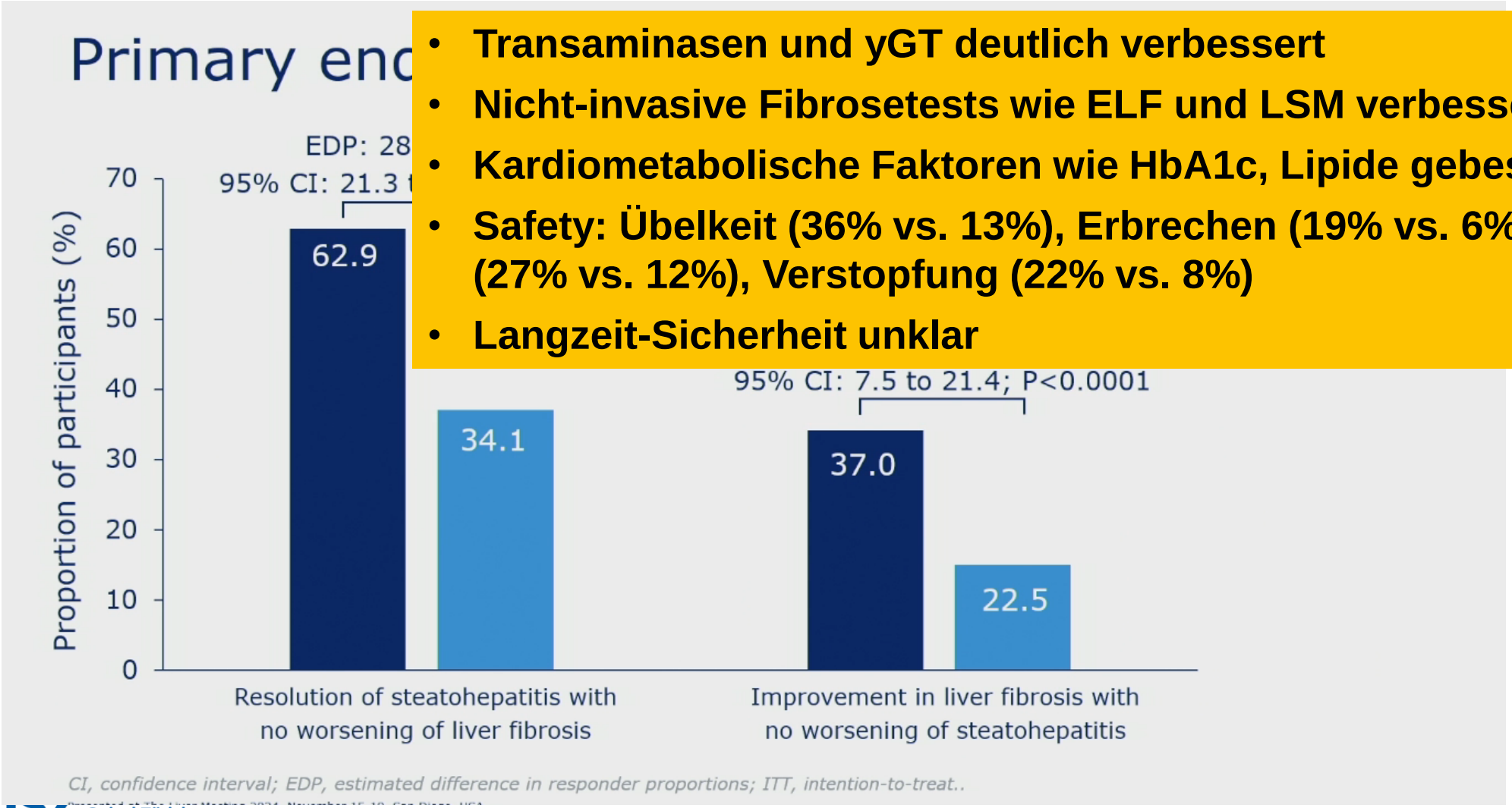
Newsome PN et al., AASLD 2024, Late Braker Session, 19.11.2024

Semaglutid in MASH mit F2/F3 Fibrose

- Phase III-Studie (N=800), BMI: 34.3 kg/m^2; 56% Typ 2 DM -



- **Transaminasen und yGT deutlich verbessert**
- **Nicht-invasive Fibrosetests wie ELF und LSM verbessert**
- **Kardiometabolische Faktoren wie HbA1c, Lipide gebessert**
- **Safety: Übelkeit (36% vs. 13%), Erbrechen (19% vs. 6%), Durchfälle (27% vs. 12%), Verstopfung (22% vs. 8%)**
- **Langzeit-Sicherheit unklar**

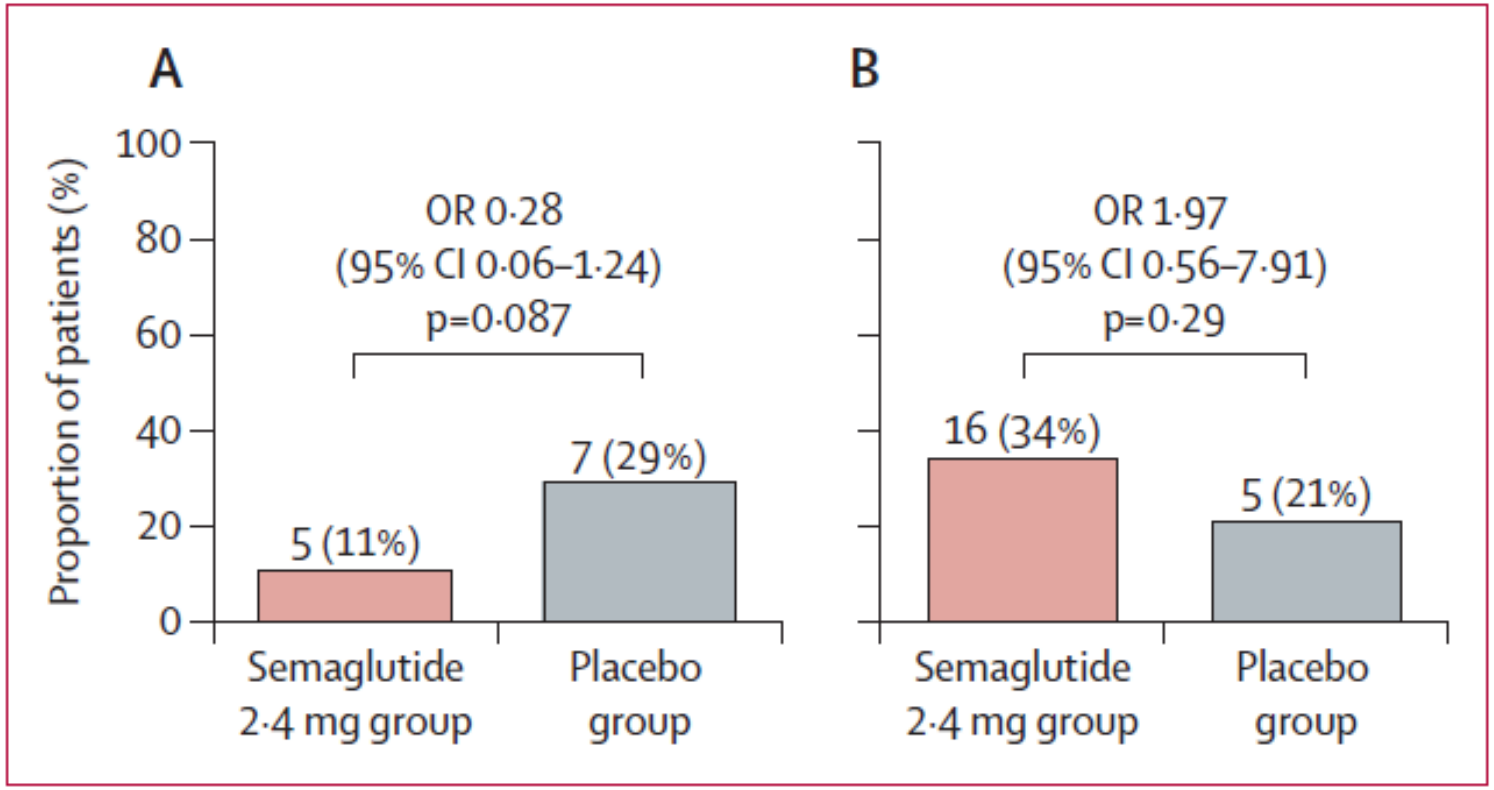
Newsome PN et al., AASLD 2024, Late Braker Session, 19.11.2024

Semaglutid bei MASLD-Zirrhose ?

- N=71; BMI > 27 mg/kg2; Start 0.25 mg; Steigerung bis 2.4 mg/Wo -

Fibrosis improvement
without worsening of NASH

NASH resolution
without worsening of fibrosis



Gewichtsreduktion: 8.7 kg; Verbesserung kardio-metabolischer Parameter
Keine Sicherheitsbedenken

Loomba R et al., Lancet Gastro Hepatol 2023;8:511

The NEW ENGLAND JOURNAL of MEDICINE

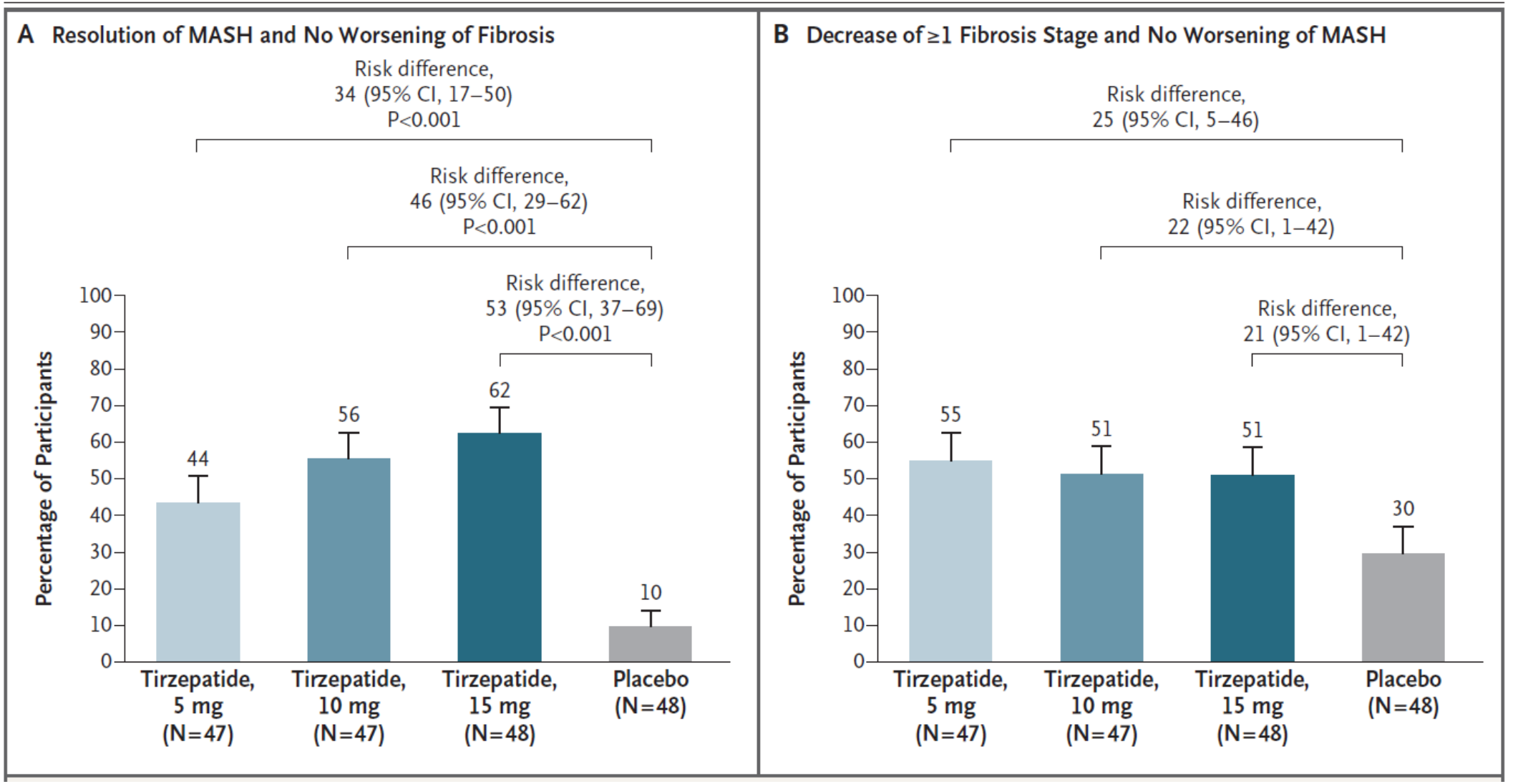
ESTABLISHED IN 1812 JULY 25, 2024 VOL. 391 NO. 4

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

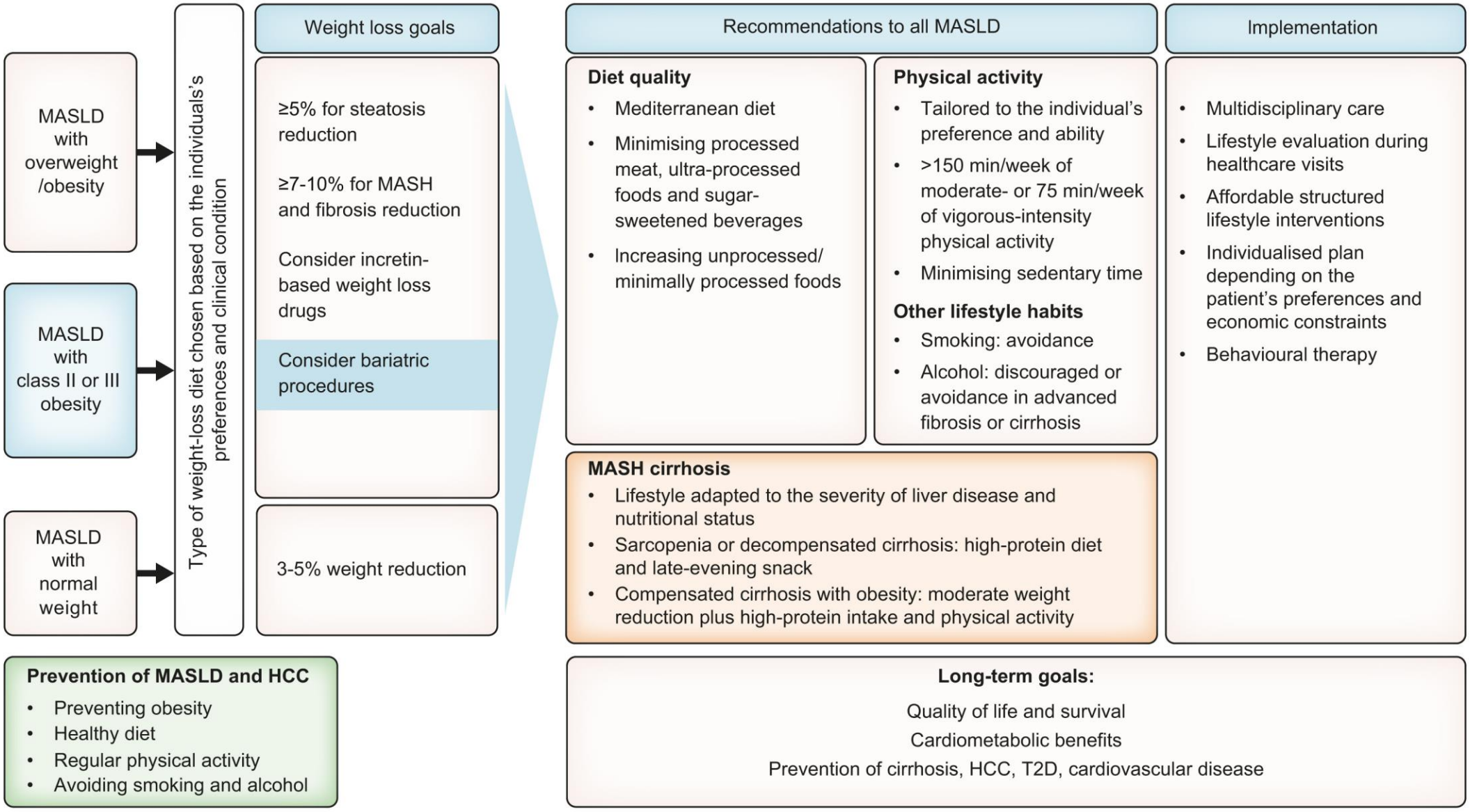
Tirzepatide bei MASH mit F2/F3-Fibrose

- Phase II (N=190); BMI > 36.1 mg/kg2; DM II: 58%; NAS-Score: 5.3



Loomba R et al., New Engl J Med 2024; 391:299

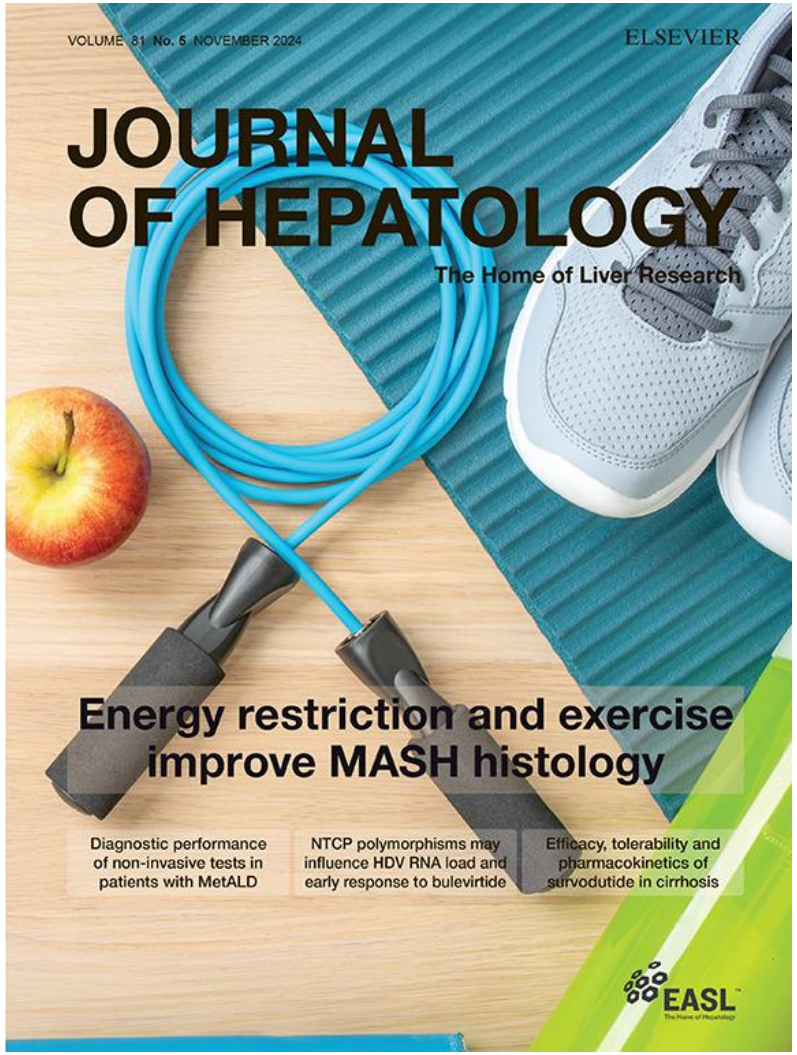
Lifestyle management algorithm for MASLD

