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Update on Forum NIT Literature Review

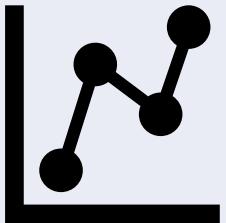
Richard Haubrich, MD
FCR

OUTLINE



Literature Review Methods

NIT data: i) Prognosis-predicting Liver Related Events (LRE) and ii) response to treatment

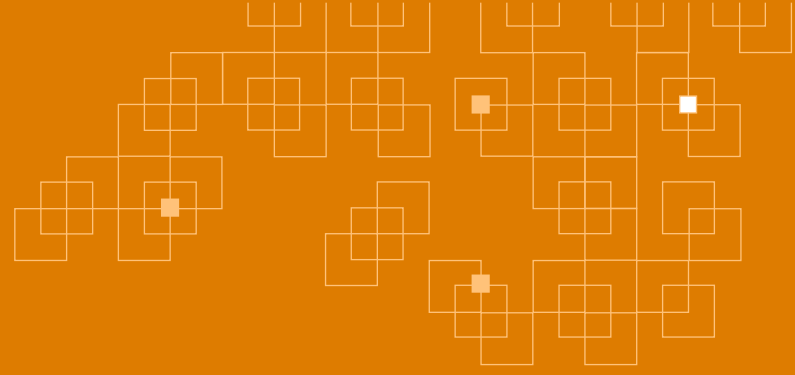


- LSM
 - VCTE
 - MRE
- Plasma markers of fibrosis
 - ELF
- Hepatic fat content
 - MRI-PDFF

Summary of Literature Review (Manuscripts)-9/7/25

| Topic | Total NIT papers | Prognosis: Baseline +/- change NIT and LRE | Treatment: NIT changes |
|-----------------------|-------------------------|---|-------------------------------|
| VCTE | 37 | 17 | 20 |
| MRE | 18 | 8 | 10 |
| ELF | 33 | 5 | 28 |
| MRI-PDFF | 24 | 0 | 24 |
| ALL | 68* | 29* | 39* |
| Total Patients | 39,372 | 29,912 | 9,460 |

*multiple NIT may be present in one study



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Literature Review: VCTE

Summary of Literature Review: VCTE updated 9/9/25

| Number of papers | |
|--|--------------------------------|
| Prognosis: Baseline +/- change VCTE and LRE | Treatment: VCTE changes |
| 17 | 20 |

| N of patients | LRE endpoints | Percent with endpoints |
|---------------|---------------|------------------------|
| 25,066 | 1,549 | 6.2% |

| N of patients |
|---------------|
| 7,774 |

Prognosis: Baseline and Change in **VCTE** and LRE

17 studies: 25,066 patients, 1,549 events

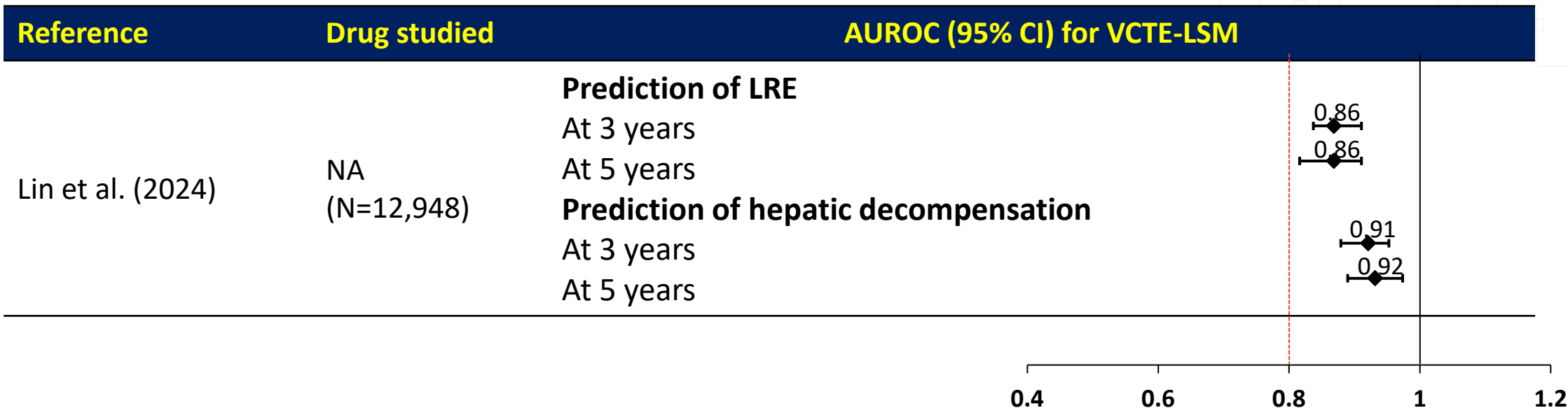
Baseline predicting LRE (n=12)

