GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of April 4 - 8, 2022

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Antihypertensives Can Reduce Onset of Diabetes

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Blood pressure lowering and risk of new-onset type 2 diabetes: an individual participant data meta-analysis

Nazarzadeh M, Bidel Z, Canoy D, et al. Blood pressure lowering and risk of new-onset type 2 diabetes: an individual participant data meta-analysis. *Lancet*. 2021; 398(10313):1803–1810. doi:10.1016/S0140-6736(21)01920-6

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KEY TAKEAWAY: Antihypertensives decrease the incidence of type II diabetes onset. Compared to placebo, ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) decrease the risk of developing type II diabetes, while beta-blockers and thiazide diuretics increase the risk.

STUDY DESIGN: Meta-analysis of 22 trials (19 RCTs; N=145,939)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Evidence supports the importance of controlling both blood pressure and type II diabetes. However, there is minimal evidence on the effect of reducing blood pressure to decrease the risk of type II diabetes.

PATIENTS: Adults with hypertension without type II diabetes

INTERVENTION: Antihypertensive treatment

CONTROL: No antihypertensive treatment

OUTCOME: Onset of type II diabetes

METHODS (BRIEF DESCRIPTION):

- 8 of the included trials were placebo-controlled, while 14 were comparisons between multiple antihypertensives.
- Exclusion criteria for trials included participants with diagnosis of type II diabetes or trials with high number of diabetic patients.
- Two arms: comparator and intervention
  - Comparator: Either placebo or a medication that had different effects than treatment
  - Treatment: Antihypertensive treatment included ACEI, ARB, calcium channel blockers (CCB), B-blockers, and thiazide diuretics
- Population included 60% men and 40% women with a mean age of 65 years old and mean blood pressure of 153/89.
- Meta-analysis calculated a hazard ratio and relative risk of comparative arms.

INTERVENTION (# IN THE GROUP): 65,042

COMPARISON (# IN THE GROUP): 80,887

FOLLOW UP PERIOD: median of 4.5 years

RESULTS:

- Antihypertensives decreased the rate of new onset type II diabetes (HR 0.89; 95% CI, 0.84–0.95).
- ACE/ARB treatment reduced onset of type II diabetes compared to placebo (RR 0.84; 95% CI, 0.76–0.93).
- Thiazide diuretics increased onset of type II diabetes compared to placebo (RR 1.2; 95% CI, 1.1–1.4).
- B-blockers increased onset of type II diabetes compared to placebo (RR 1.5; 95% CI, 1.3–1.7).
- CCBs had no effect on type II diabetes onset compared to placebo (RR 1.0; 95% CI, 0.92–1.1).

LIMITATIONS:

- Limited generalizability due to 70% of participants having BMI <30 and mean age of 65 years old.
- The study did not account for alteration in antihypertensive treatment, provide medication dosages, or investigate combinations of antihypertensive medications.

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Antenatal Exercise Regimen Can Help Reduce Postpartum Urinary Incontinence

Regular antenatal exercise including pelvic floor muscle training reduces urinary incontinence 3 months postpartum-Follow up of a randomized controlled trial

Johannessen HH, Frøshaug BE, Lysåker PJG, et al. Regular antenatal exercise including pelvic floor muscle training reduces urinary incontinence 3 months postpartum-Follow up of a randomized controlled trial. *Acta Obstet Gynecol Scand*. 2021; 100(2):294–301. doi:10.1111/aogs.14010

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KEY TAKEAWAY: Routine antenatal exercise including pelvic floor training reduces the prevalence of urinary incontinence in mothers three months postpartum.

STUDY DESIGN: Secondary analysis of a randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Pregnancy and vaginal birth are risk factors for urinary incontinence in women with an incidence of 30%. The study's authors had previously found that an antenatal exercise program had improved urinary incontinence in pregnancy and subsequently decided to study if these improvements continued into postpartum.

PATIENTS: Healthy, pregnant Norwegian woman

INTERVENTION: Pelvic floor muscle training

CONTROL: No exercise training

OUTCOME: Urinary incontinence

Secondary Outcomes: delivery, epidural, length of second stage of labor, episiotomy, OASIS, newborn head circumference, newborn weight

METHODS (BRIEF DESCRIPTION):

- Subjects: Healthy, pregnant, adult women with a singleton live fetus
- Intervention: 12-week standardized exercise program consisting of one hour of weekly guided exercise, and twice weekly home exercises
  - Patient guided exercise included pelvic floor therapy.
- Questionnaires were given at 18-22 weeks of pregnancy and three months postpartum. These were based on standards provided by the International Urogynecological Association(IUGA)/International Continence Society (ICS) and distinguished between stress, urgency, and mixed urinary incontinence from continence.
- Prevalence of urinary incontinence using the Sandvik Severity Index

INTERVENTION (# IN THE GROUP): 429

COMPARISON (# IN THE GROUP): 426

FOLLOW UP PERIOD: three months postpartum

RESULTS:

Primary Outcome –

- Pelvic floor muscle training decreased urinary incontinence compared to no training (29% vs 38%, respectively; *P*=.01).
- Pelvic floor muscle training decreased urinary incontinence in women with urinary incontinence compared to no training (44% vs 59%, respectively; *P*=.014).