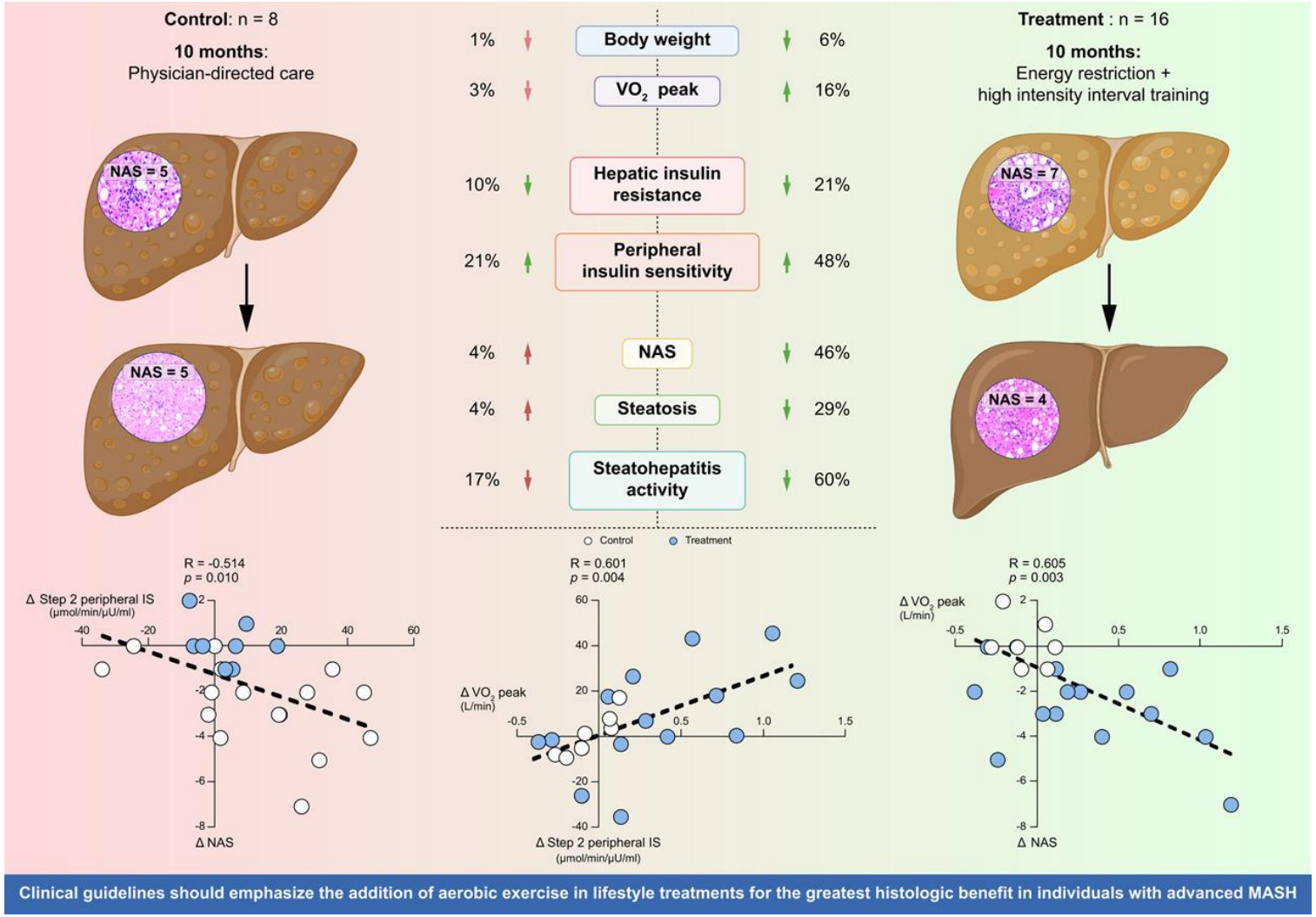


EASL–EASD–EASO Clinical Practice Guidelines on the management of MASLD, J Hepatol 2024

Histological improvements following energy restriction and exercise:
The role of insulin resistance in resolution of MASH

Following medical diagnosis of MASH, individuals were randomized to **treatment (n = 16) or control (n = 8).** Liver fat (magnetic resonance spectroscopy), 18-hour plasma biochemical measurements, and isotopically labeled hyperinsulinemic-euglycemic clamps were completed pre- and post-intervention. Body composition and cardiorespiratory fitness (VO2peak) were also measured mid-intervention. Those in the treatment group were **counseled to reduce energy intake** and completed **supervised, high-intensity interval training (3x/week) for 10 months**. Controls continued physician-directed care.

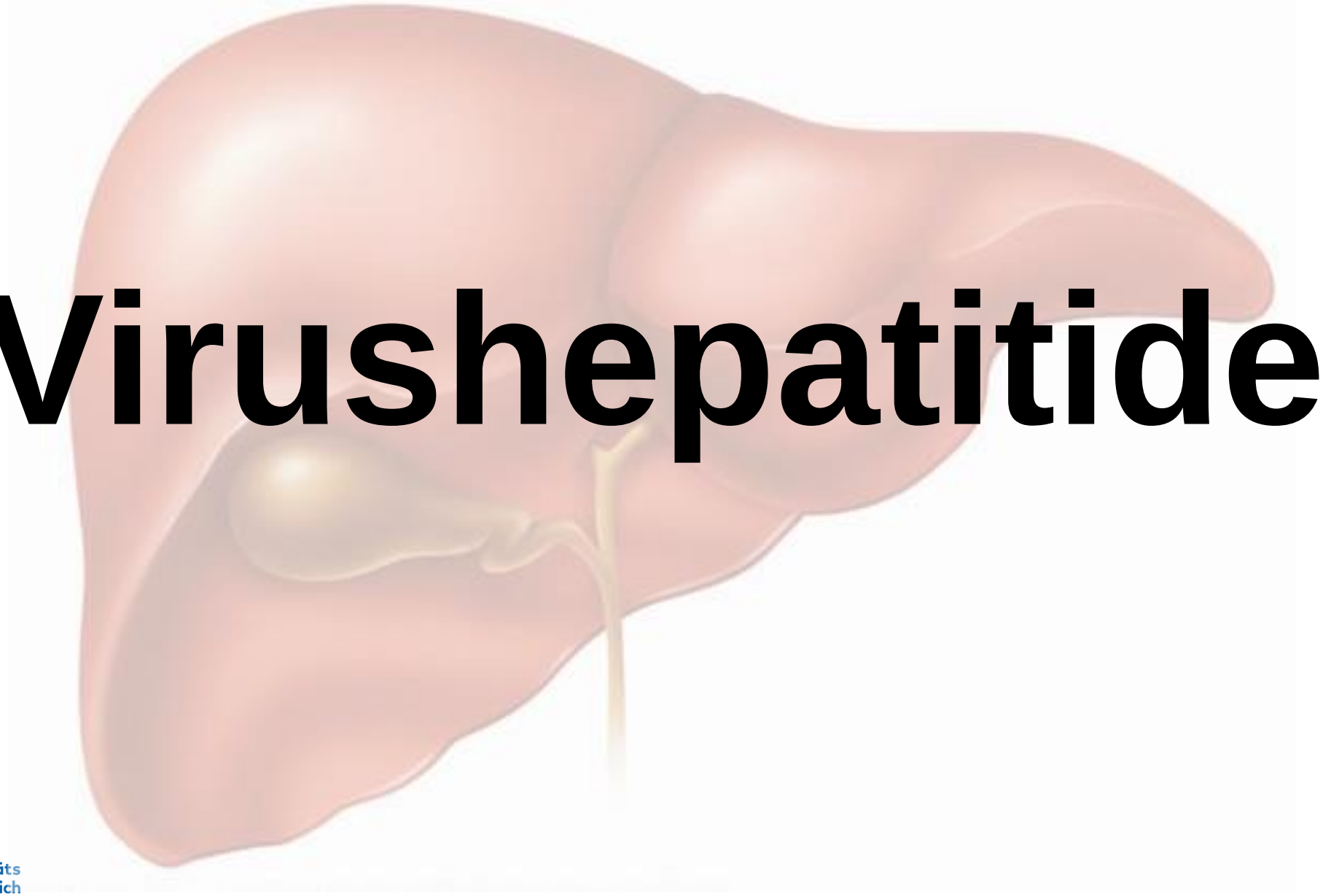




Mucinski JM et al., J Hepatol 2024, Epub

Take Home Message – MASH / MASLD

- Das **MASLD** betrifft etwas **20–30% der Gesamtbevölkerung.**
- **Ein zuckerhaltiges Getränk pro Tag** erhöht das **Risiko für Leberzellkrebs** und **Leber-assoziierter Mortalität.**
- Nicht-invasive Marker (NFS, **FIB-4, Elastographie**) unterstützen bei der Entscheidung über eine Leberbiopsie.
- Die **Therapieoptionen** sind limitiert: Änderung der Lebensgewohnheiten, Gewichtsreduktion, Optimierung der Diabetestherapie, bariatische Chirurgie und Lebertransplantation.
- **Resmetirom** erst durch FDA zugelassene Therapie, **zahlreiche Studienpräparate** in Phase III-Studien. **Positive Daten für GLP-1** sowie **duale/triple-Agonisten.**
- Zukünftig **hohe klinische** wie **ökonomische Belastung.**



Virushepatitiden

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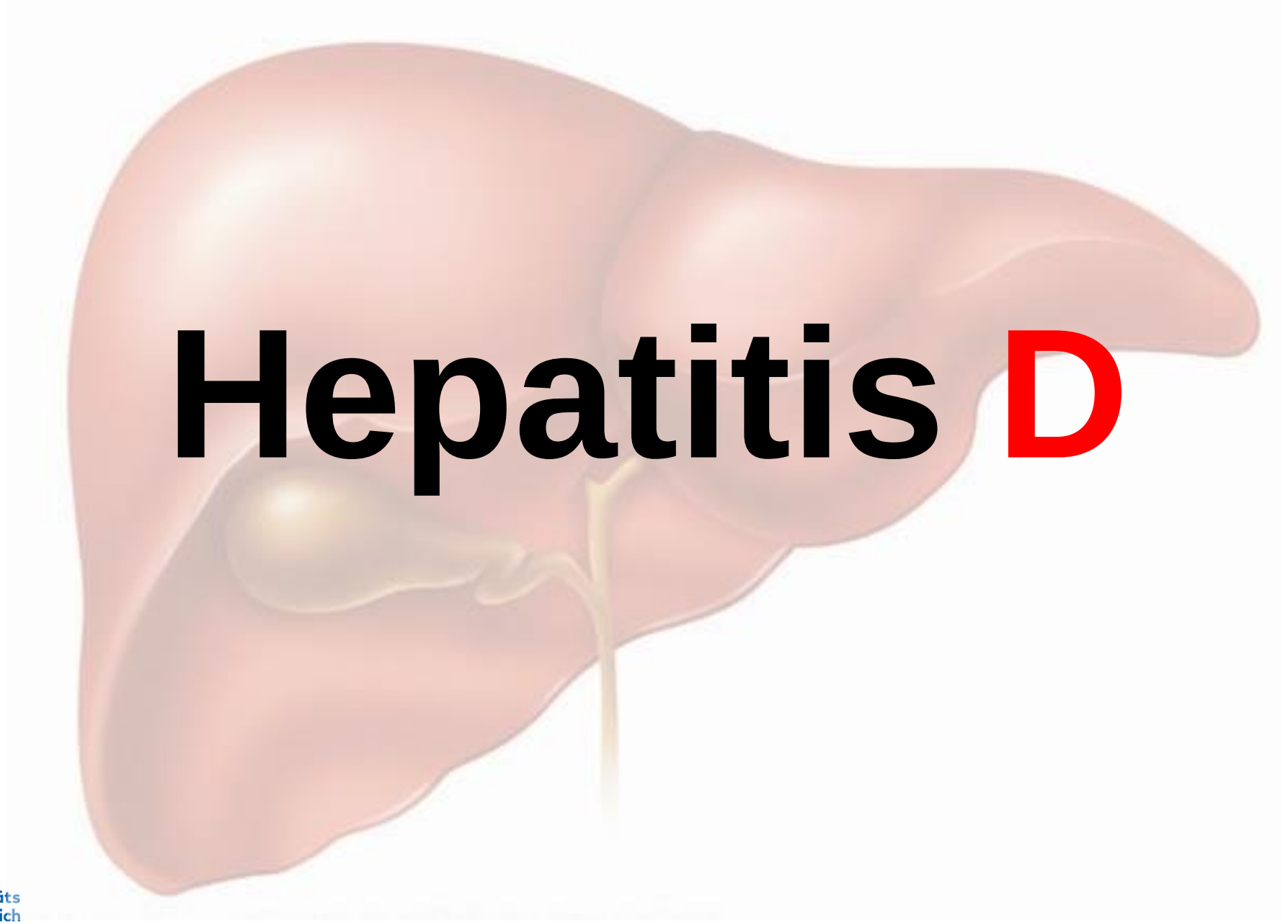

Hepatitis D

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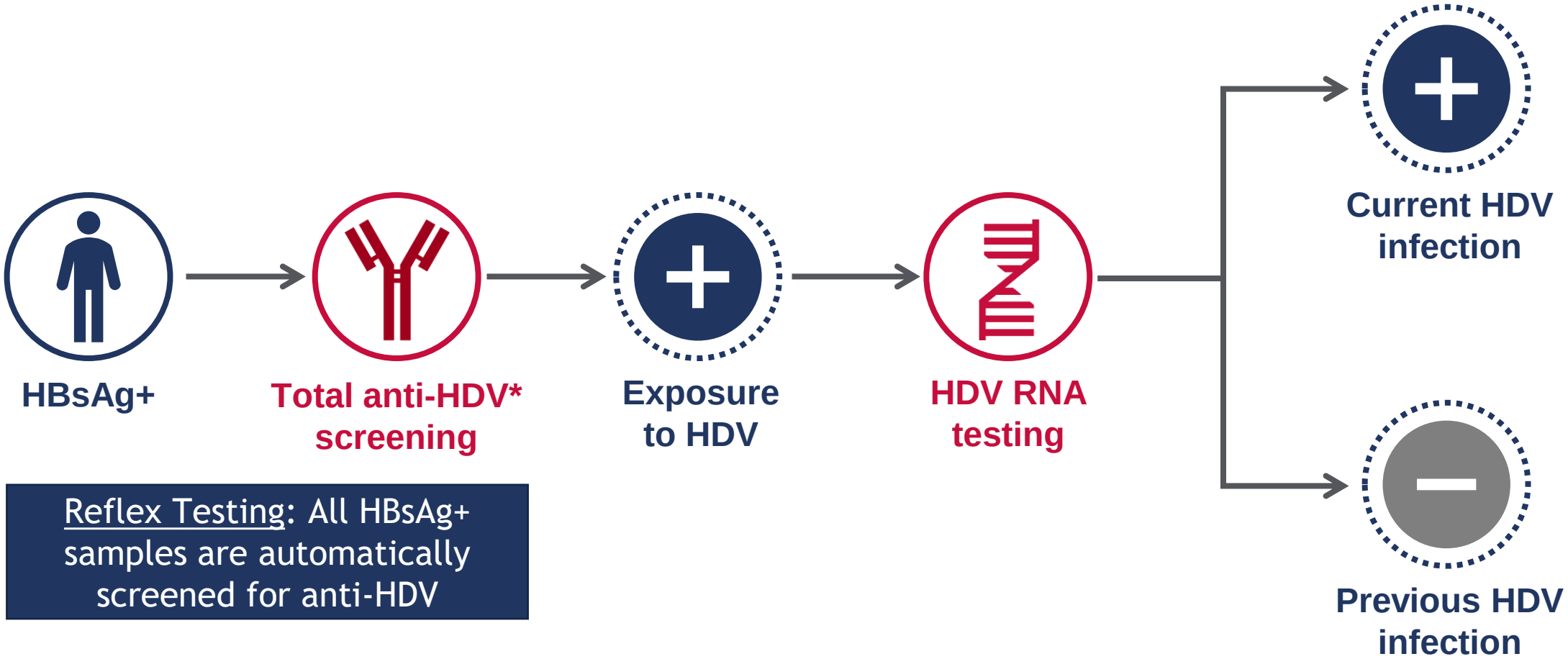
Diagnose einer HBV-HDV-Co-Infektion