- All studies: LSM predicted LRE (or cirrhosis progression)
- Measures of model prediction (AUROC, tAUROC, C statistic) were mostly > 0.8
 - Not significantly different compared to histology (2 studies)
- HR predicting LRE ranged from 1.1 - > 10 (depend on cut point and analysis method)

Change from base (n=5)

- Addition of serial LSM increased prediction
 - Exception is if include latest LSM in the model with base and previous values
- Stable LSM and low have the best prognosis
- LSM progression (however defined) are more likely to have LRE

Prognosis: VCTE -Example



eTable 12: Transitioning between risk groups based on LSM at the cut-offs of 8 and 12 kPa (N = 10 920) and incident liver-related events after the last test in the serial model.

| First test | Second test | N (%) | LREs (N) | Percentage in total LREs | 5-year LRE (%) | LRE incidence per 1 000 PY (95% CI) |
|------------|-------------------|--------------|----------|--------------------------|------------------|-------------------------------------|
| Low risk | Low risk | 7 353 (67.3) | 16 | 12.9 | 0.4 (0.2-0.6) | 0.7 (0.4-1.1) |
| | Intermediate risk | 516 (4.7) | 6 | 4.8 | 1.3 (0.4-3.2) | 3.7 (1.7-8.2) |
| | High risk | 100 (0.9) | 2 | 1.6 | 3.8 (0.6-11.9) | 5.8 (1.5-23.0) |
| High risk | Low risk | 190 (1.7) | 1 | 0.8 | 0.7 (0.1-3.7) | 1.6 (0.2-11.1) |
| | Intermediate risk | 348 (3.1) | 11 | 8.9 | 3.8 (1.7-7.3) | 9.3 (5.2-16.8) |
| | High risk | 747 (6.8) | 73 | 58.9 | 14.7 (11.0-18.7) | 31.5 (25.1-39.4) |

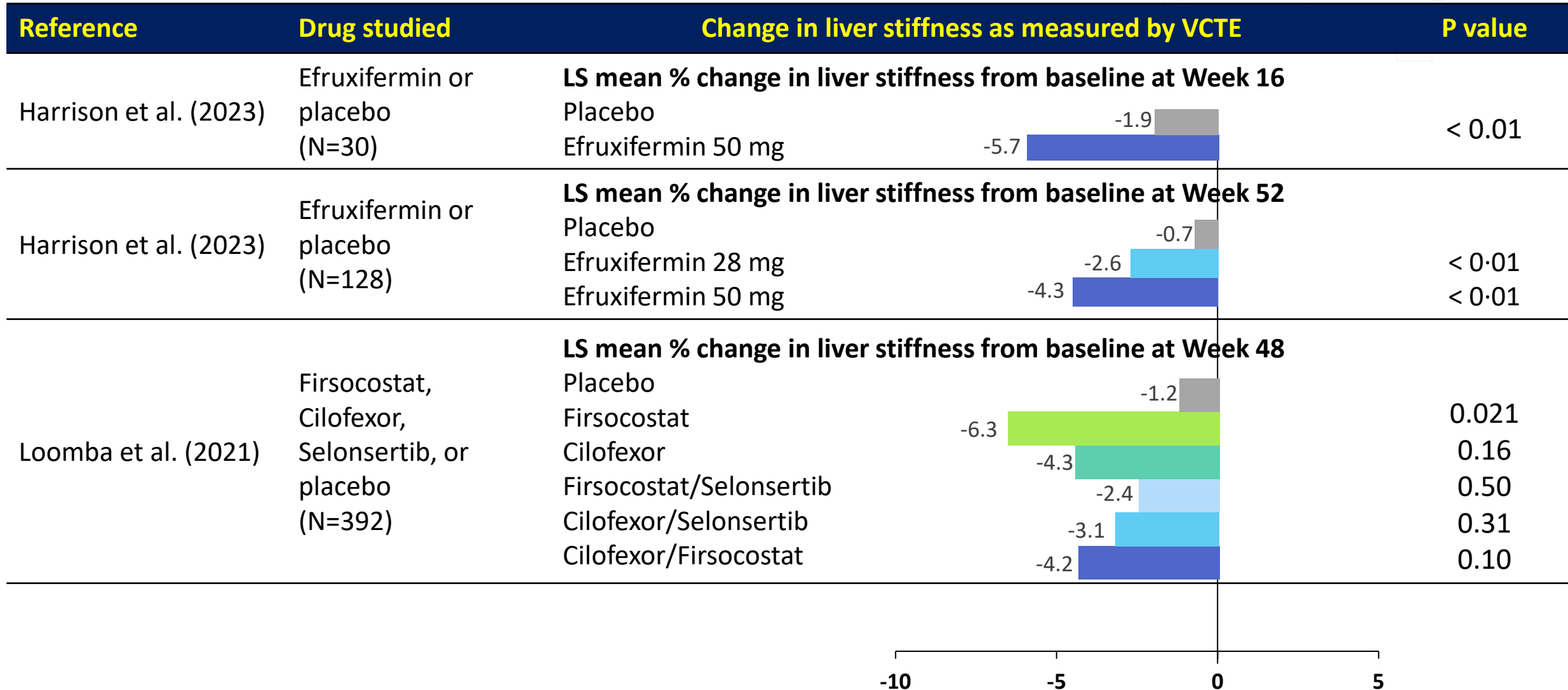
Abbreviations: CI, confidence interval. LREs, liver-related events. LSM, liver stiffness measurement. PY, person-year.