Secondary Outcome –

- Urinary incontinence late in pregnancy is correlated with a four-fold increase in urinary incontinence at three months postpartum.
- OASIS was correlated with a significant increase in postpartum urinary incontinence (OR 2.6, 95% CI 1.1–6.1).
- Cesarean section was associated with an 80% reduction in risk of postpartum urinary incontinence (*P* < .001).
- Patient age correlates with increased risk of postpartum urinary incontinence (OR 1.1, 95% CI 1.0–1.1).
- Newborn weight of greater than 4000 g was associated with increased risk of postpartum urinary incontinence (OR 1.8, 95% CI 1.2–2.8).

LIMITATIONS:

- Majority of subjects were not obese.
- The population was women who were Scandinavian, white, healthy, and highly educated.
- Mode of delivery was not specified for deliveries involving multiples.
- Effect beyond three months is unknown
- The exercise program was designed specifically for pregnant women.

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An Empagliflozin a Day Keeps the Hospital Away for Heart Failure with Preserved Ejection Fraction

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med.* 2021; 385(16):1451–1461. doi:10.1056/NEJMoa2107038

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KEY TAKEAWAY: Addition of empagliflozin to ongoing therapy for patients with heart failure and preserved ejection fraction (HFpEF) reduces composite relative risk of hospitalization for heart failure and cardiovascular death.

STUDY DESIGN: Double-blinded, parallel-group, event-driven, randomized, placebo-controlled trial (622 sites in 23 countries)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Treatment options for HFpEF are limited. Those that exist demonstrate underwhelming benefit for specific patient subgroups. Evidence suggests sodium-glucose cotransporter 2 (SGLT2) inhibitors improve outcomes in heart failure with reduced ejection fraction (HFrEF), but data is limited on the effect for patients with HFpEF. This randomized-controlled trial evaluates outcomes in patients with HFpEF treated with empagliflozin.

PATIENTS: Adults with New York Heart Association (NYHA) class II-IV chronic heart failure with or without diabetes

INTERVENTION: Empagliflozin 10mg

CONTROL: Placebo

OUTCOME: Combined incidence of cardiovascular death and hospitalizations for heart failure

Secondary Outcomes: Total hospitalizations for heart failure, rate of decline in eGFR during treatment, all-cause mortality

METHODS (BRIEF DESCRIPTION):

- Qualifying patients were adults with NYHA class II-IV chronic heart failure with:
  - Preserved left ventricular ejection fraction of > 40%.
  - N-terminal pro-B-type natriuretic peptide (NT-proBNP) exceeding 300 pg/mL (> 900 pg/mL if atrial fibrillation present at baseline).
  - Patients excluded if a comorbid condition would affect patient safety or would immediately alter clinical course.
- Subjects randomly assigned in 1:1 ratio to experimental and control groups.
  - Experimental group received 10 mg empagliflozin daily with usual therapy.
  - Control group received daily placebo with usual therapy.
- Demographics:
  - Mean age was 72 years old
  - 45% of patients lived in Europe and 25% in Latin America.
  - 82% of patients in both the empagliflozin and placebo groups had a NYHA class II heart failure.
- Patient follow-ups were in clinic and by telephone in predefined intervals throughout trials.

INTERVENTION (# IN THE GROUP): 2,997

COMPARISON (# IN THE GROUP): 2,991

FOLLOW UP PERIOD: Median of 26.2 months

RESULTS:

Primary Outcome –

- The empagliflozin treatment group demonstrated a reduced composite rate of hospitalization for heart failure and cardiovascular death compared to placebo (6.9 vs. 8.7 events per 100 patient-years, respectively; [HR] 0.79; 95% CI, 0.69-0.90; number needed to treat [NNT] =56).