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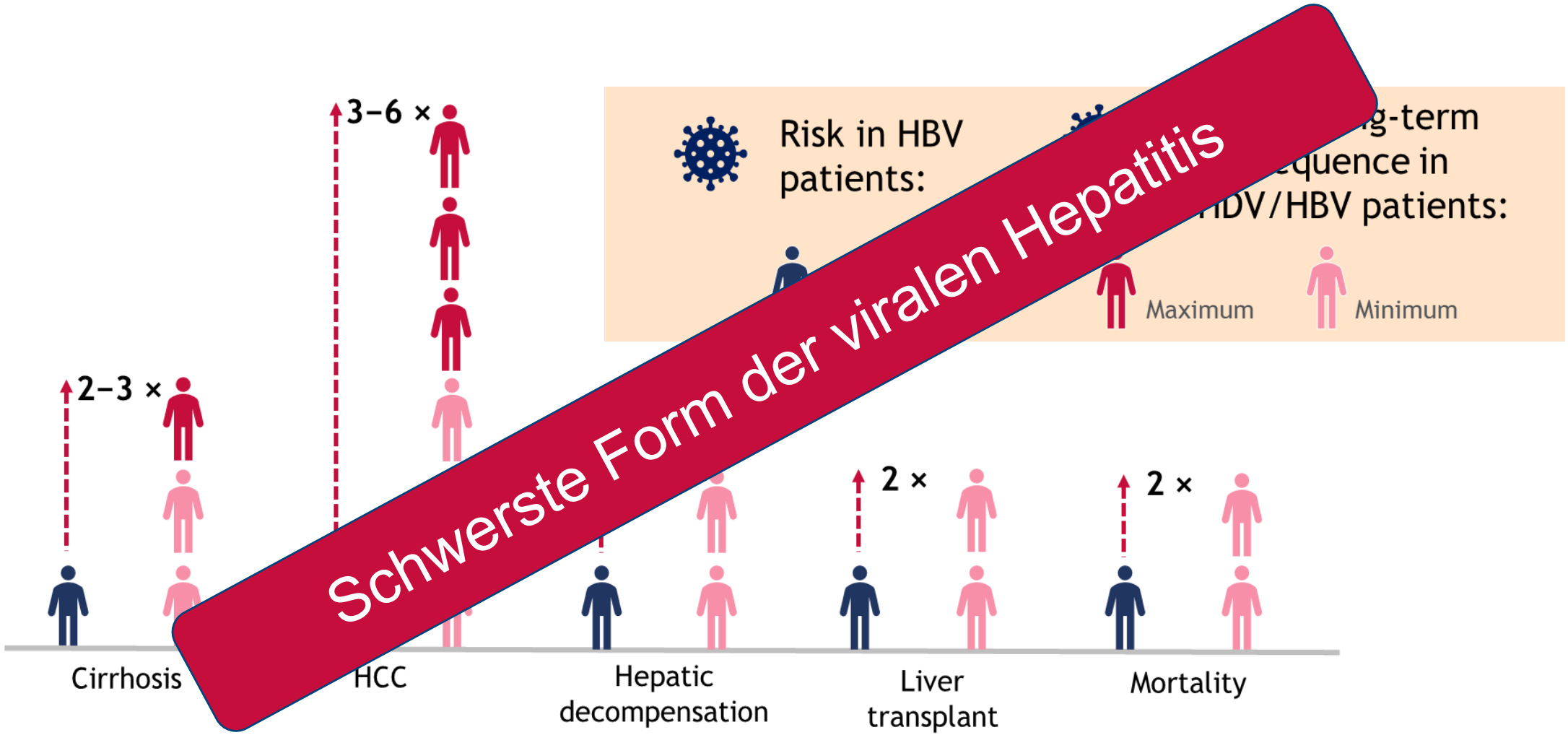
Rizzetto M, et al. J Hepatol 2021;74:1200–11; Terrault NA, Ghany MG. Dig Dis Sci 2021;66:2483–2485

Deutlich erhöhtes Risiko bei HBV-HDV-Coinfektion



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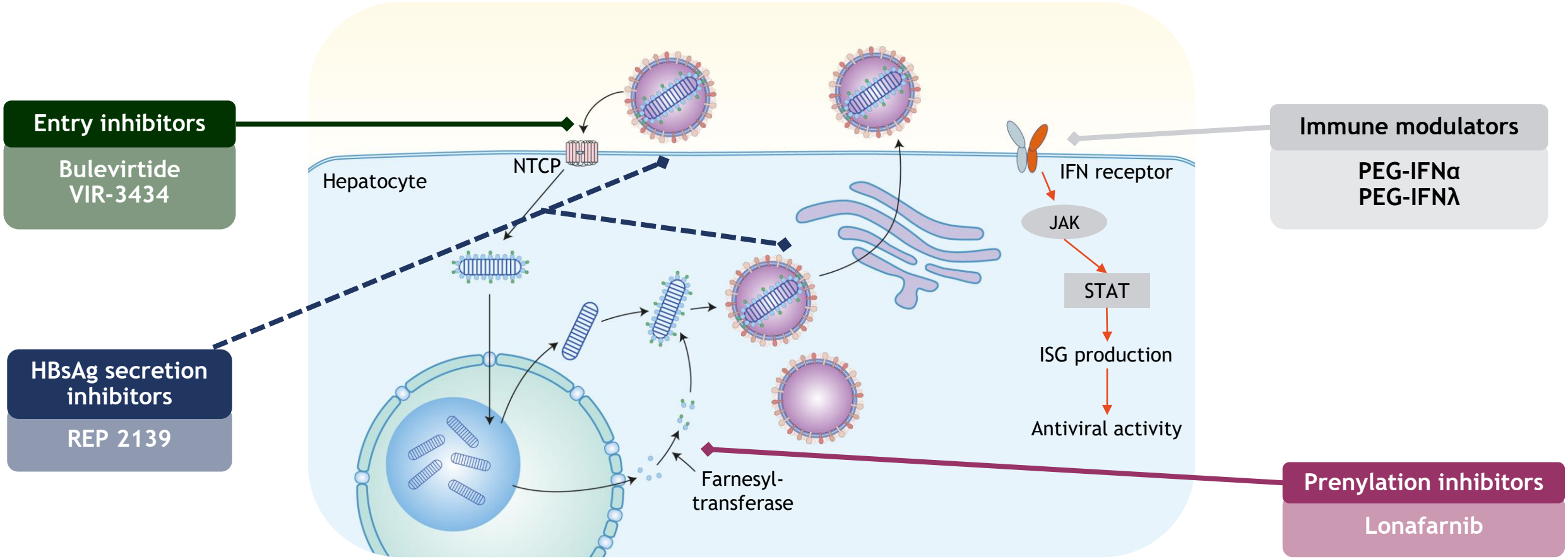
Da BL, et al. Gastroenterol Rep 2019;7:231; Chen VL, et al. Clin Gastroenterol Hepatol 2016;14:887.

Therapeutische Ziele im HDV Replikationszyklus



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Gilman C, et al. World J Gastroenterol 2019;25:4580; Bazinet M, et al. Lancet Gastroenterol Hepatol 2017;2:877; Park A, Iwasaki A. Cell Host Microbe 2020;27:870

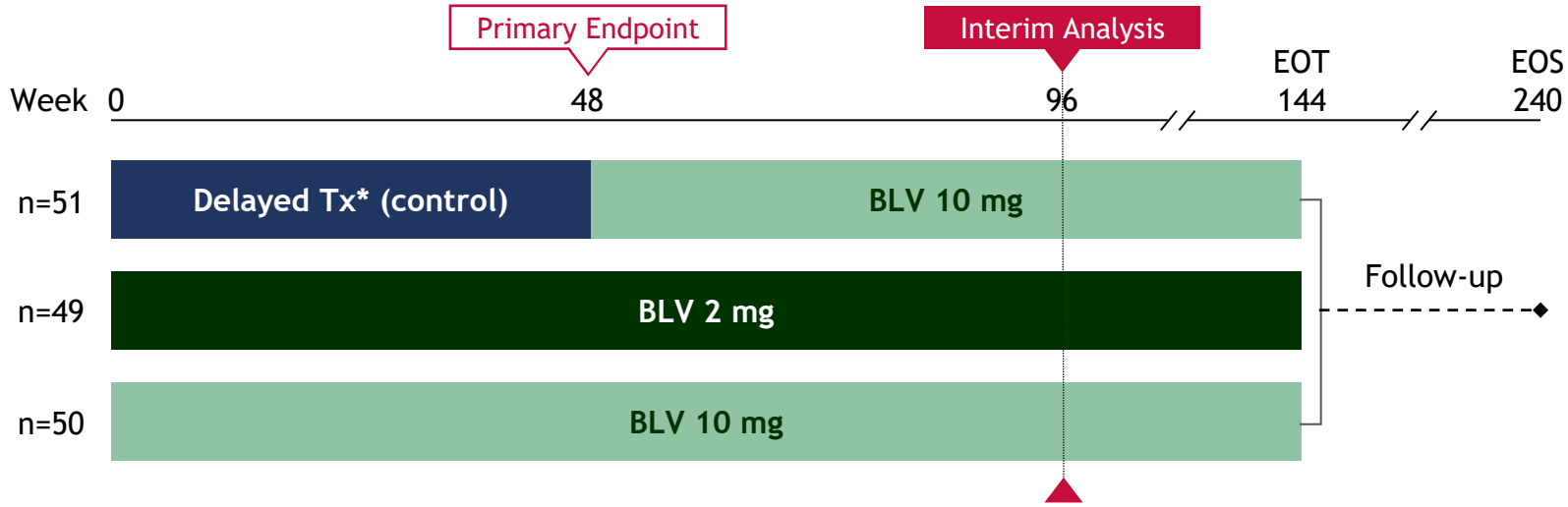
Bulevirtid Monotherapie – Phase III-Studie

Primary endpoint: HDV RNA undetectable or decrease by ≥2 log10 IU/mL from baseline and ALT normalization

Key inclusion criteria:

- Adults with chronic hepatitis delta
- With or without compensated cirrhosis
- ALT >1× to <10× ULN, and positive serum HDV RNA

MYR301:
N=150
Randomized
1:1:1



Multicenter, open-label, randomized, Phase 3 study

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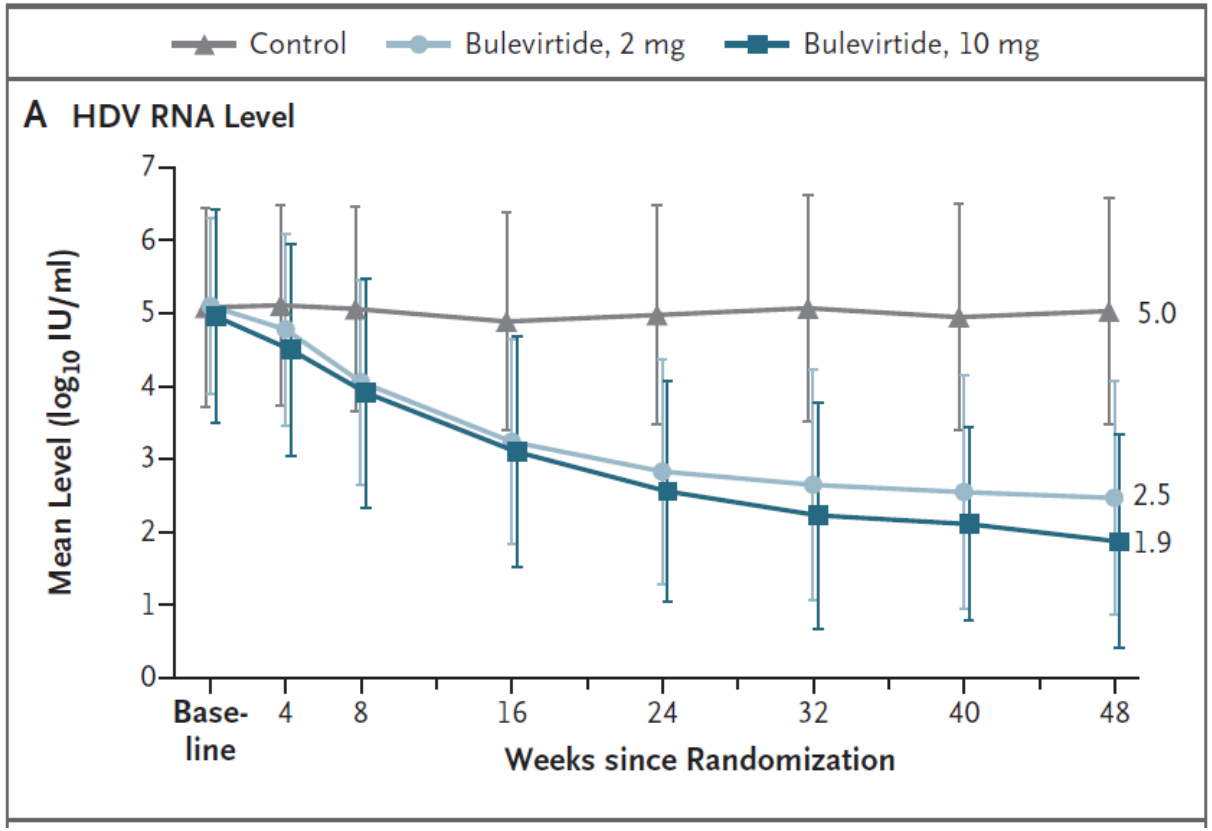
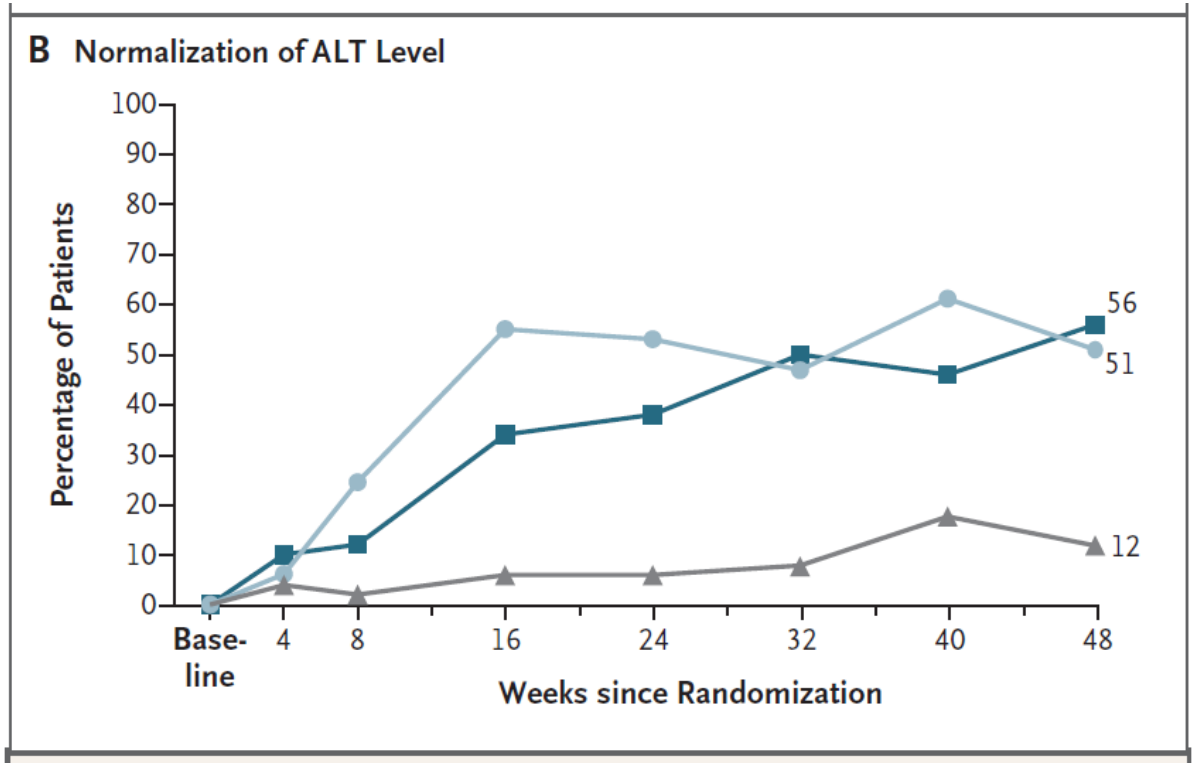
Wedemeyer H et al., NEJM 2023; 389: 22

Bulevirtid Monotherapie – Ansprechen nach 48 Wochen





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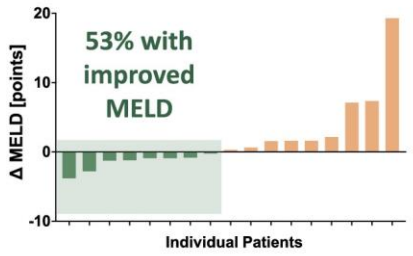
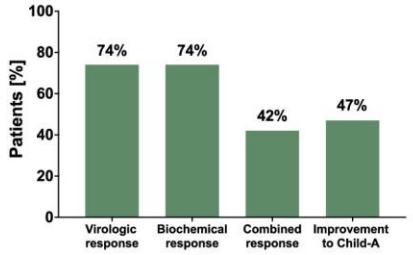
Wedemeyer H et al., NEJM 2023; 389: 22.

HDV Therapie bei Dekompensation

Safety and efficacy of off-label bulevirtide monotherapy in HDV patients with decompensated Child-B cirrhosis

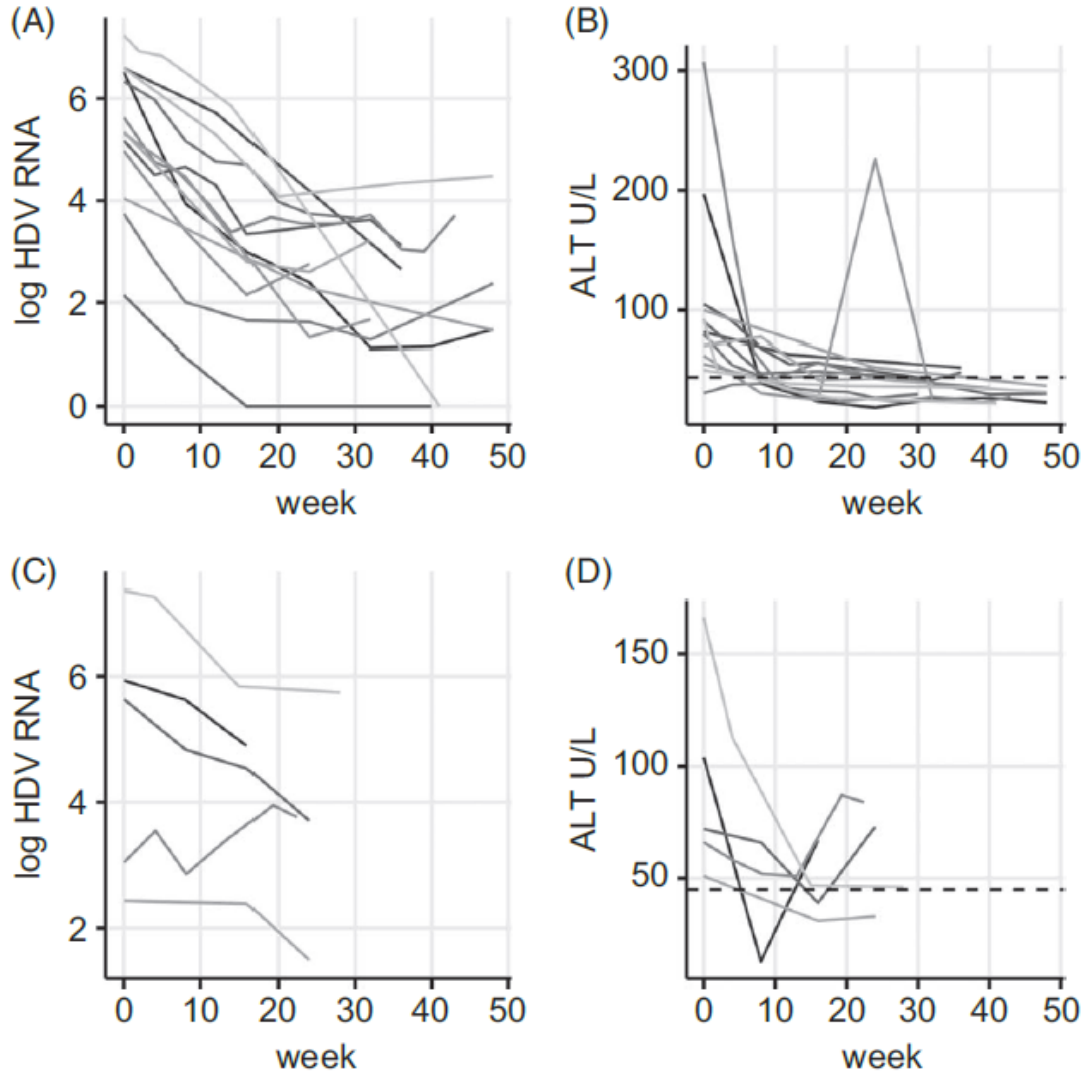
- Retrospective study including 19 European patients with decompensated HDV cirrhosis
- 41 (IQR: 26-75) weeks of bulevirtide treatment
- Response rates similar as reported for compensated HDV patients
- No serious bulevirtide-related AE
- Asymptomatic increases of serum bile acids
- Median MELD remained stable
- Prospective trial needed





Dietz-Fricke, et al. *Hepatology*.