Treatment: **VCTE** change with treatment

20 studies: 7,774 patients

- Analysis
 - Both continuous and categorical variables:
 - mean change from baseline
 - 25% or 30% reduction
- In studies of a drug without activity (e.g. selonsertib)
 - No difference between treated and placebo
 - No association between histologic response and LSM
- In studies of active drugs
 - LSM differences demonstrated between treated and placebo patients (numerically or statistically)
 - LSM changes are sensitive: some studies with small numbers (30-50) show a trend or statistical difference and dose response
 - LSM changes parallel changes in other NIT
 - Some studies statistical testing not done
 - Lack of statistical significance may be analysis dependent (mean change vs responder)

Treatment: VCTE change with treatment



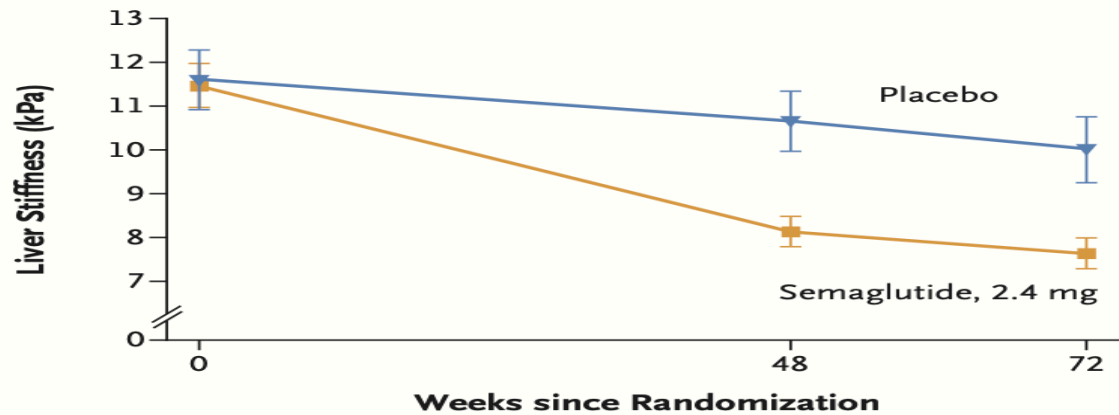
Treatment: VCTE change with treatment

| Reference | Drug studied | ≥30% improvement in liver stiffness as assessed by VCTE | P value |
|------------------------|---------------------------------|---|---------|
| Harrison et al. (2024) | Resmetirom or placebo (N=966) | Proportion of patients at Week 52 | |
| | | Placebo | 23.2 |
| | | Resmetirom 80 mg | 41.7 |
| | | Resmetirom 100 mg | 60.0 |
| Harrison et al. (2023) | Resmetirom or placebo (N=1,143) | Proportion of patients at Week 52 | |
| | | Placebo | 21.0 |
| | | Resmetirom 100 mg OL | 26.0 |
| | | Resmetirom 80 mg DB | 36.0 |
| | | Resmetirom 100 mg DB | 43.0 |
| | | | -- |

Treatment: **VCTE** change with treatment

VCTE Analysis- Continuous and Categorical

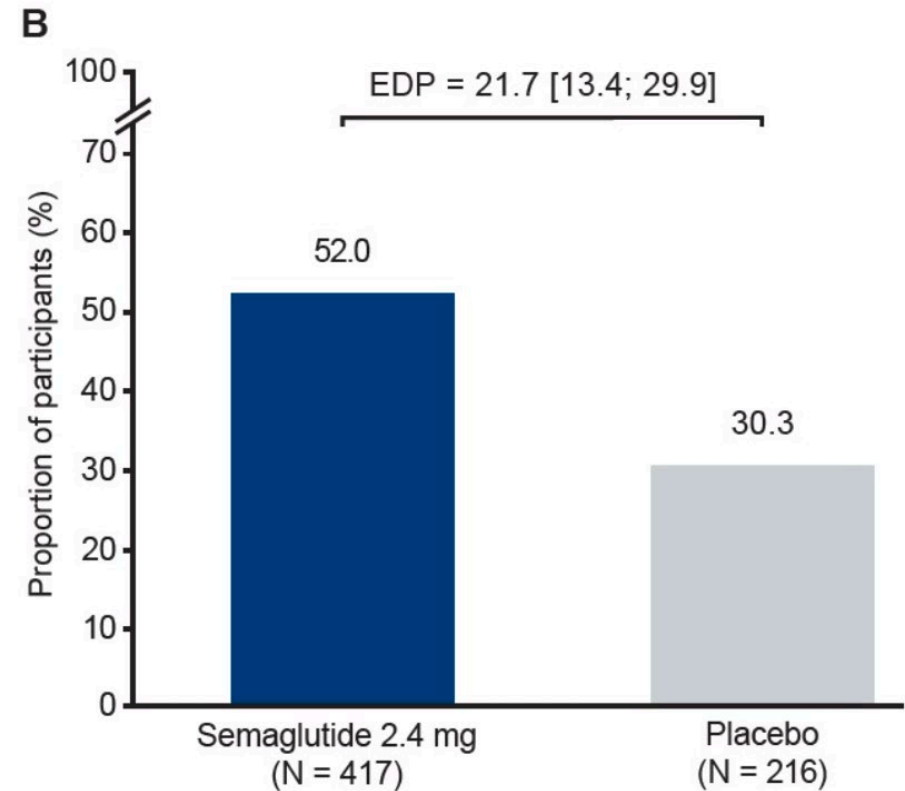
B Liver Stiffness Measured by Vibration-Controlled Transient Elastography