Secondary Outcomes –

- The empagliflozin group demonstrated a significantly lower total number of hospitalizations for heart failure relative to the placebo group (407 vs. 541 hospitalizations, respectively; HR 0.73; CI 95%, 0.61-0.88; *P*<.001; NNT=23).
- The rate of decline in eGFR was significantly reduced in the empagliflozin group relative to the placebo group (–1.3±0.11 vs –2.6±0.11 mL/min/1.7 m^2, respectively; HR 1.4; CI 95%, 1.1–1.7).

LIMITATIONS:

- Industry funded study
- Physiologic mechanism of action in the experimental treatment was not well-defined or hypothesized.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

Fluid Choice in Sepsis: Balanced Crystalloids vs Saline

Balanced Crystalloids versus Saline in Sepsis: A Secondary Analysis of the SMART Clinical Trial

Brown RM, Wang L, Coston TD, et al. Balanced Crystalloids versus Saline in Sepsis. A Secondary Analysis of the SMART Clinical Trial. *Am J Respir Crit Care Med*. 2019; 200(12):1487–1495. doi:10.1164/rccm.201903-0557OC

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KEY TAKEAWAY: Balanced crystalloids (BC) reduce 30-day mortality in critically ill patients with sepsis.

STUDY DESIGN: Secondary analysis of a single site, cluster randomized, non-blinded, multiple crossover

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: While the use of saline (S) for fluid resuscitation has been the default solution in North America for many years, BC fluid more closely resembles plasma electrolyte concentrations. Moreover, the high concentration of chloride anions within S have been implicated in hyperchloremic metabolic acidosis and acute kidney injury. This has fueled much debate about the superiority of BC vs S in fluid resuscitation.

PATIENTS: ICU Adults with Sepsis

INTEVENTION: Administration of balanced crystalloids (BC)

CONTROL: Saline (S)

OUTCOME: 30-day mortality

Secondary outcomes:

- 60-day in-hospital mortality rate after ICU admission
- Renal replacement therapy-free days during the 28 days after ICU admission

METHODS (BRIEF DESCRIPTION):

- Secondary analysis of SMART trial that included patients admitted to medical ICU with a diagnosis of sepsis
  - Patient Demographics: median age 60 years old, 55% male, 75% white
  - 56% were admitted directly from ED
  - 70% of patients with sepsis as their primary diagnosis per retrospective physician chart review
  - Treatment: BC (LR or Plasma-Lyte A based on provider preference) or S (0.9%); treatment randomized based on the month of admission
  - In-hospital 30-day mortality rate was measured via EHR review.
- Primary outcome: intention-to-treat comparison analysis was used to calculate adjusted odds ratio between groups; variables in the adjustment model included age, sex, race, admission location, mechanical ventilation, and vasopressors
- Secondary outcomes: logistic regression and proportional odds modeling analysis was performed based on variable type

INTERVENTION (# IN THE GROUP): 824

COMPARISON (# IN THE GROUP): 817

FOLLOW UP PERIOD: 30 days after ICU admission

RESULTS:

Primary Outcome:

- The BC group had lower 30-day in-hospital mortality rates after ICU admission compared to the S group (26% vs 31%; OR 0.74; 95% CI, 0.59–0.93).

Secondary Outcomes:

- The BC group had more renal replacement therapy-free days during the 28 days after ICU admission compared to the S group (20 vs 19; OR 1.4; 95% CI, 1.1–1.7).
- There was no difference in 60-day in-hospital mortality rates after ICU admission or vasopressor-free days during the 28 days after ICU admission between the two groups.

LIMITATIONS:

- Fluid group assignment was not blinded.
- All patients were enrolled at a single academic center, risk of type I error.
- ICD codes, rather than standardized sepsis criteria were used in analyses.
- There was a low number of patients requiring dialysis in both groups (BC vs S) which may limit the power of this comparison.

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Are Steroid Hip Injection Dosages Predictors of Rapidly Destructive Hip Disease?

Rapidly Destructive Hip Disease Following Intra-Articular Corticosteroid Injection of the Hip

Okike K, King RK, Merchant JC, Toney EA, Lee GY, Yoon HC. Rapidly Destructive Hip Disease Following Intra-Articular Corticosteroid Injection of the Hip. *J Bone Joint Surg Am*. 2021; 103(22):2070–2079. doi:10.2106/JBJS.20.02155

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KEY TAKEAWAY: Corticosteroid injection dosage and number of injections were found to be significantly associated with development of rapidly destructive hip disease (RDHD) when considered alongside other factors such as age, sex, and baseline arthritis severity.

STUDY DESIGN: Case-control and retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Recent evidence suggests RDHD may be a complication of steroid hip injections, but only case reports and case series support this claim. Clarity of this association would benefit patients considering corticosteroid hip injections.