HEPATOLOGY



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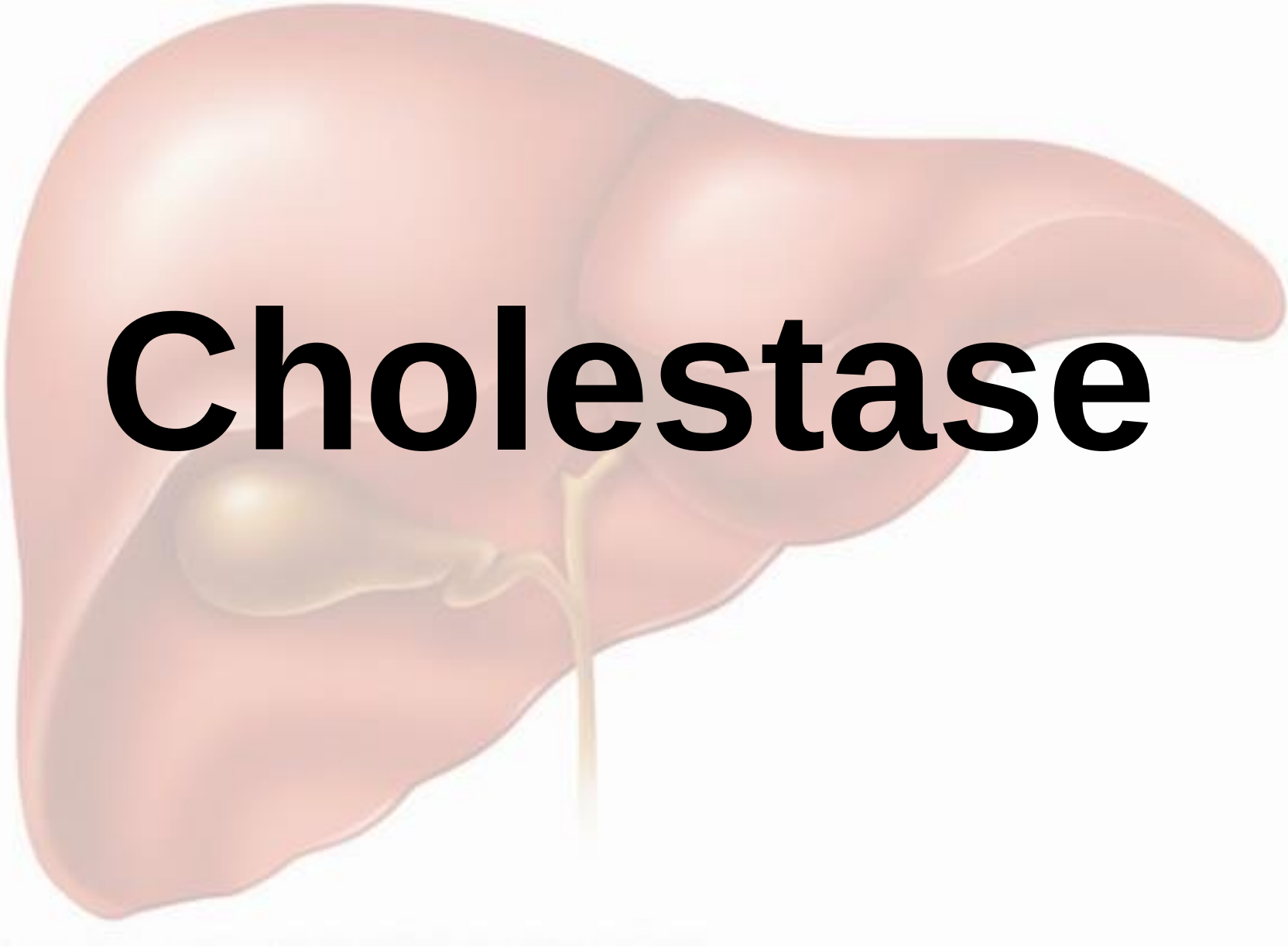
Dietz-Fricke C et al., Hepatology 2024; 80: 64

Take Home Message – Virushepatitis

- **Jeder HBsAg+ Patient soll** einmalig auf **anti-HDV-AK getestet** werden.
- Falls **anti-HDV positiv,** soll eine **HDV-PCR** durchgeführt werden.
- **Bulevirtid (Hepcludex)** ist für die Therapie der HDV-Infektion bei kompensierter Lebererkrankung zugelassen.
- Diese Therapie ist **sicher,** wahrscheinlich auch in fortgeschrittenen Zirrhosestadien.



Cholestase

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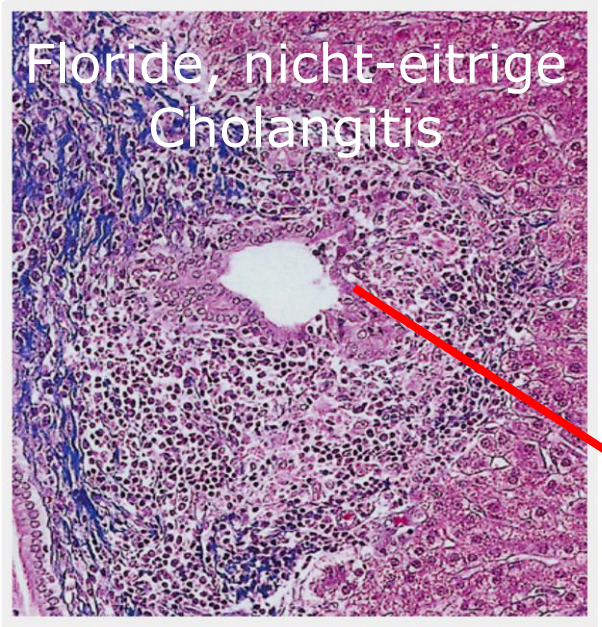
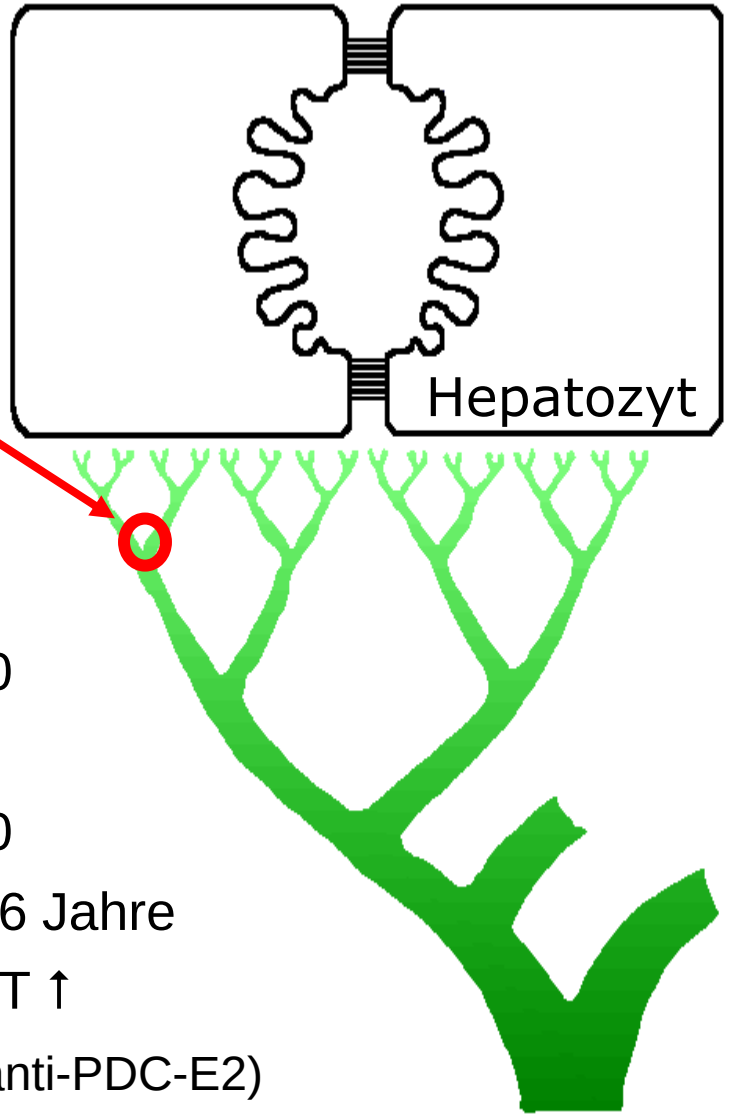
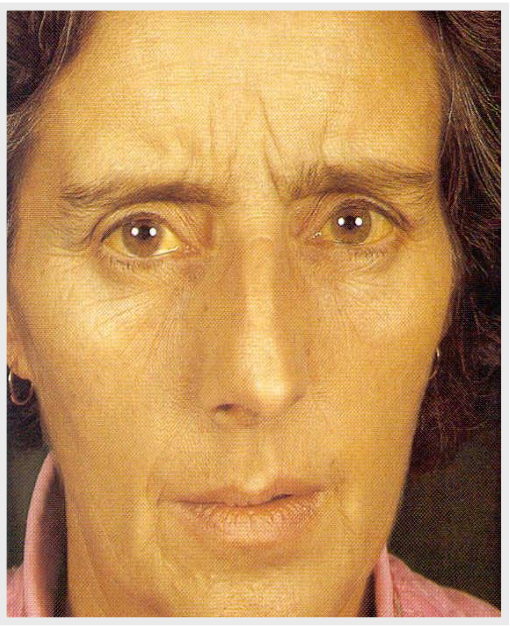
Primär Biliäre Cholangitis
- Klinische Aspekte -







Sherlock and Summerfield 1979

Prävalenz (pro 100.000)	25 – 40
Geschlecht (w : m)	9 : 1
Manifestationsalter	40 – 60
Überleben (ohne Therapie)	7,5 – 16 Jahre
Cholestase	AP/ γGT ↑
Auto-Antikörper	AMA (anti-PDC-E2)
	ANA (sp100, gp210)

Symptome
- Fatigue
- Pruritus
- Sicca-Syndrom
- Gelenkbeschwerden
- …

Standardtherapie und Therapieziele bei PBC

- **UDCA (13-15 mg/kg)** ist **Erstlinientherapie.**

- **Obeticholsäure (OCA)** oder **Bezafibrat (beide Off-Label)** sind Wahl zur zusätzlichen **Zweitlinientherapie bei unzureichendem Therapieansprechen.**

- **Therapieziel** ist die **Normalisierung der Alkalischen Phosphatase** und **Verbesserung der Symptomlast (Pruritus).**

EASL CPG AIH. J Hepatol 2015;63:971-1004

EMA recommends revoking conditional marketing authorisation for Ocaliva

28 June 2024

Benefits of Ocaliva no longer considered to outweigh its risks

News | Human | Referrals

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis

G.M. Hirschfield, C.L. Bowlus, M.J. Mayo, A.E. Kremer, J.M. Vierling, K.V. Kowdley, C. Levy, A. Villamil, A.L. Ladrón de Guevara Cetina, E. Janczewska, E. Zigmond, S.-H. Jeong, Y. Yilmaz, Y. Kallis, C. Corpechot, P. Buggisch, P. Invernizzi, M.C. Londoño Hurtado, S. Bergheanu, K. Yang, Y.-J. Choi, D.B. Crittenden, and C.A. McWherter, for the RESPONSE Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis

K.V. Kowdley, C.L. Bowlus, C. Levy, U.S. Akarca, M.R. Alvares-da-Silva, P. Andreone, M. Arrese, C. Corpechot, S.M. Francque, M.A. Heneghan, P. Invernizzi, D. Jones, F.C. Kruger, E. Lawitz, M.J. Mayo, M.L. Shiffman, M.G. Swain, J.M. Valera, V. Vargas, J.M. Vierling, A. Villamil, C. Addy, J. Dietrich, J.-M. Germain, S. Mazain, D. Rafailovic, B. Taddé, B. Miller, J. Shu, C.O. Zein, and J.M. Schattenberg, for the ELATIVE Study Investigators' Group*

USZ Universitäts Spital Zürich

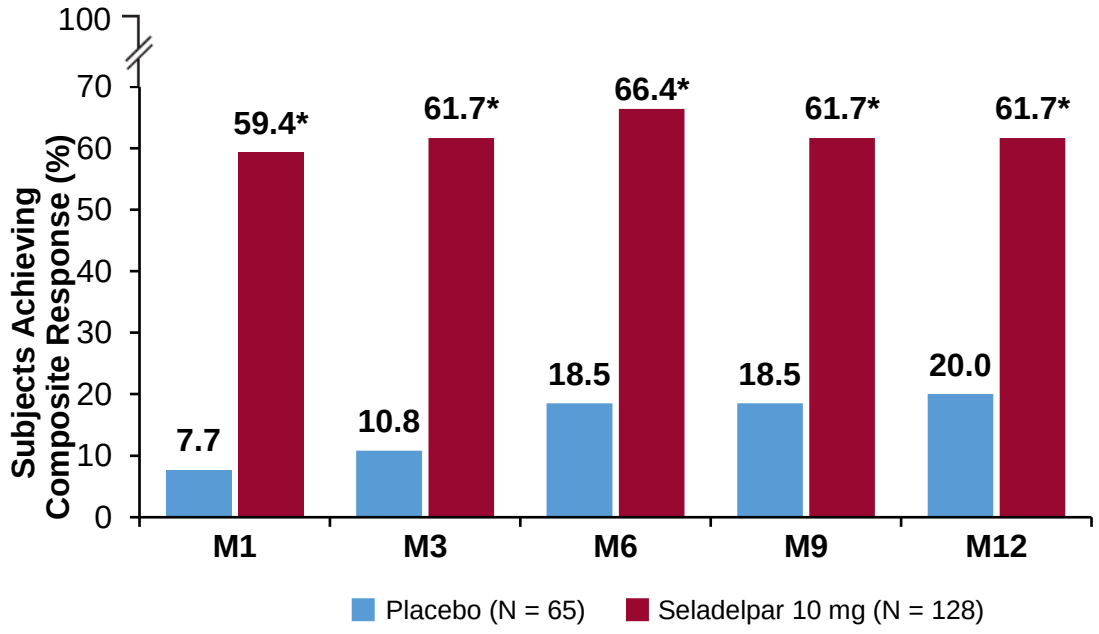
Hirschfield GM et al., NEJM 2014; Feb 29;390(9):783-794