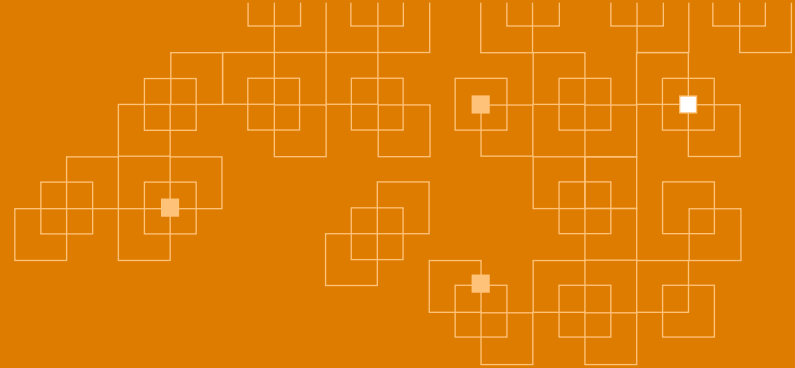


No. of Patients

| | | | |
|---------------------|-----|-----|-----|
| Placebo | 216 | 204 | 193 |
| Semaglutide, 2.4 mg | 417 | 399 | 381 |

Proportion with $\geq 30\%$ reduction VCTE





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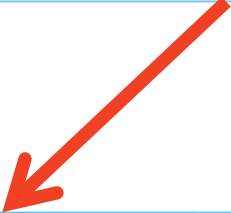
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Literature Review: MRE

Summary of Literature Review: MRE

| Number of papers | |
|--|------------------------|
| Prognosis: Baseline +/- change MRE and LRE | Treatment: MRE changes |
| 8 | 10 |



| N of patients | LRE endpoints | Percent with endpoints |
|---------------|---------------|------------------------|
| 2,916 | 457 | 15.7% |



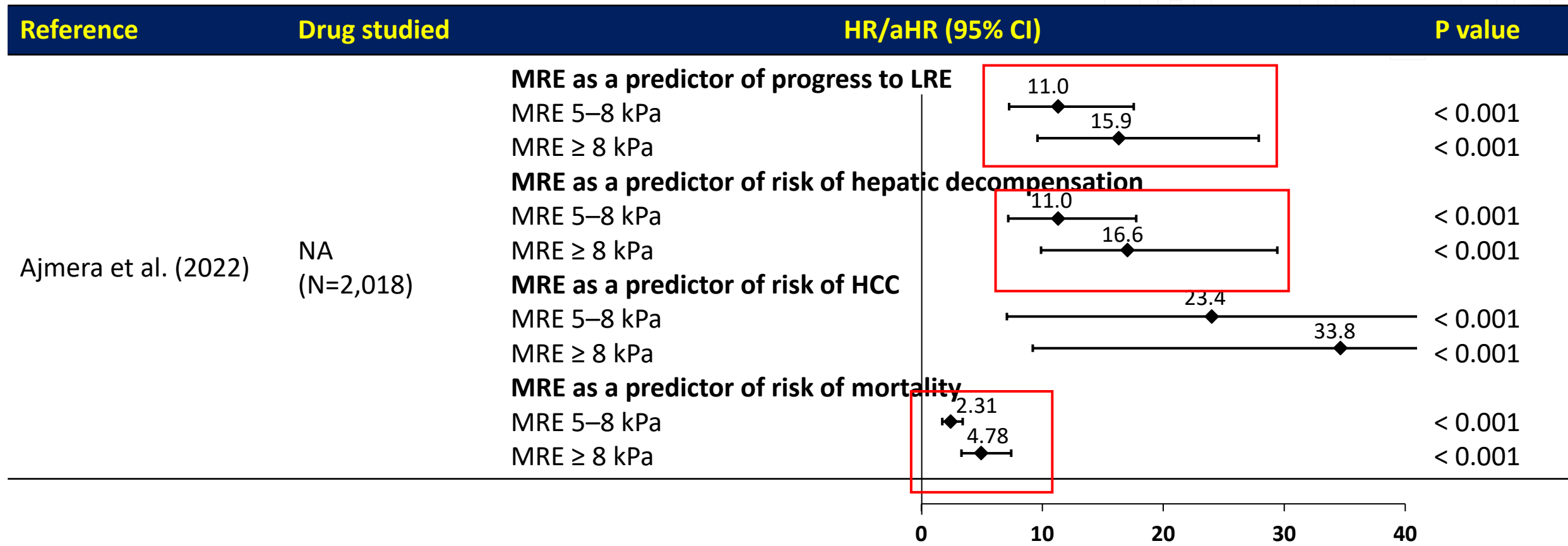
| N of patients |
|---------------|
| 3,135 |