PATIENTS: Adult patients who received hip corticosteroid injections

INTERVENTION: Developed RDHD

CONTROL: Did not develop RDHD

OUTCOME: Association, rate of RDHD, and risk factors for post-injection RDHD

METHODS (BRIEF DESCRIPTION):

- Investigation at Kaiser Moanalua Medical Center in Honolulu, Hawaii between 2013–2016
- RDHD was defined as Rapidly Progressive Osteoarthritis of the Hip (RPOH) Grade II and Grade III.
- All patients received injections at the same institution using similar techniques by board-certified radiologists between 2013 and 2016.
- 99% of injections were performed with triamcinolone 40 mg/mL with doses of either 1 mL or 2 mL.
- Chart review was performed by one person who was not aware of RDHD presence.
- Age, sex, BMI, smoking status, and arthritis severity were analyzed as confounders.

INTERVENTION (# IN THE GROUP):

- Case-control analysis: 40
- Cohort analysis: 37

COMPARISON (# IN THE GROUP):

- Case-control analysis: 717
- Cohort analysis: 651

FOLLOW UP PERIOD: Four years

RESULTS:

Primary Outcome –

- Multiple injections were associated with increased risk for RDHD:
  - Case-control: OR 12; 95% CI, 4.4–33
  - Cohort: OR 2.5; 95% CI, 1.2–4.8
- Rate of RDHD in patients with injections:
  - Case-control: 88%
  - Cohort: 5.4%
- Risk factors for developing RDHD included (information from case-control studies):
  - Prior injections: OR 8.6; 95% CI, 3.3–22
  - Corticoid injection dose:
    - Low-dose: OR 5.4; 95% CI, 1.6–18
    - High-dose: OR 9.7; 95% CI, 3.7–26
  - Number of prior injections:
    - 1: OR 6.0; 95% CI, 2.1–17
    - ≥2: OR 12; 95% CI, 4.4–33

LIMITATIONS:

- A small number of cases were found.
- Different corticosteroids, other than triamcinolone, were not controlled for in the results.
- Awareness of RDHD spread in the institution in 2015 and injections, particularly high dose injections, declined.

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Prolonged Duration of Antimicrobial Treatment of Uncomplicated *Pseudomonas aeruginosa* Bacterium May Not Be Necessary

Short versus prolonged courses of antimicrobial therapy for patients with uncomplicated Pseudomonas aeruginosa bloodstream infection: a retrospective study

Bae M, Jeong Y, Bae S, et al. Short versus prolonged courses of antimicrobial therapy for patients with uncomplicated Pseudomonas aeruginosa bloodstream infection: a retrospective study. *J Antimicrob Chemother.* 2021; 77(1):223–228. doi:10.1093/jac/dkab358

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KEY TAKEAWAY: Short-course antimicrobial therapy may be as effective as prolonged-course therapy for patients with uncomplicated *Pseudomonas aeruginosa* bloodstream infection, but inadequate study power limits the conclusions.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to inadequate sample size and lack of statistical power)

BRIEF BACKGROUND INFORMATION: *Pseudomonas aeruginosa* bacteremia is associated with high mortality rates with evolving multidrug resistance. This makes it challenging to find effective treatment options. Currently, there has been no concrete evidence regarding duration of treatment.

PATIENTS: Adults with uncomplicated *Pseudomonas aeruginosa* bloodstream infections

INTERVENTION: Short course of antibiotics (7-11 days)

CONTROL: Prolonged course of antibiotics (12-21 days)

OUTCOME: Recurrent *P. aeruginosa* infection, all-cause mortality within 30 days of discontinuing antimicrobial therapy

Secondary Outcome: Recurrence of *P. aeruginosa* infection within 180 days

METHODS (BRIEF DESCRIPTION):

- All adult patients with a positive blood culture for *P. aeruginosa* receiving treatment at Asian Medical Center, a university affiliated tertiary care teaching hospital in Seoul, Korea, were enrolled.
- Exclusion criteria included inability to complete, transitioning to hospice care, failure to receive appropriate antibiotics, <7 days or >21 days of antibiotics therapy, polymicrobial bacteremia, or persistent bacteremia (three days or greater).
- 290 patients met eligibility criteria for the study with 33% engaged in short-course therapy (median of nine days) and 67% engaged in long-course therapy (median of 15 days).
- Source control was obtained in approximately 95% of patients in both treatment groups.
  - Source control defined as removal of infected line, drainage of fluid collections, debridement of soft tissues, or resolution of biliary/urinary obstruction.
- Propensity scores and inverse probability of treatment weighting controlled for confounding.