Kowdley K et al., NEJM 2024; Feb 29;390(9):795-805

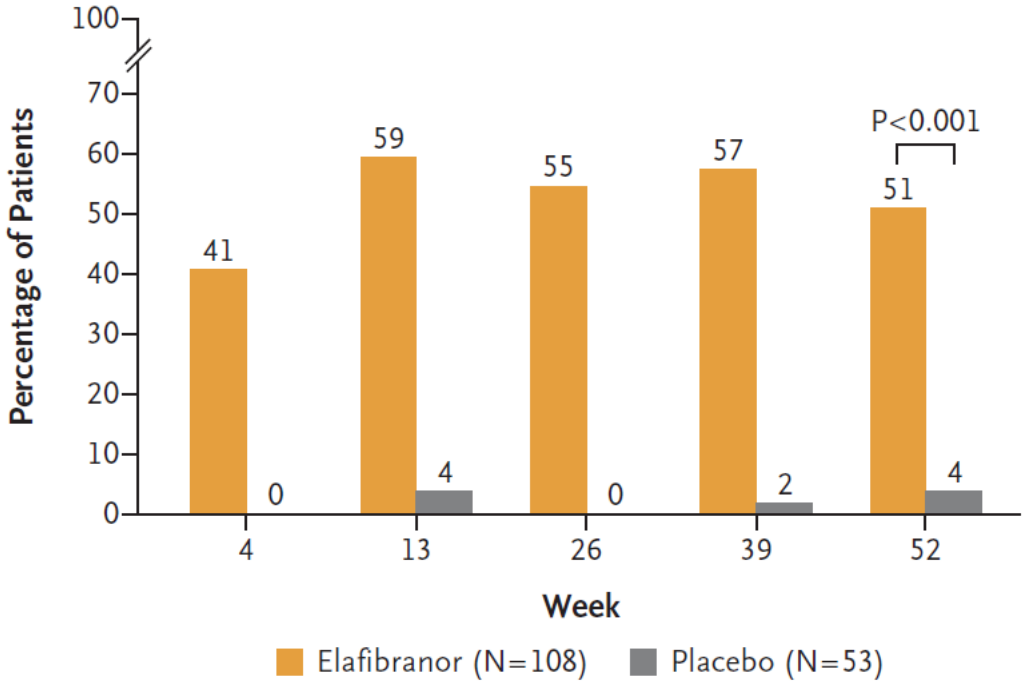
Primärer Endpunkt: Composite Response

AP < 1.67x ULN, AP-Abfall um > 15% und normwertiges Bilirubin

RESPONSE



ELATIVE



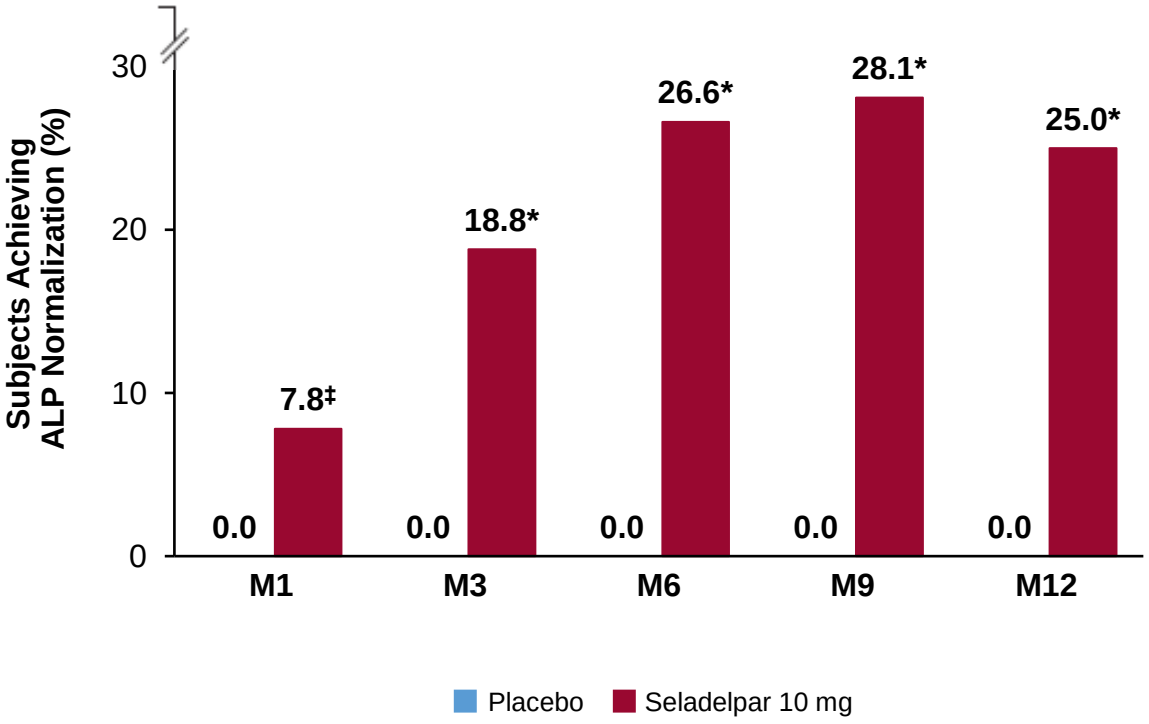
USZ Universitäts Spital Zürich

Hirschfield GM et al., NEJM 2014; Feb 29;390(9):783-794

Kowdley K et al., NEJM 2024; Feb 29;390(9):795-805

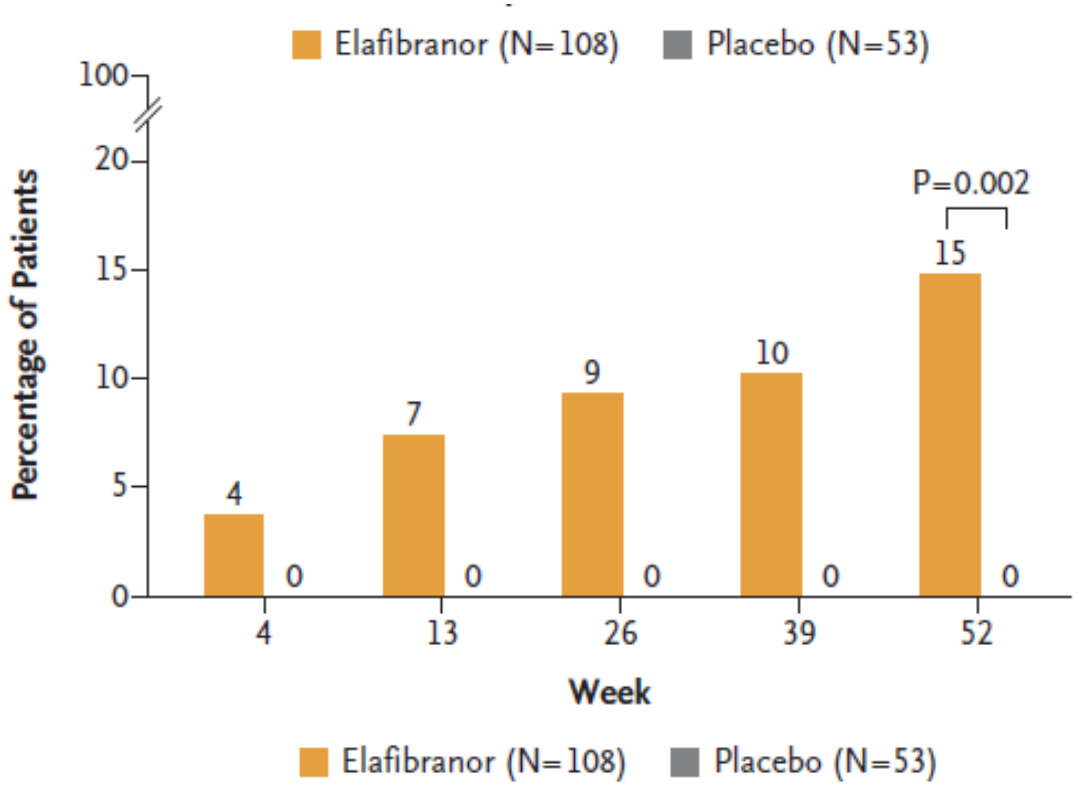
Normalisierung der Alkalischen Phosphatase

RESPONSE



Hirschfield GM et al., NEJM 2014; Feb 29;390(9):783-794

ELATIVE



Kowdley K et al., NEJM 2024; Feb 29;390(9):795-805

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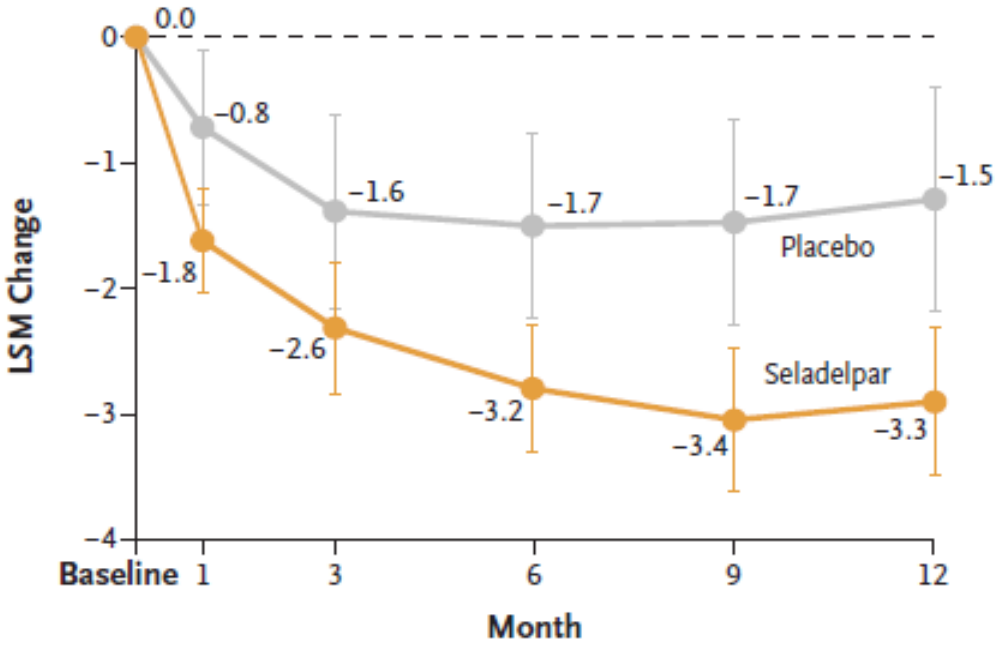
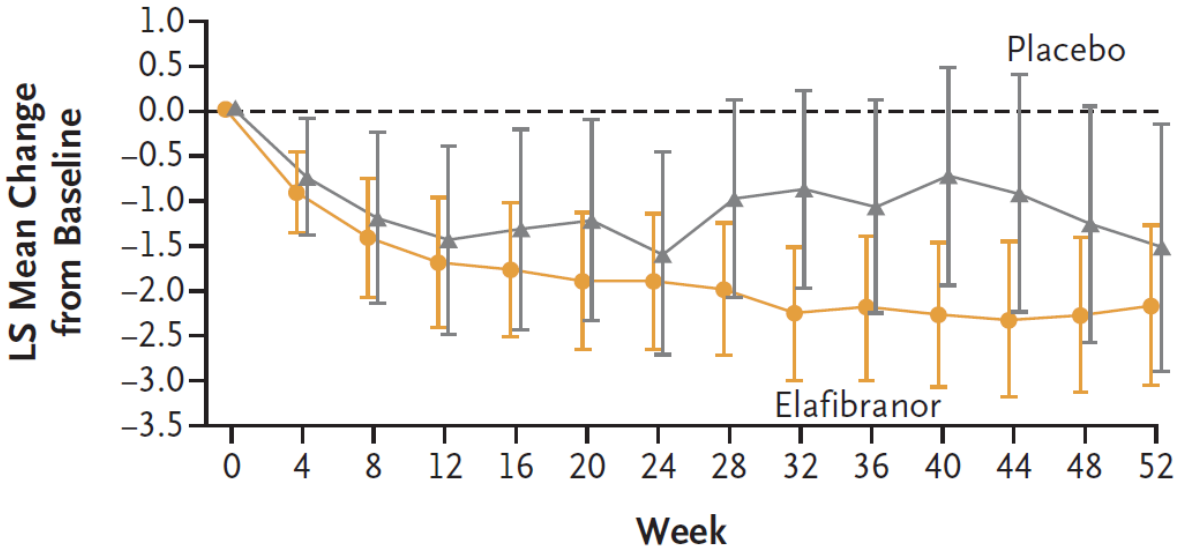
Verbesserung des Pruritus (NRS)
- Moderat bis schwerwiegender Pruritus -

RESPONSE



No. at Risk						
Placebo	23	22	22	20	20	16
Seladelpar	49	48	46	45	36	39

ELATIVE



No. at Risk														
Placebo	22	21	19	18	18	17	16	15	15	16	15	14	13	12
Elafibranor	44	41	40	39	40	38	37	34	35	34	32	34	35	32

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Hirschfield GM et al., NEJM 2014; Feb 29;390(9):783-794

Kowdley K et al., NEJM 2024; Feb 29;390(9):795-805

Zulassungsstatus

RESPONSE	ELATIVE
	
FDA Zulassung, EMA Zulassung voraussichtlich ab Anfang 2025	**FDA und EMA Zulassung**

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Hirschfield GM et al., NEJM 2014; Feb 29;390(9):783-794

Kowdley K et al., NEJM 2024; Feb 29;390(9):795-805

Sicherheitsdaten

RESPONSE

Table 2. Adverse Events and Serious Adverse Events.*

Event	Placebo (N=65)	Seladelpar (N=128)
	number (percent)	
Any adverse event	55 (84.6)	111 (86.7)
Any serious adverse event	4 (6.2)	9 (7.0)
Adverse events in ≥5% of patients		
Coronavirus disease 2019	10 (15.4)	23 (18.0)
Pruritus	10 (15.4)	6 (4.7)
Upper respiratory tract infection	6 (9.2)	1 (0.8)
Nausea	3 (4.6)	8 (6.2)
Abdominal distention	2 (3.1)	8 (6.2)
Asthenia	4 (6.2)	5 (3.9)
Urinary tract infection	4 (6.2)	4 (3.1)
Hypertension	4 (6.2)	4 (3.1)
Positional vertigo	4 (6.2)	1 (0.8)

CAVE:
Erhöhtes Frakturrisiko unter Seladelpar (Livdelzi): 4% vs. 0% unter Placebo
Press Release: 14. August 2024

Hirschfield GM et al., NEJM 2014; Feb 29;390(9):783-794

ELATIVE

Table 3. Summary of Adverse Events and Adverse Events Occurring in More than 10% of Patients in Either Group.

Event	Elafibranor (N=108)	Placebo (N=53)
	no. of patients (%)	
Any adverse event that emerged during treatment period*	104 (96)	48 (91)
Covid-19	31 (29)	20 (38)
Pruritus	22 (20)	14 (26)
Abnormal weight gain	21 (19)	10 (19)
Abdominal pain, including upper and lower abdomen	12 (11)	3 (6)
Diarrhea	12 (11)	5 (9)
Any severe adverse event†	12 (11)	6 (11)
Any adverse event attributed to the trial regimen that emerged during treatment period‡	42 (39)	21 (40)
Any serious adverse event that emerged during treatment period§	11 (10)	7 (13)
Any adverse event leading to discontinuation of the trial regimen that emerged during treatment period	11 (10)	5 (9)
Any fatal adverse event	2 (2)	0

CAVE:
Erhöhtes Frakturrisiko unter Elafibranor (Iqirvo): 6% vs. 0% unter Placebo
Press Release: 10. Juni 2024

Kowdley K et al., NEJM 2024; Feb 29;390(9):795-805

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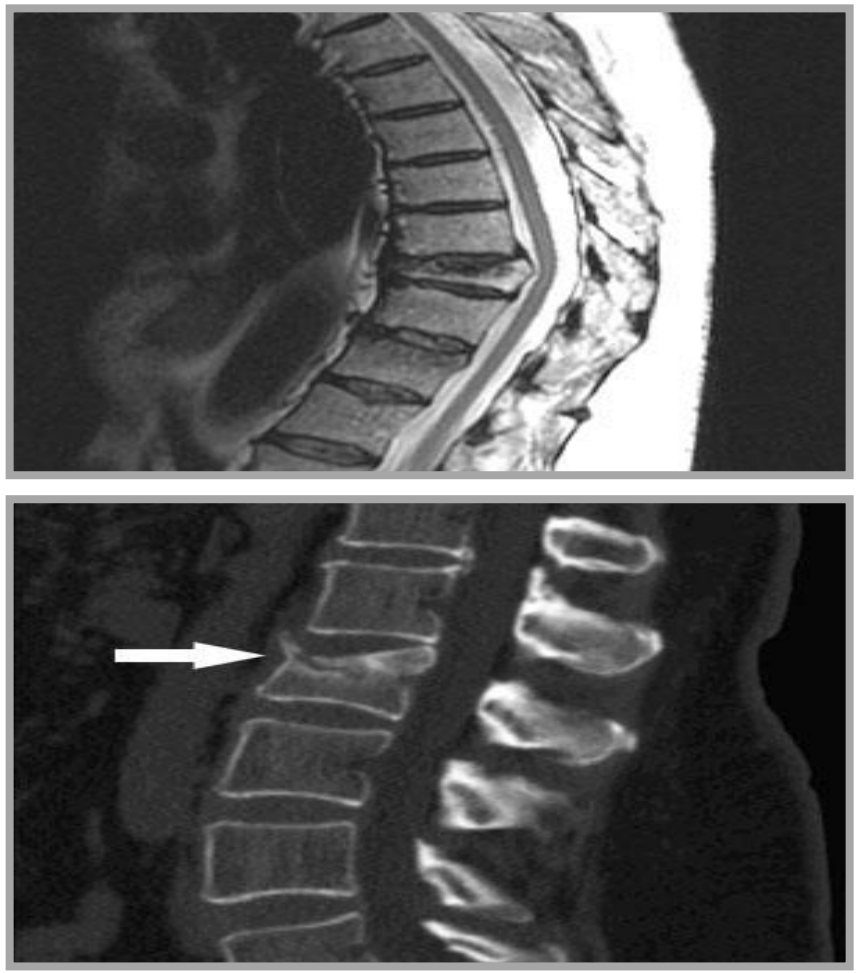
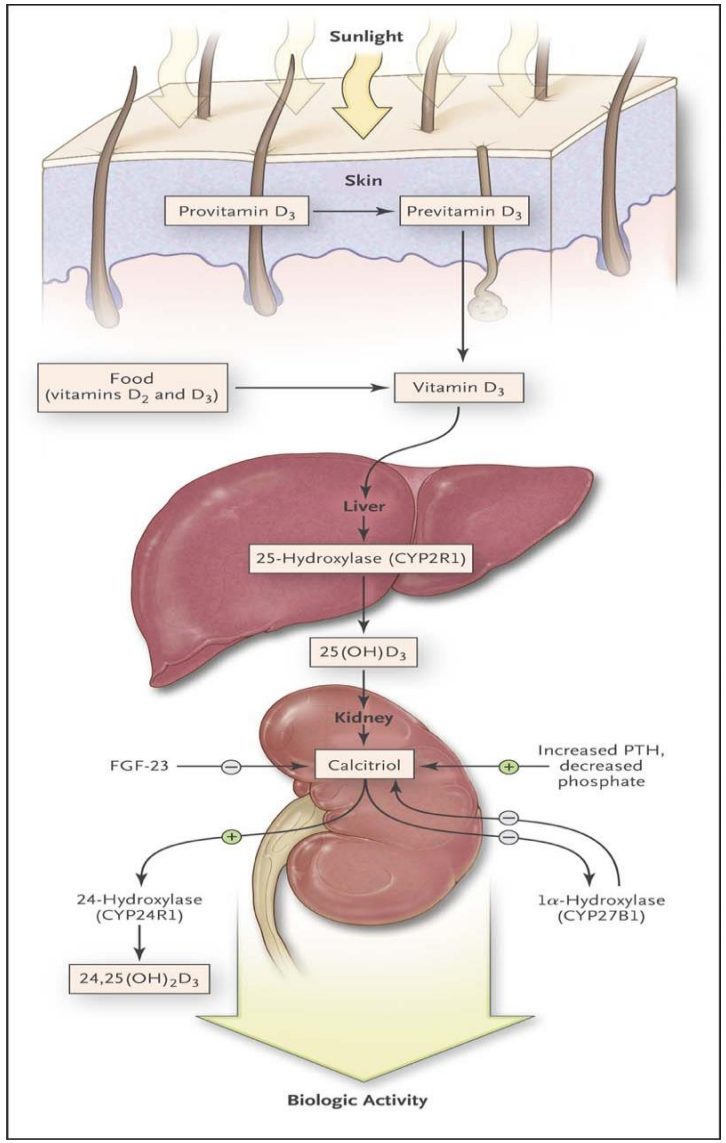
Vitamin D und Knochenmineralisierung