Prognosis: Baseline and Change in **MRE** and LRE

8 studies: 2,916 patients, 457 events

- Overall fewer studies
- Baseline MRE solid predictor of LRE (or cirrhosis progression)
- At least 1 study demonstrates association of base + change in MRE and LRE

Prognosis: MRE- Hazard Ratio



aHR, adjusted hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; LRE, liver-related event; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NA, not applicable/data not provided

Prognosis: MRE- Hazard Ratio

| Reference | Drug studied | HR/aHR (95% CI) | P value | |
|-------------------|-----------------|--|---------|--------|
| Kim et al. (2024) | NA (N=1,254) | MRE as a predictor of risk of hepatic decompensation | 2.58 | 0.0262 |
| | | MRE as a predictor of risk of HCC | 3.9 | 0.0412 |
| | | MRE as a predictor of risk of all-cause mortality | 1.55 | 0.0637 |

0 5 10

| Relative risk of clinical outcomes in patients with LSM increase ≥ 19% | | | | |
|--|---------------|--------------------------------|-------|---------|
| Kobayashi et al. (2023) | NA (N=405) | LRE | 12.79 | 0.001 |
| | | Decompensated cirrhosis | 12.08 | 0.009 |
| | | HCC | 25.02 | 0.008 |
| | | Overall mortality | 1.21 | 0.821 |
| | | Extrahepatic malignancies | 2.67 | 0.180 |
| | | Cardiovascular events | 5.40 | 0.317 |
| | | Overall events | 3.72 | 0.008 |
| | | New onset of cirrhosis (n=386) | 60.15 | < 0.001 |

0 20 40 60 80

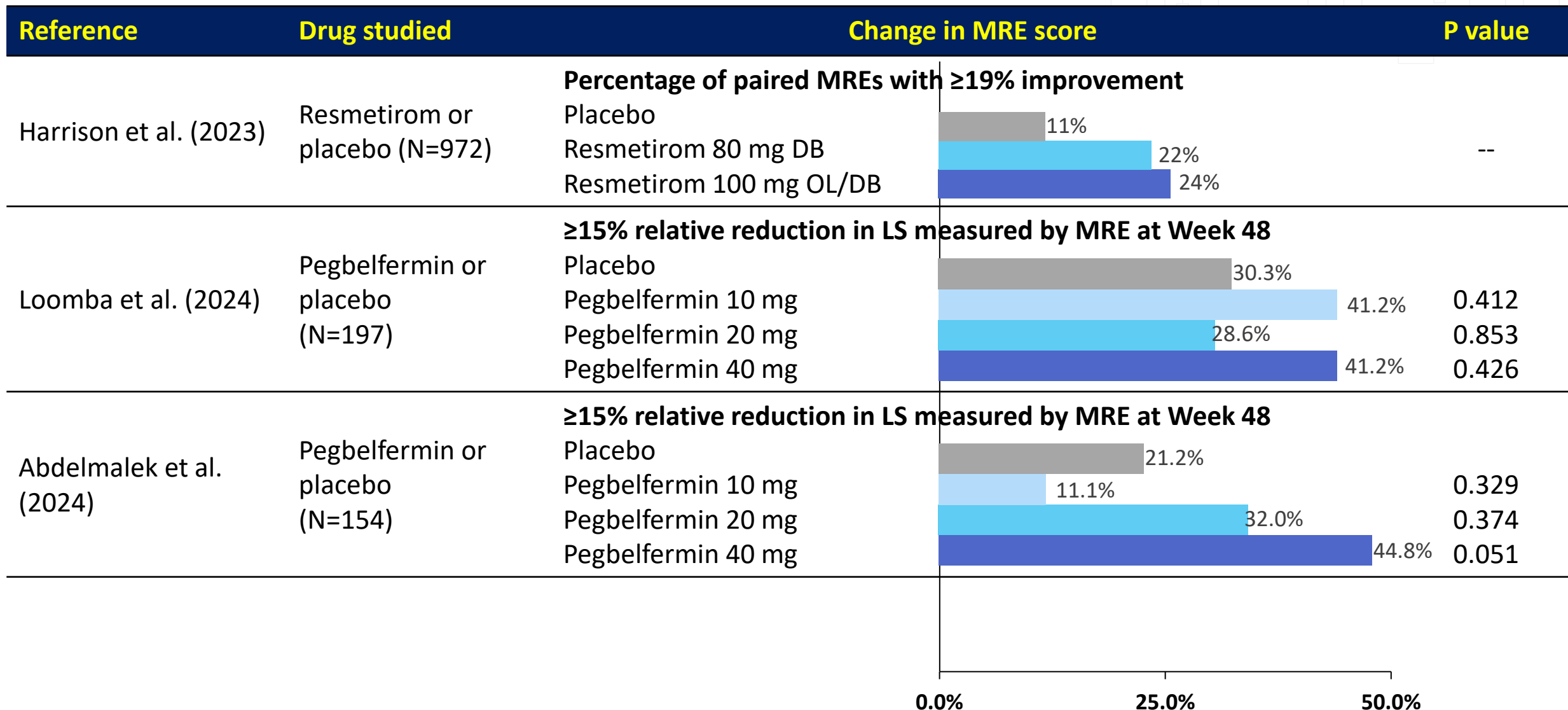
aHR, adjusted hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; LRE, liver-related event; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NA, not applicable/data not provided