INTERVENTION (# IN THE GROUP): 97

COMPARISON (# IN THE GROUP): 193

FOLLOW UP PERIOD: 180 days

RESULTS:

Primary Outcome –

- There was no difference in recurrent *P. aeruginosa* between short-course and prolonged-course treatment at 30 days [HR 0.68; 95% CI, 0.34 –14].
- There was no difference in 30-day mortality between the two groups.

Secondary Outcome –

- There was no difference in the risk of recurrence of *P. aeruginosa* infection within 180 days between the two groups (HR 0.57; 95% CI, 0.29–1.1].

LIMITATIONS:

- Inadequate sample size
  - No power analysis was performed.
  - Impossible to determine whether lack of statistically significant difference in findings was due to lack of effect or inadequate power.
- Antibiotic regimen consisted of both oral and IV antimicrobial routes.
- Antibiotic regimen differed in spectrum ranging from cephalosporins to carbapenems.
- Excluded 400 patients who were transitioned to hospice or death.

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Efficacy of Aldafermin in Preventing the Progression of NASH

Efficacy and Safety of Aldafermin, an Engineered FGF19 Analog, in a Randomized, Double-Blind, Placebo-Controlled Trial of Patients with Nonalcoholic Steatohepatitis

Harrison SA, Neff G, Guy CD, et al. Efficacy and Safety of Aldafermin, an Engineered FGF19 Analog, in a Randomized, Double-Blind, Placebo-Controlled Trial of Patients With Nonalcoholic Steatohepatitis. *Gastroenterology.* 2021; 160(1):219–231.e1. doi:10.1053/j.gastro.2020.08.004

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KEY TAKEAWAY: Aldafermin treatment reduces liver fat content, ALT, C4 levels, NAS, bile acid secretion, and improves fibrosis in patients with Nonalcoholic Steatohepatitis (NASH). Patient-oriented outcomes were not assessed.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: NASH affects millions of people around the world and is one of the most neglected medical problems. Aldafermin is an engineered analog of FGF19 which inhibits bile acid synthesis and is involved in metabolic homeostasis. Previous studies with aldafermin have shown reduction in liver enzymes and liver fat content.

PATIENTS: Adults with NASH

INTERVENTION: Aldafermin

CONTROL: Subcutaneous placebo

OUTCOME: Liver fat content

Secondary Outcome: C4, ALT, fibrosis, serum bile, NAS

METHODS (BRIEF DESCRIPTION):

- Adults 18-75 years old were randomly assigned to either treatment or placebo groups.
  - These groups included both males and females.
  - The population was mostly white.
  - Patients in both groups had NASH and elevated biomarkers of fibrosis.
- The treatment group received 1 mg of aldafermin daily while the control group received matched placebo daily by subcutaneous injection for 24 weeks.
- Stratification was done based on baseline fibrosis stage.
- Serum level of C4 was the marker of target engagement.
- NASH fibrosis score (NAS): ≥ 1 point in each component of steatosis, lobular inflammation, and hepatocellular ballooning
  - Higher score = improvement in fibrosis
  - Fibrosis improvement was defined as 1-stage decrease in NAS.
- Liver fat content (LFC) was measured at baseline and then again at 24 weeks.
- Other measures included liver enzymes, 7alpha-hydroxy-4-cholesten-3-one, bile acids, markers of liver fibrosis, lipid levels, and histology.

INTERVENTION (# IN THE GROUP): 78

COMPARISON (# IN THE GROUP): 53

FOLLOW UP PERIOD: 30 weeks

RESULTS:

Primary Outcome –

- Aldafermin treatment resulted in a greater reduction in LFC compared to placebo (7.7% vs 2.7%, respectively; *P*=.002).

Secondary Outcomes –

- Aldafermin treatment compared to placebo significantly decreased:
  - C4 levels: 65% vs 1%, *P* <.001
  - Serum bile: 55% vs 35%, *P* < .001
  - ALT: 49% vs 6%, *P* <.001
  - NAS: 62% vs 9%, *P* < .001
    - This was done without worsening fibrosis.
- Aldafermin treatment increased LDL levels at week two. This was expected due to the on-target inhibition of the conversion of cholesterol to bile acids. This was managed by adding rosuvastatin.

LIMITATIONS:

- There was a lack of racial diversity (white patients: 87%) in this study which limits the generalizability of the study findings.
- Small sample size
- Increase in LDL >10 was used as a trigger to initiate the use of rosuvastatin as compared to ASCVD risk.
- Only one endpoint (liver fat reduction) was chosen, compared to NASH resolution or liver fibrosis.
- Patient-oriented outcomes were not assessed.

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