Synthese des Vitamins D



- UV light in the skin
- 25-Hydroxylation in the liver
- 1-Hydroxylation in the kidney

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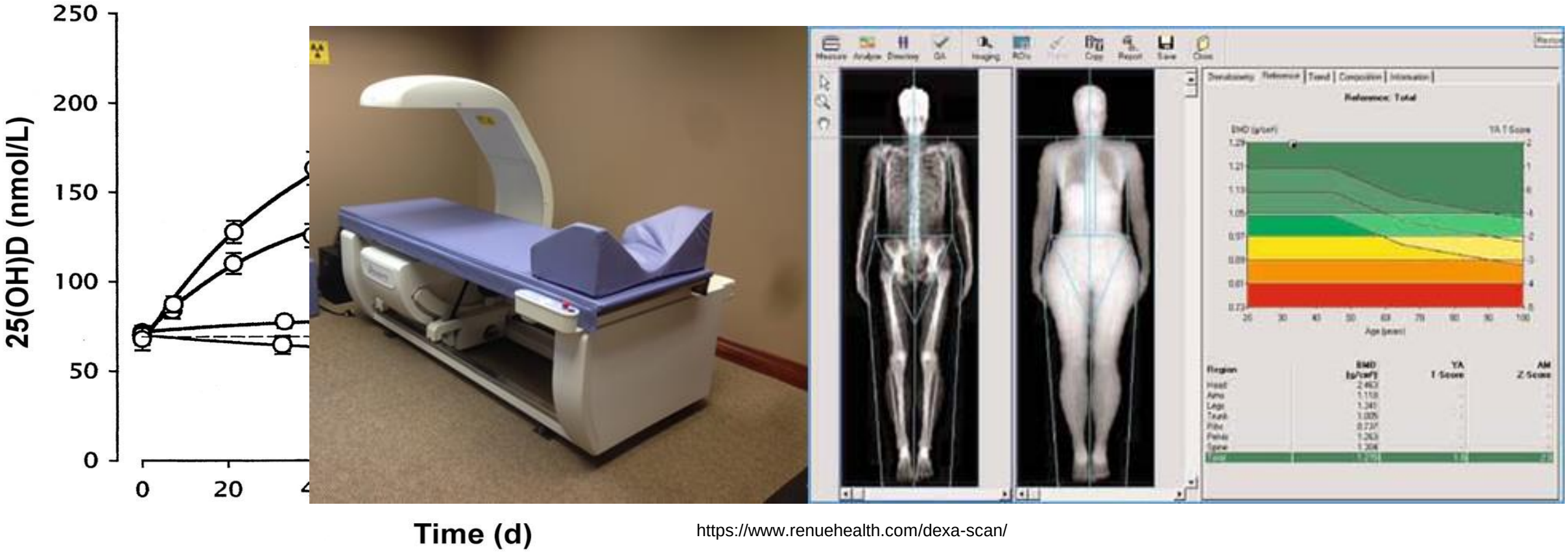
Holick M. N Engl J Med 2007;357:266-281

Ausreichende D Substitution und regelmässige DXA Scans

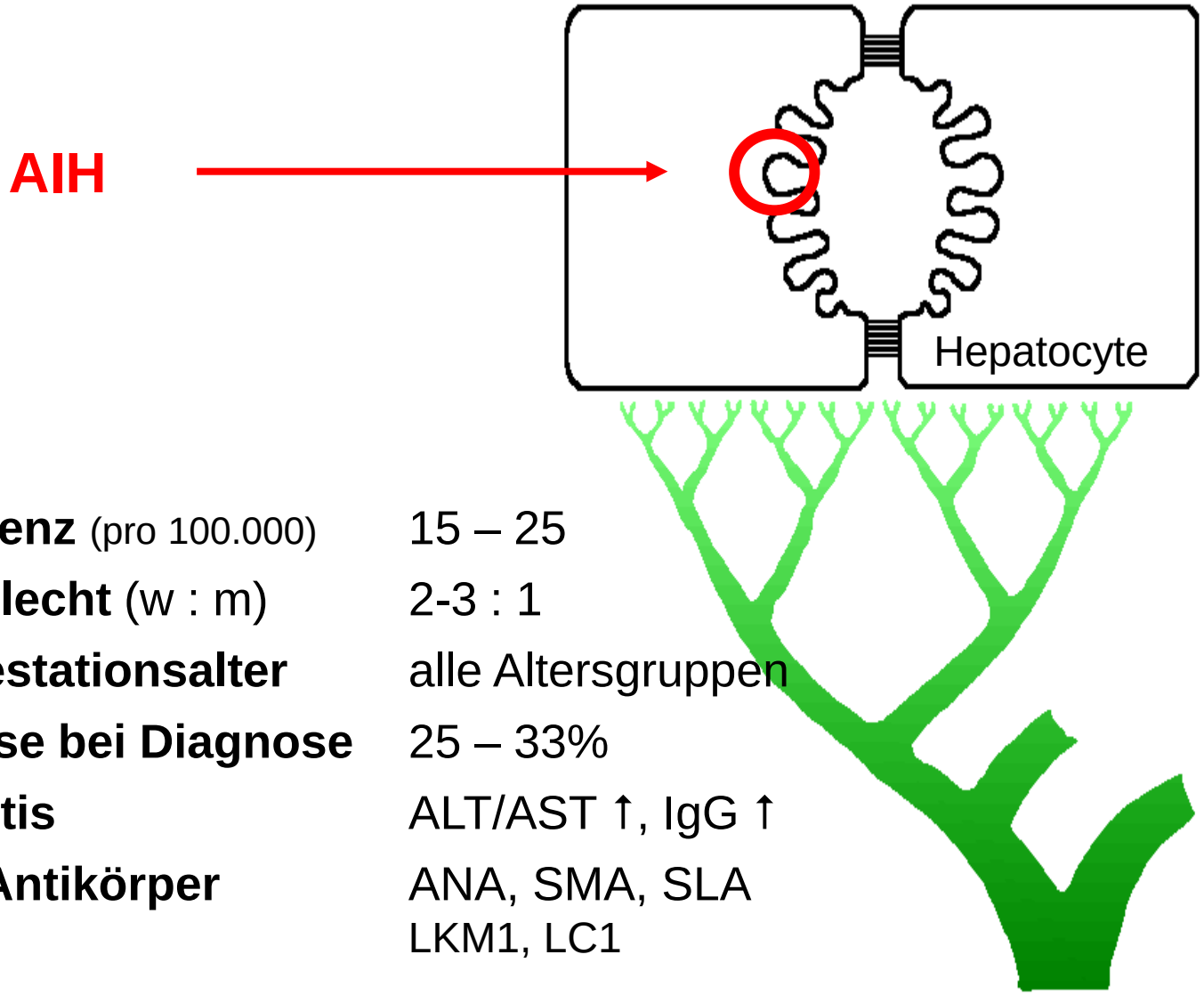


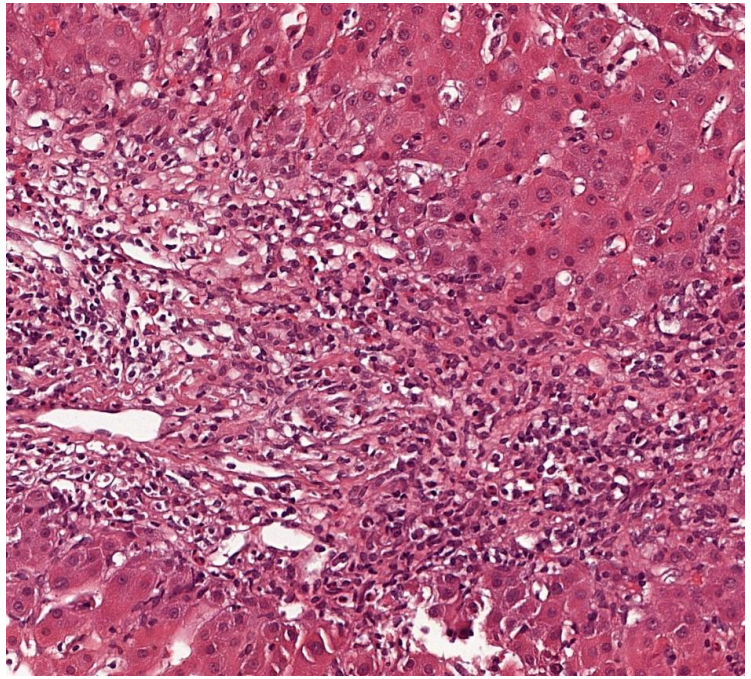
https://www.renuehealth.com/dexa-scan/

CAVE: Erhöhtes Frakturrisiko wahrscheinlich auch bei Fibraten!

Heaney RP et al., Am J Clin Nutr 2003; 77: 204

Autoimmunhepatitis (AIH)
- Klinische Aspekte -





Prävalenz (pro 100.000)	15 – 25
Geschlecht (w : m)	2-3 : 1
Manifestationsalter	alle Altersgruppen
Zirrhose bei Diagnose	25 – 33%
Hepatitis	ALT/AST ↑, IgG ↑
Auto-Antikörper	ANA, SMA, SLA LKM1, LC1

Symptome
- Fatigue
- Malaise
- Gelenkbeschwerden
- Amenorrhoe
- …

Standardtherapie bei der Autoimmunhepatitis

- **Steroide** sind Mittel der Wahl zur **Remissionsinduktion**
- **Azathioprin** ist Mittel der Wahl zur **Erhaltungstherapie**
- **Therapieziel** sind die vollständige biochemische Remission: **normwertige Transaminasen und IgG**

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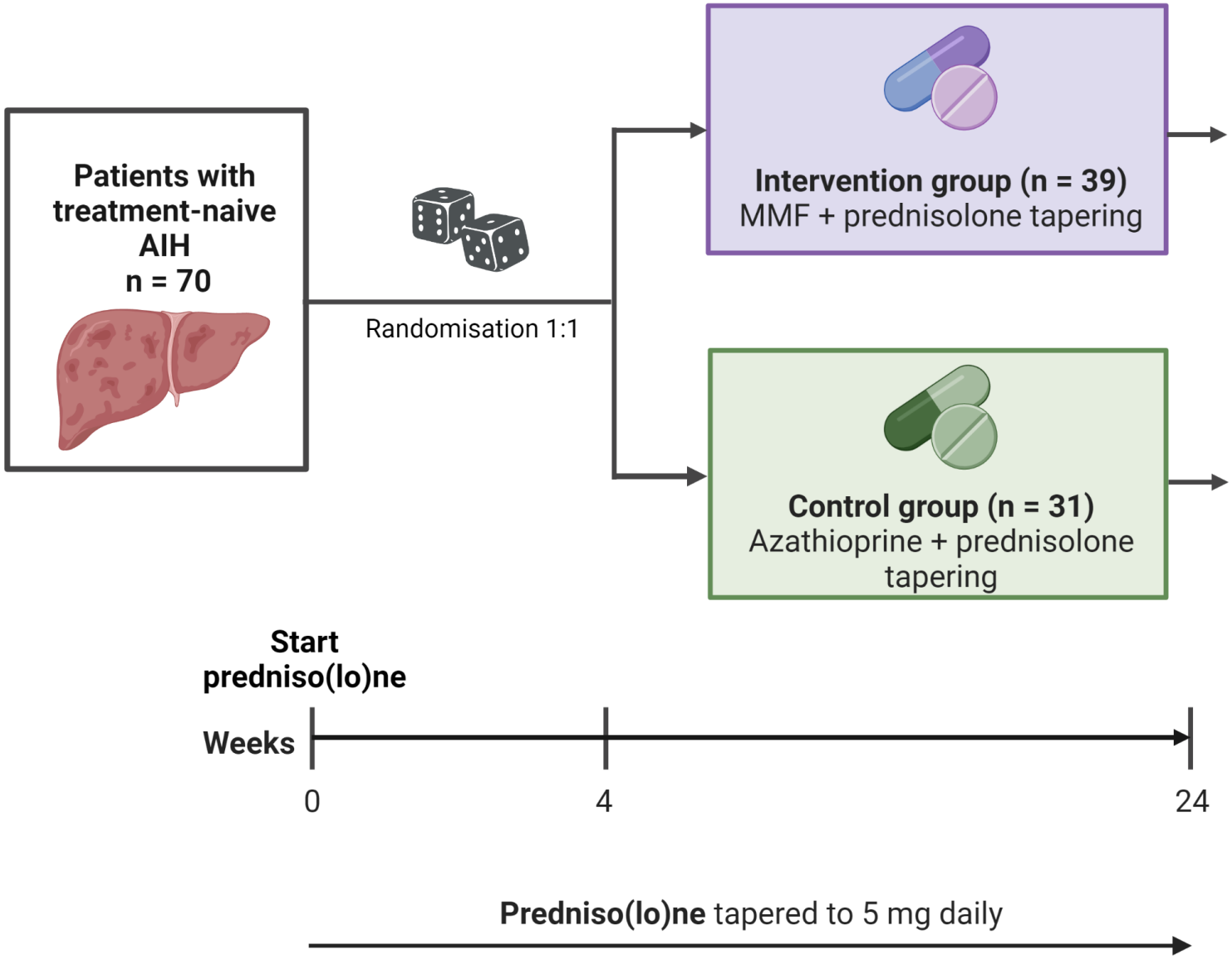
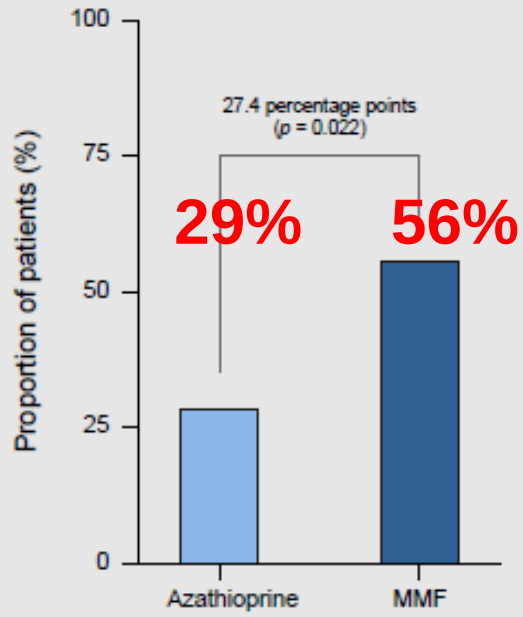
EASL CPG AIH. J Hepatol 2015;63:971-1004

CAMARO-Trial: Azathioprin gegenüber MMF bei AIH



Results

Primary outcome
Biochemical remission



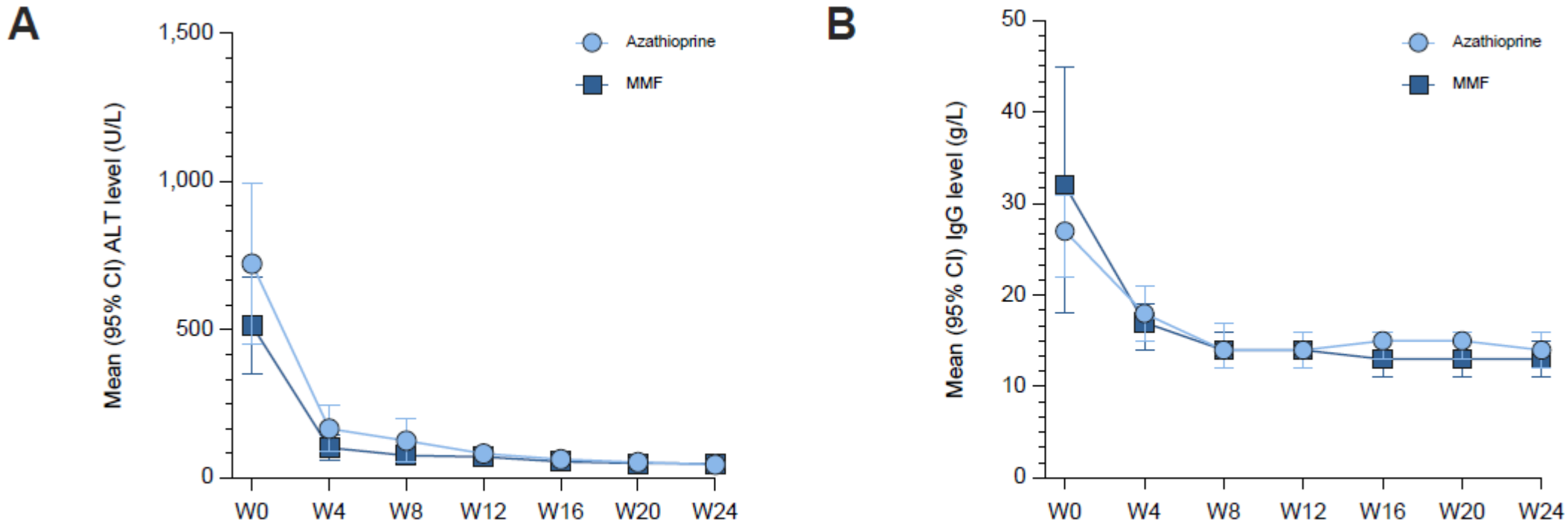
Secondary outcomes

SAEs occured in 4 patients in the azathioprine group and were absent with MMF (12.9% *vs.* 0%, $p = 0.034$)

Cessation of treatment due to (S)AEs occurred more often with azathioprine than MMF (25.8% *vs.* 5.1%, $p = 0.018$)

Snijders R et al., J Hepatol 2024; 80: 576

CAMARO-Trial: Azathioprin gegenüber MMF bei AIH



- Vergleichbare mittlere kumulative Predniso(lo)n-Dosis
- Nach 24 Wochen: mittlere Dosis Aza 1.16 mg/kg / MMF 1853 mg/d
- TRSAE: 3 in Aza, 0 in MMF
- Behandlungsabbruch wegen (S)AE Aza (25.8%) vs. MMF (5.1%; p=0.018)

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Snijders R et al., J Hepatol 2024; 80: 576

Ist eine IgG Normalisierung relevant für die Prognose?