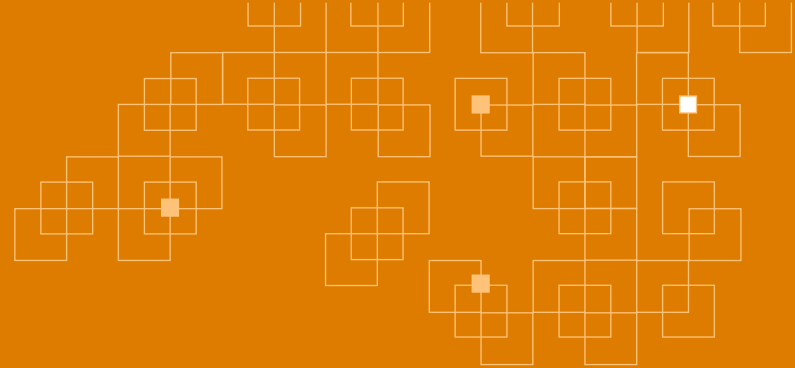
Treatment: **MRE** change with treatment

10 studies: 3,135 patients

- Analysis
 - Continuous and categorical: mean change from baseline or 15-19% reduction from baseline
- Often a subgroup of larger studies so statistical testing is limited by sample size
- Although numerically in right direction (to show treatment effect), no study with significant change in MRE between treated and placebo

Treatment: MRE change with treatment





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Literature Review: ELF

Summary of Literature Review: ELF

| Number of papers | |
|---|-------------------------------|
| Prognosis: Baseline +/- change ELF and LRE | Treatment: ELF changes |
| 5 | 28 |



| N of patients | LRE endpoints | Percent with endpoints |
|---------------|---------------|------------------------|
| 3,180 | 534 | 16.8% |



| N of patients |
|---------------|
| 8,628 |

Prognosis: Baseline and Change in **ELF** and LRE

5 studies: 3,342 patients, 221 events

Baseline or change in ELF predicting LRE

- Overall fewer studies
- For most studies baseline ELF predicted LRE (or progression to cirrhosis)
- Base ELF associated with progression to cirrhosis and LRE, while change in ELF associated with progression to cirrhosis in STELLAR studies

Prognosis: ELF- Hazard Ratio

| Reference | Drug studied | HR/aHR (95% CI) | P value |
|-----------------------|--------------------------------------|---|------------------------|
| Sanyal et al. (2022) | Simtuzumab and selonsertib (N=1,135) | ELF as a predictor for LREs Baseline ELF, per 0.5 units Change in ELF, per 0.5 units | 1.68 1.09 0.2274 |
| Sanyal et al. (2019) | Simtuzumab (N=475) | ELF predictor of cirrhosis progression Higher baseline ELF | 2.58 < 0.001 |
| | | Greater change ELF | 1.64 < 0.001 |
| | | ELF as predictor of LREs Baseline ELF Change from baseline in ELF | 2.11 1.32 0.09 |
| Pearson et al. (2024) | NA (N=1,327) | With per unit change in the ELF score Increase in hepatic decompensation | 2.22 -- |
| | | Increase in liver-related mortality | 2.02 -- |
| | | Increase in all-cause mortality | 1.86 -- |
| Are et al. (2021) | Belapectin (N=161) | ELF score as a predictor for LREs ELF score 9.8 to 11.2 | 1.46 -- |
| | | ELF score of 11.3 | 4.81 -- |



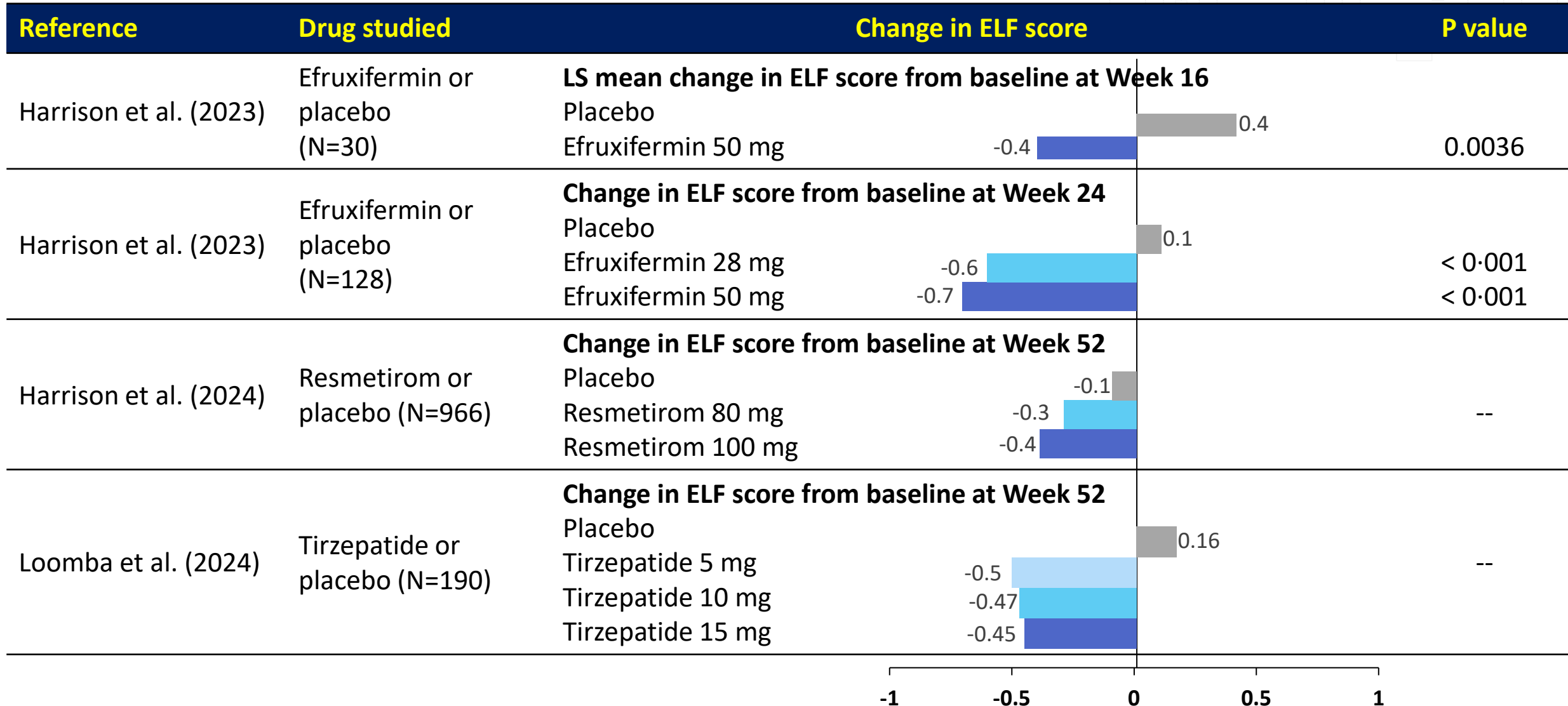
aHR, adjusted hazards ration; CI, confidence interval; ELF, enhanced liver fibrosis; HR, hazards ratio; LRE, liver-related event; NA, not applicable/data not provided

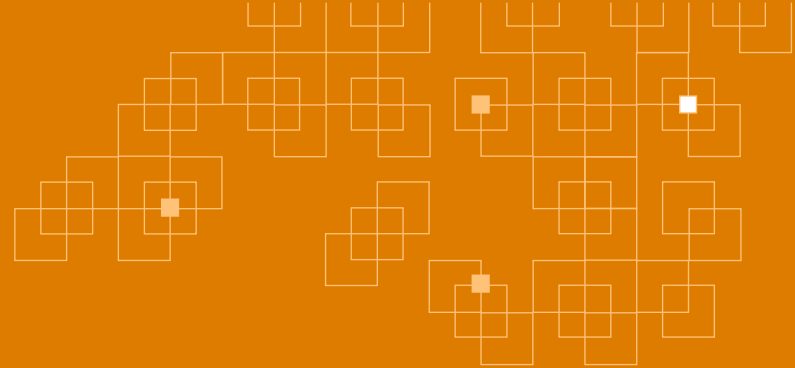
Treatment: **ELF** change with treatment

28 studies: 8,628 patients

- Analysis
 - Mean change from baseline
- In studies of a drug without activity (e.g. selonsertib)
 - No difference between treated and placebo
 - No association between histologic response and ELF
- In studies of active drugs
 - Very robust data
 - ELF differences demonstrated between treated and placebo patients (numerically or statistically)
 - ELF changes are sensitive: some studies with small numbers (30-50) show a trend or statistical difference and dose response
 - ELF changes parallel changes in other NIT
- Not all studies of potentially active drugs show significant ELF changes
- Several studies with significant histological fibrosis improvement without ELF changes
 - Sub-groups with base ELF > 9-9.8 do demonstrate differences
 - Denifanstat improved histologic assessment of fibrosis (30% versus 14%), ELF reductions (-0.4 Den vs -0.1 placebo) in subgroup with ELE 9.8 (p = 0.1)
 - Similar ELF responses noted with resmitirom