Kanadische Multicenter Kohorten-Studie: N=691; 75% Frauen; Median follow-up: 6 Jahre

	Univariable analysis			Multivariable analysis		
Variable	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Sex, female	0.82	0.55–1.23	0.334	0.75	0.49–1.14	0.171
Age at diagnosis (by 10 years)	**1.25**	**1.12–1.40**	**<0.001**	**1.26**	**1.12–1.41**	**<0.001**
Cirrhosis at diagnosis, yes	**3.67**	**2.48–5.43**	**<0.001**	**3.47**	**2.32–5.18**	**<0.001**
Baseline bilirubin xULN	**1.36**	**1.17–1.58**	**<0.001**	**1.35**	**1.15–1.58**	**<0.001**
Elevated ALT (by 10% time)	**1.07**	**1.00–1.13**	**0.036**	**1.08**	**1.01–1.15**	**0.034**
Elevated AST (by 10% time)	**1.13**	**1.06–1.21**	**0.001**	-	-	-
Elevated IgG (by 10% time)	1.01	0.95–1.07	0.809	0.99	0.93-1.06	0.817
Prednisone dose, >30 mg/day	1.31	0.82–2.08	0.254	-	-	-

Highlights

- **Baseline markers** of disease severity **and initial prednisone dose do not predict ALT reduction** over 18 months.
- **Persistent elevations in ALT and AST,** but **not IgG,** are **associated with decreased clinical event-free survival**.

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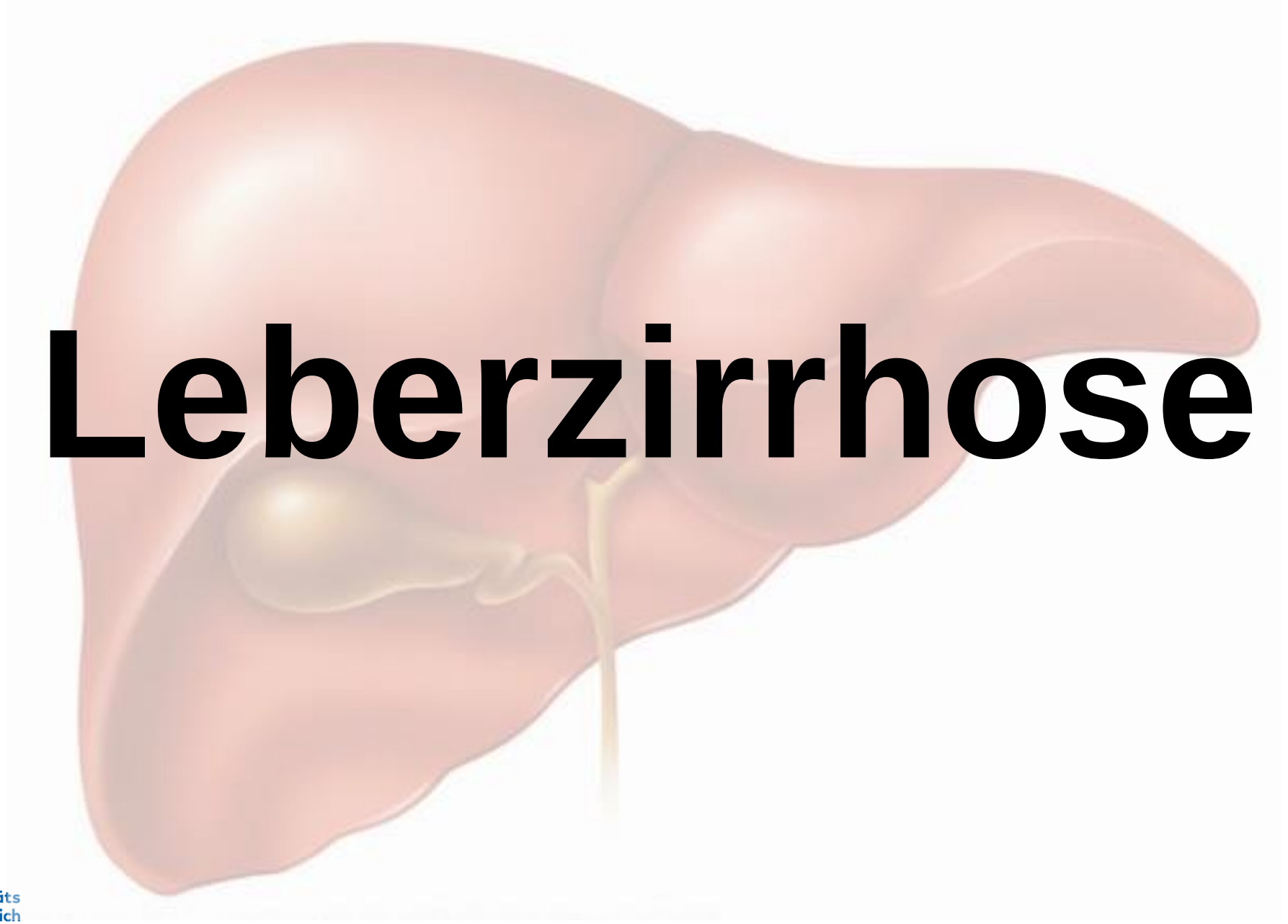
Plagiannakos CG et al., J Hepatol 2024; 81: 227

Take Home Message – PBC und AIH

- Das **neue Therapieziel** bei der **PBC** ist eine **vollständige Normalisierung** der Cholestaseparameter.
- **Risikofaktoren für Erkrankungsprogress** sind **junges Alter** und **höhergradige Fibrose.**
- Als **Zweitlinientherapie** stehen **Obeticholsäure** bzw. **Bezafibrat** (beide Off-Label!) zur Verfügung.
- Neue Therapieoptionen sind **Elafibranor** und **Seladepar (EMA approval 02/2025).**
- Auf **erhöhtes Frakturrisiko** bei **allen PPAR-Agonisten** achten.
- Das **Therapieziel** bei der **AIH** ist eine **vollständige Normalisierung** der Transaminasen (und ggf. auch des IgG).
- Als **Erstlinientherapie** kann neben **Azathioprin** auch **MMF** bei besserer Verträglichkeit eingesetzt werden.

Leberzirrhose



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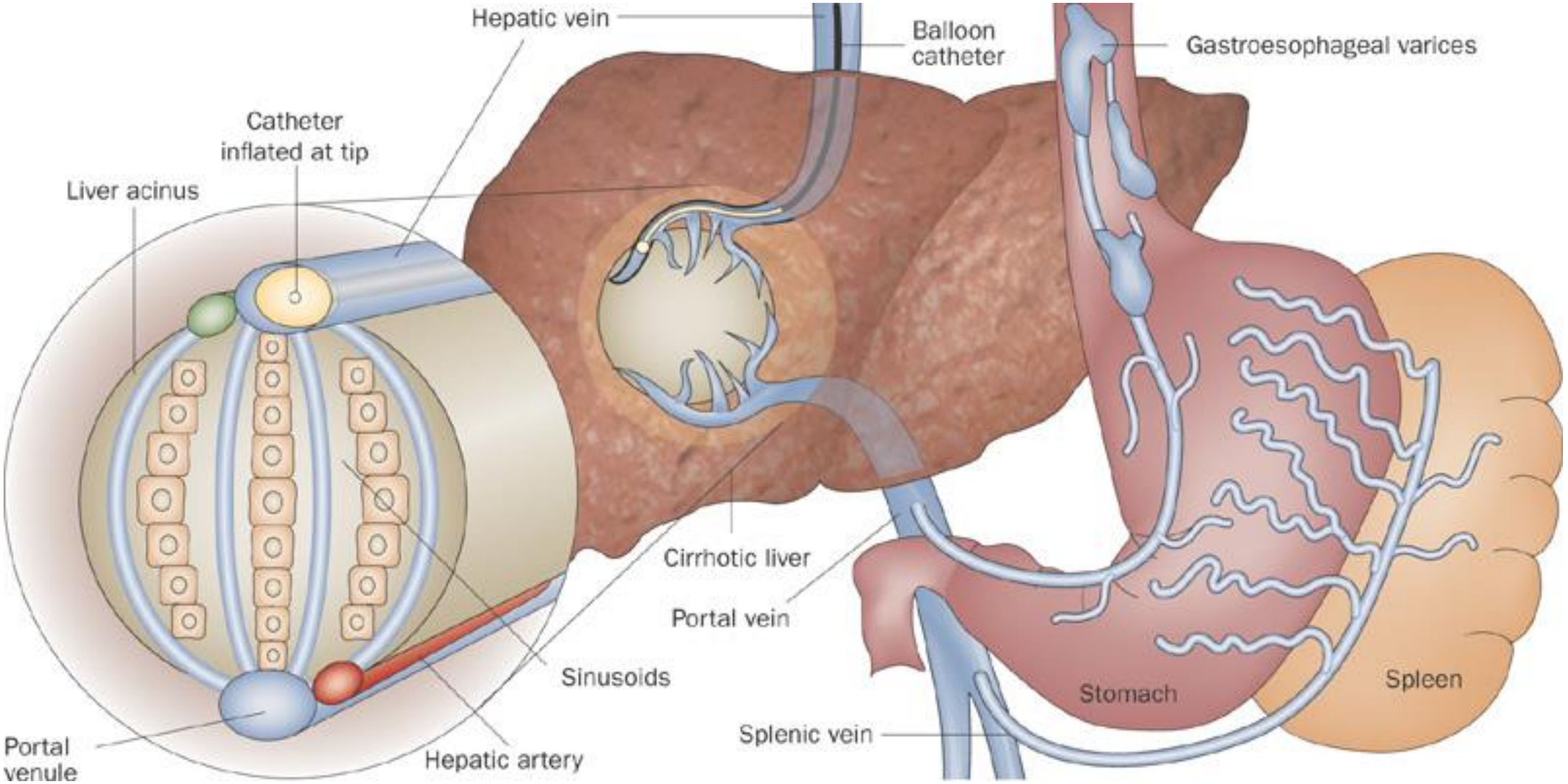
Blutungskomplikationen bei Zirrhose und portaler Hypertonie



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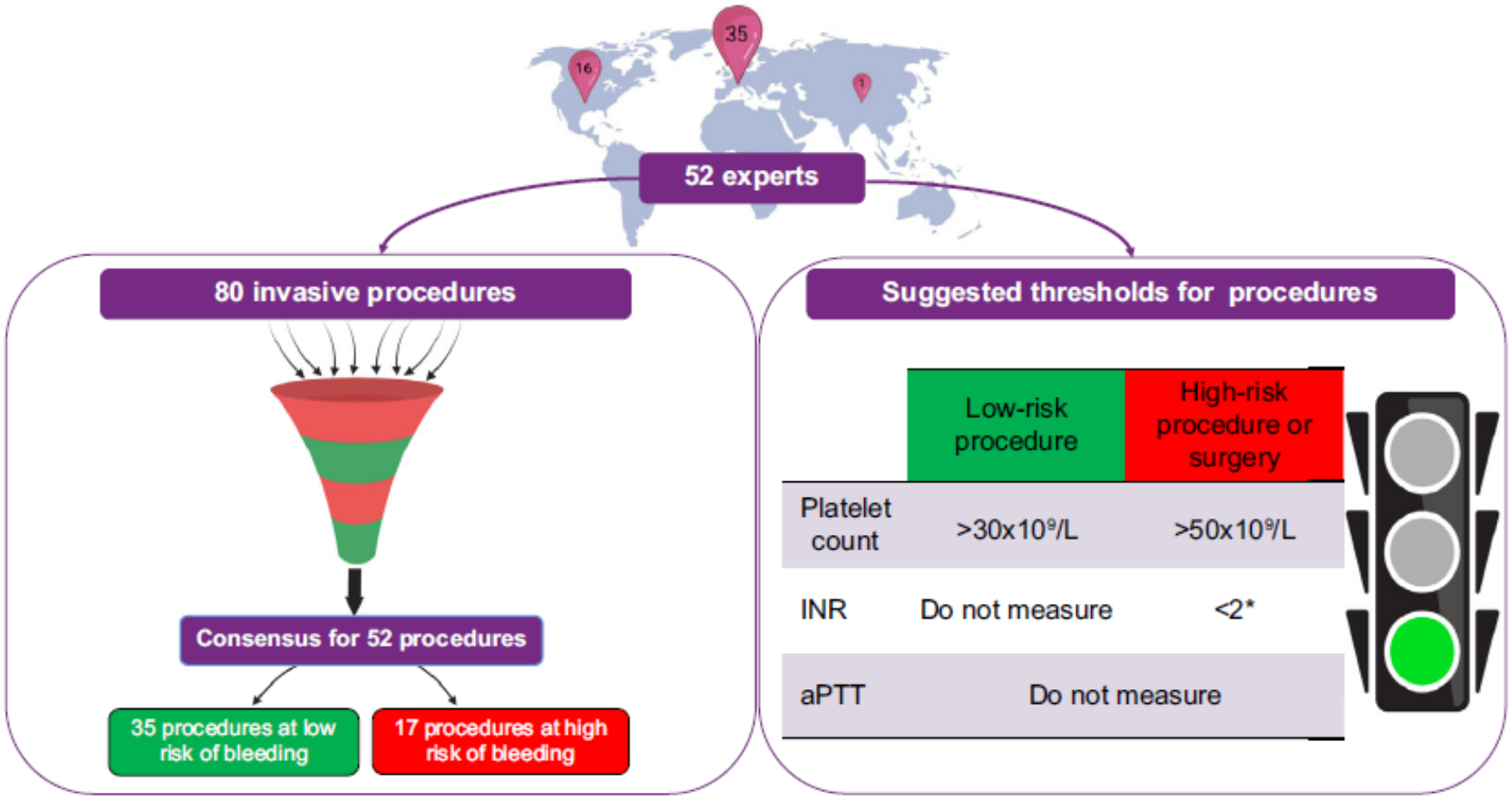
Bosch J et al., Nat Rev Gastroenterol Hepatol 2009; 6: 573

Blutungsrisiko durch invasive Eingriffe bei Leberzirrhose



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Riescher-Tuczkiewicz A et al., JHEP Report 2024; Epub

Blutungsrisiko durch invasive Eingriffe bei Leberzirrhose

		Procedure	Voting percentage	
			Low risk	High risk
Digestive endoscopy	ERCP	Without sphincterotomy	90%	10%
		With biliary or pancreatic sphincterotomy	12%	88%
		With papillary balloon dilatation without sphincterotomy	67%	33%
		With biliary or pancreatic stent placement without sphincterotomy	80%	20%
	Upper and lower	Mucosal resection	25%	75%
		Submucosal dissection	8%	92%
		Hemostasis with argon plasma coagulation	92%	8%
		Radiofrequency ablation	67%	33%
		Video capsule	100%	0%
		Ultrasound without fine-needle aspiration	98%	2%
		Ultrasound with fine-needle aspiration	59%	41%
		Stricture dilatation (pneumatic or bougie)	32%	68%
		Stricture dilatation (balloon)	38%	63%
		Enteral stent deployment	77%	23%
		Cystogastrostomy	13%	87%
		Polypectomy <1 cm	76%	24%
		Polypectomy >1 cm	12%	88%
		Diagnostic (with or without biopsy)	98%	2%

	Procedure	Voting percentage	
		Low risk	High risk
Hepatology	Percutaneous liver biopsy	33%	67%
	Transjugular liver biopsy	83%	17%
	Laparoscopic liver biopsy	46%	54%
	Hepatic venous pressure gradient measurement	92%	8%
	Portal recanalization	40%	60%
	Transjugular intrahepatic portosystemic shunt	38%	62%
	Transcatheter arterial chemoembolization or radioembolization	62%	38%
	Percutaneous ablation of liver cancer	40%	60%
	Cholecystostomy or percutaneous biliary drain placement	22%	78%
	Diagnostic paracentesis	98%	2%
	Therapeutic paracentesis	96%	4%
	Tunneled ascitic drain placement	59%	41%
Pulmonary medicine	Thoracentesis	78%	22%
	Bronchoscopy without biopsy	96%	4%
	Bronchoscopy with biopsy	29%	71%
	Therapeutic bronchoscopy	26%	74%
	Intrathoracic organ biopsy	9%	91%
	Tunneled pleural drain placement	44%	56%

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Consensus for a procedure to be at "low bleeding risk" | Consensus for a procedure to be at "high bleeding risk" | No consensus

Riescher-Tuczkiewicz A et al., JHEP Report 2024; Epub

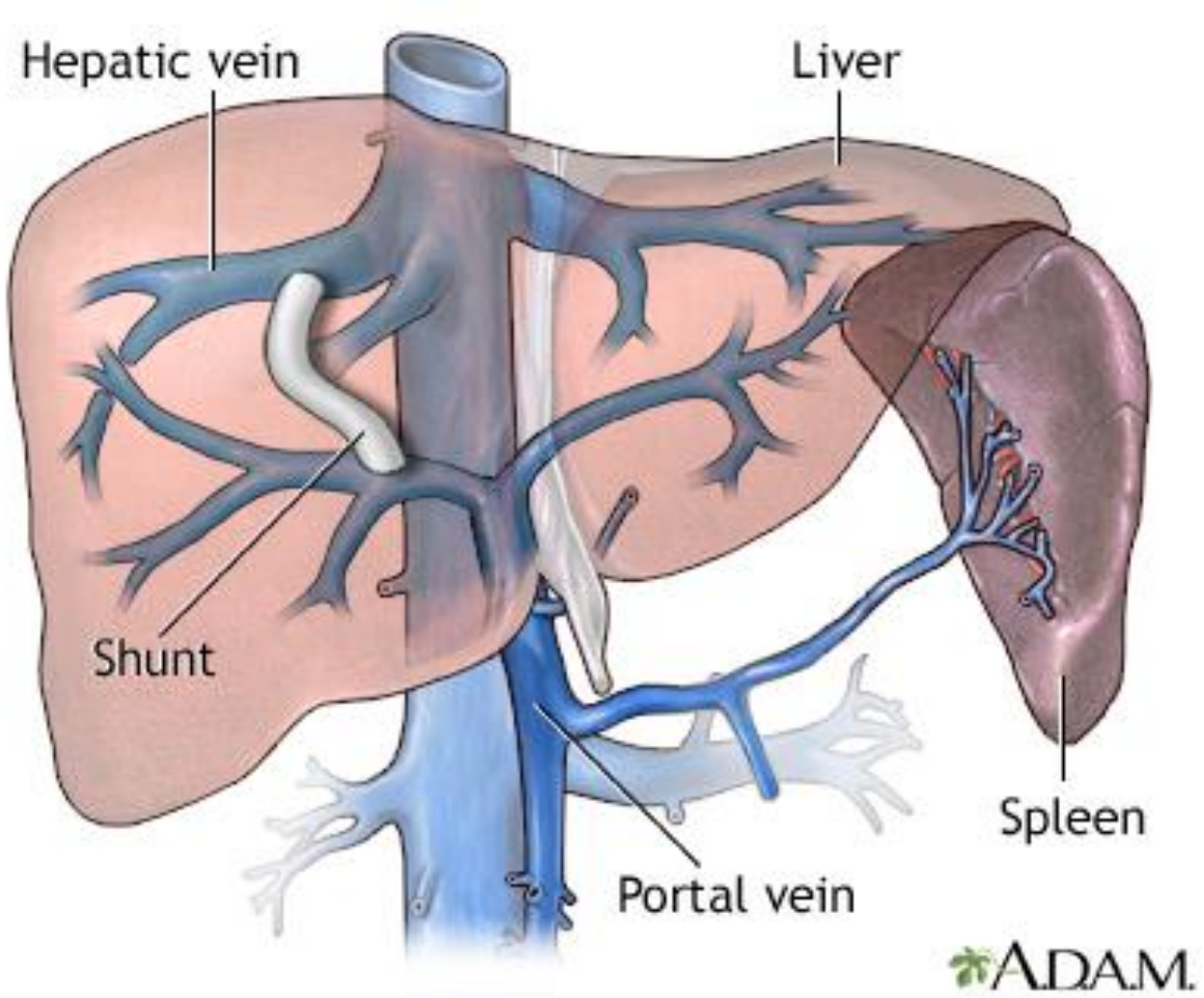
AASLD Konsensus-Empfehlungen: Laboranalyse, Transfusion

		A role for laboratory testing prior to procedure?			A role for prophylactic transfusion?		Permissible to continue medications?		
		INR	Platelet count	Viscoelastic testing	Plasma	Platelets	Aspirin	Clopidogrel	Anticoagulants (within 24 h)
Diagnostic paracentesis	Outpatient	No	No	No	No	No	Yes	Yes	All
	Inpatient	No		No	No	Uncertainty when <20,000 mm^3			
Therapeutic paracentesis	Outpatient	No		No	No	Uncertainty when <20,000 mm^3	Yes	Yes	All
	Inpatient	No			No	Uncertainty when <20,000 mm^3			
Diagnostic endoscopy	Compensated	No	No		No	No	Yes	Yes	
	Decompensated	No			No	Uncertainty when <20,000 mm^3			
Upper endoscopy with therapeutic intent	Compensated					Uncertainty when <20,000 mm^3	Yes		DOAC warfarin / Enoxaparin
	Decompensated					Uncertainty when <20,000 mm^3			
Endoscopy for hemorrhage						Uncertainty when <20,000 mm^3	N/A	N/A	N/A

Note: Consensus is denoted with green color (>75% agreement), yellow indicates that there was 50%–75% agreement, and red indicates that there was <50% agreement on whether to endorse the process measures. All raw data are abstracted from Tables 2 and 3.

Tapper EB et al., Hepatology 2024; 80: 488

Transjugulärer intrahepatischer portosystemischer Shunt (TIPS)



TIPS verhindert weitere Dekompensationen und verbessert das Überleben

Background

- Further decompensation

Second/recurrent liver decompensation

→ Ascites

→ Variceal bleeding

→ Hepatic encephalopathy

→ Jaundice, HRS-AKI, SBP

- Indication of TIPS

➢ Refractory ascites

➢ Pre-emptive TIPS

➢ Prevention of rebleeding

Aims

To assess (i) the incidence of further decompensation and (ii) survival after TIPS *vs.* standard of care (SOC)

Methods

IPD meta-analysis

12 controlled studies:

n = 3,949 comparing TIPS *vs.* SOC
SOC n = 3,097,
TIPS n = 852

Adjusted by PS-matching:

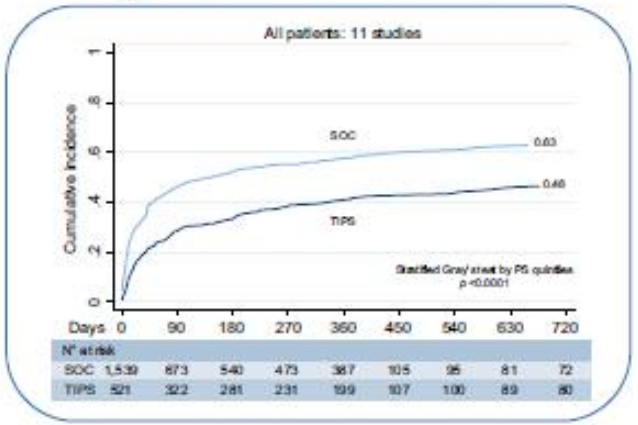
2,338 patients with similar characteristics

Outcomes

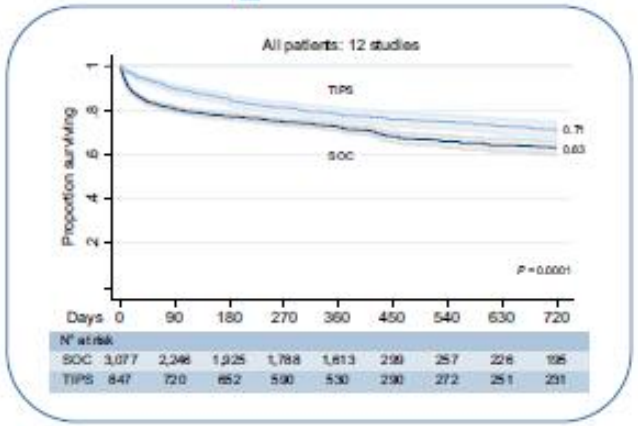
I: Incidence of further decompensation

II: Overall survival

Further decompensation

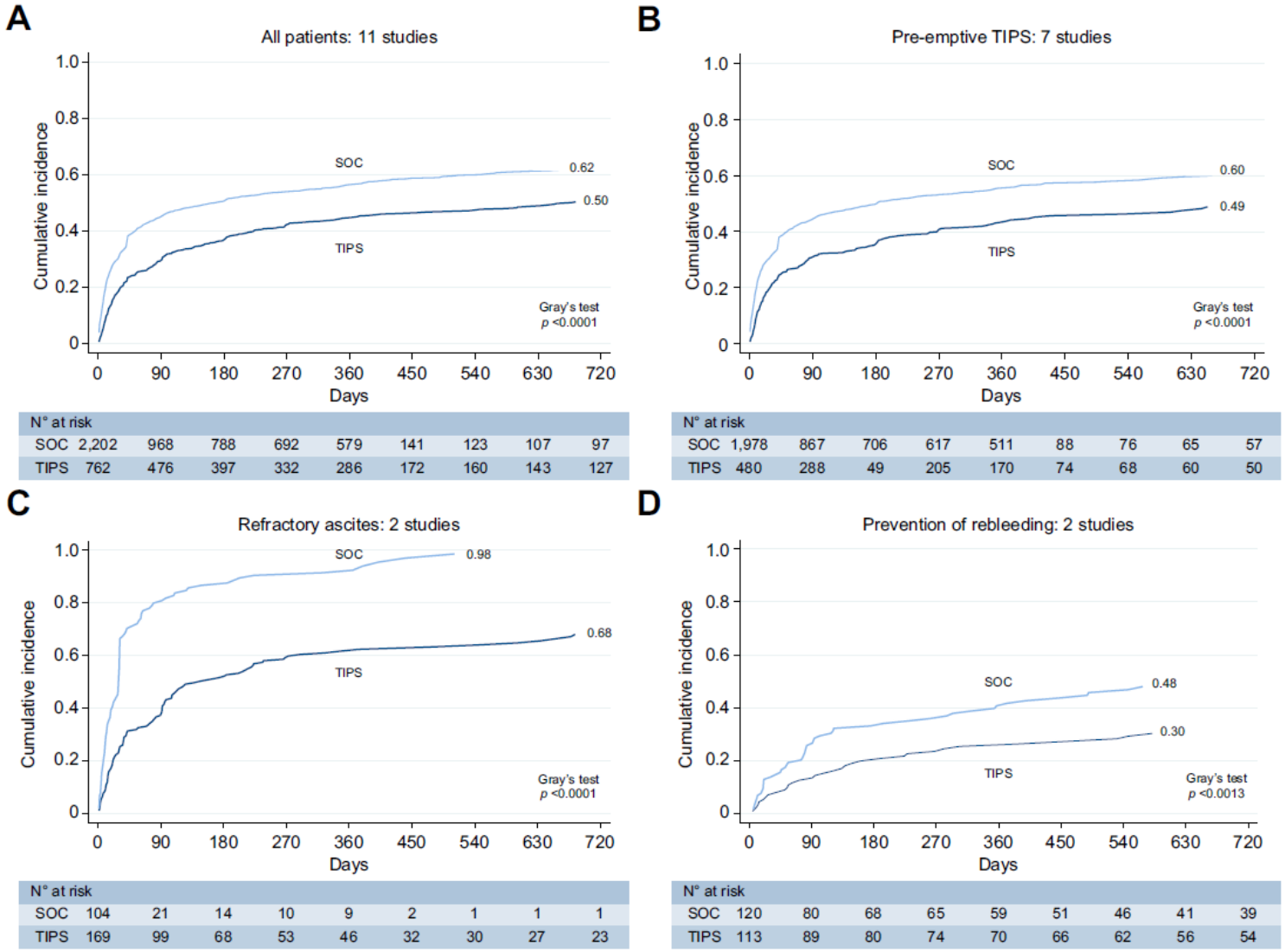


Survival



Larrue H et al., J Hep 2023; 79: 692

TIPS verhindert weitere Dekompensationen und verbessert das Überleben



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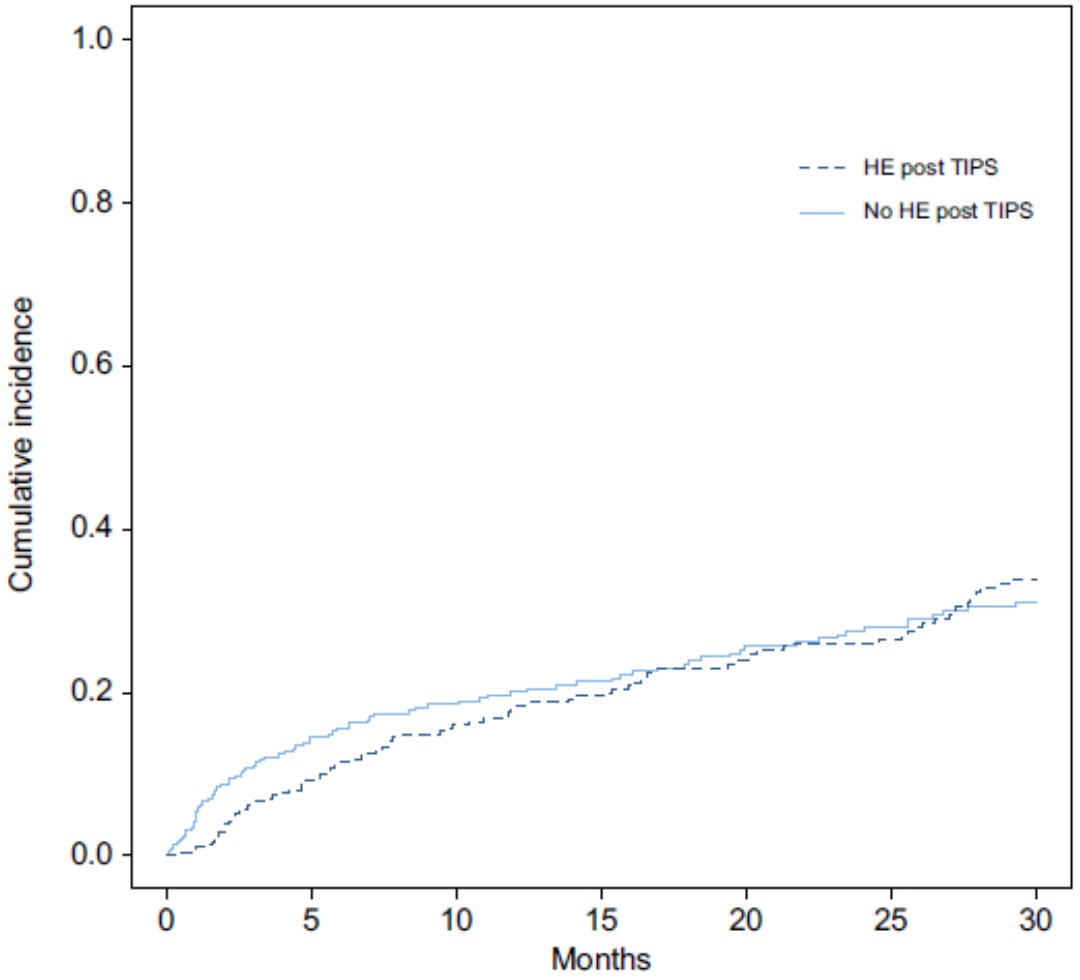
Larrue H et al., J Hep 2023; 79: 692

HE nach TIPS erhöht nicht die Mortalität bei Zirrhosepatienten

Multicenter, Non-Inferiority Beobachtungsstudie: N=614; Median follow-up: 30 Monate

Ausschlusskriterien:
- Rescue-TIPS
- HCC
- Nicht-zirrhotische portale Hypertonie
- Schweres Leberversagen
- Herzinsuffizienz
- Portopulmonale Hypertonie
- Rekurrente HE trotz adäquater Therapie
- Unkontrollierte Sepsis

Risikofaktoren für HE:
- Höheres Alter
- Niedriges Albumin
- Manifeste HE vor TIPS



N° at risk				
HE post TIPS	293	201	148	111
No HE post TIPS	321	194	143	109

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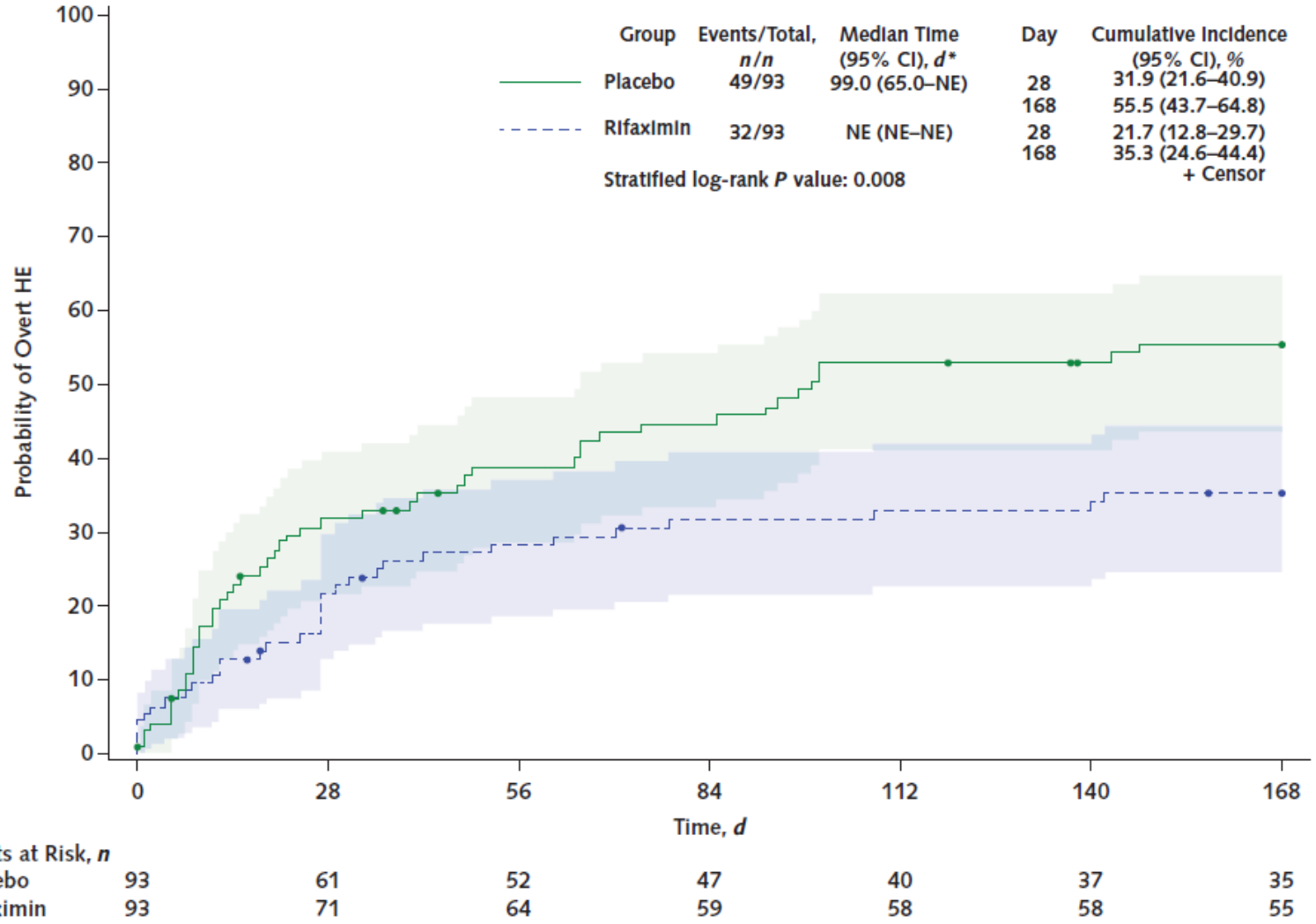
Nardelli S et al., J Hep 2024; 80: 596

Prophylaktische Rifamixin-Therapie verringert HE nach TIPS

RCT: N=197; Rifaximin-Therapie: 14 Tage vor und 168 Tage nach TIPS



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Bureau C et al., Ann Intern Med 2021; 174: 633

Take Home Message – Leberzirrhose

- Bei **Leberzirrhose** ist das **Blutungsrisiko** bei **vielen Interventionen gering.**
- Vor **Interventionen mit niedrigem Risiko** ist die **Bestimmung der Thrombozyten ausreichend,** vor solchen **mit hohem Risiko** zusätzlich der **INR** indiziert.
- **Aspirin oder Clopidogrel** können **fortgeführt** werden, **VKA und DOAKs** sollen **abgesetzt werden. Keine Substitution mittels FFP oder Thrombozytenkonzentraten.**
- Eine **TIPS-Anlage verbessert das Überleben unabhängig** vom dessen **Indikation.**
- Eine **hepatische Enzephalopathie nach TIPS** ist **nicht** mit einem **verringerten Überleben** assoziiert. Das **Auftreten einer HE** nach TIPS kann aber durch eine **prophylaktische Rifaximin-Therapie reduziert** werden.

Vielen Dank!

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