Treatment: ELF change with treatment





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Literature Review: MRI-PDFF

Summary of Literature Review: MRI-PDFF

| Number of papers | |
|--|--------------------------------|
| Prognosis: Baseline +/- change PDFF and LRE | Treatment: PDFF changes |
| 0 | 24 |

↓

| N of patients | LRE endpoints | Percent with endpoints |
|---------------|---------------|------------------------|
| 0 | 0 | 0 |

↓

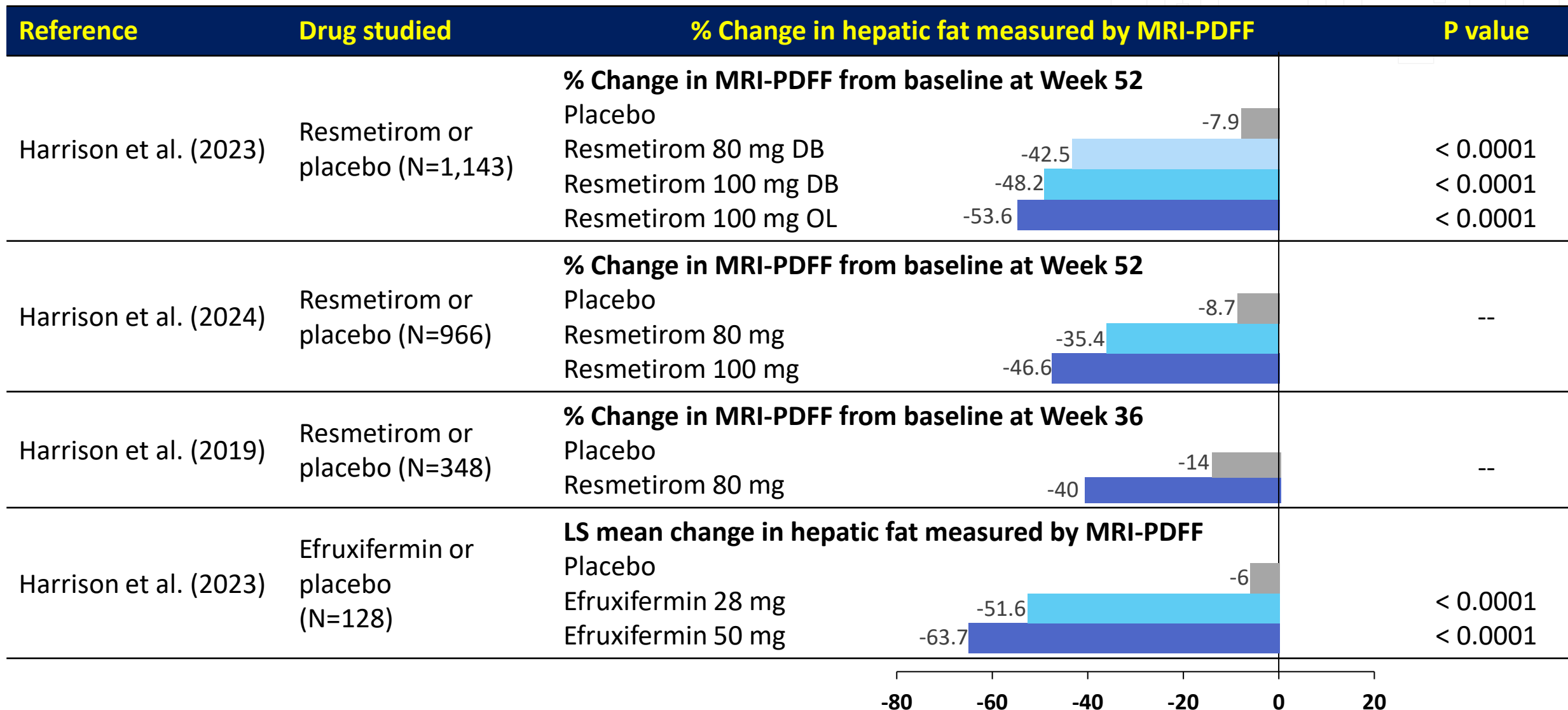
| N of patients |
|---------------|
| 4,515 |

Treatment: **MRI-PDFF** change with treatment

24 studies: 4,515 patients

- No study demonstrating baseline MRI-PDFF and LRE
 - No study demonstrating histological MASH (eg, NAS) predicts LRE
- Analysis
 - Mean change from baseline, percent change from baseline, 15 or 30% reduction from baseline
- Sensitive marker to steatosis changes
- Large treatment effect detected compared to placebo
- Larger differences seen in MRI-PDFF than with fibrosis markers for some drugs (e.g., resmitirom)

Treatment: MRI-PDFF change with treatment



Treatment: MRI-PDFF change with treatment

