Impact of Resmetirom on End-Stage Liver Disease in Noncirrhotic Metabolic-Associated Steatohepatitis (MASH): A Comparative Risk Analysis

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Introduction

- Advanced liver complications are the tipping point in MASH: once patients reach F4 (cirrhosis), risks of decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant (LT), and liver-related death rise sharply; reversals are uncommon and quality of life declines markedly.
- These events drive the bulk of clinical and economic burden—recurrent admissions, procedures, hospitalizations, and lifelong surveillance—while LT is both capacity-limited and among the most expensive interventions in medicine.
- Even a modest delay in progression to **F4** can cascade into **fewer downstream events** and substantial **population-level absolute risk reductions**, given the high prevalence of cardiometabolic disease linked to MASH.
- **Resmetirom** is an EMA and FDA conditionally approved, once-daily, liver-directed thyroid hormone receptor-β (THR-β) agonist for adults with non-cirrhotic MASH and F2–F3 fibrosis, used alongside lifestyle measures.
- Mechanistically, selective THR-β **activation normalizes hepatic lipid metabolism**, reduces **steatosis and lipotoxicity**, and attenuates **inflammation**, leading to slower fibrosis progression; improvements in histology and non-invasive biomarkers observed in MAESTRO-MASH(1) provide a biologic basis for postponing advanced complications over time.
- In lieu of a completed MAESTRO NASH trial with outcomes, a microsimulation model was developed to translate week 52 histologic changes to project changes in longer-term clinical event measures.

Objective

- To project the incidence and timing of F4, DCC, HCC, LT, and liver-related death under resmetirom vs standard of care **in a U.S. MASH population** reflecting MAESTRO-MASH (baseline F2–F3).

Methods

- We built a **patient-level microsimulation** of MASH with **10,000 sampled adults** reflecting MAESTRO-MASH baseline fibrosis (F2 39% / F3 61%). Each person moves through fibrosis stages F0–F4 annually, with both **progression and regression allowed**; once at F4 they can develop DCC, HCC, need LT, or die of liver-related causes over lifetime horizon (Mean: ~22-23 years).
- Further to liver complications, the MSM also accounts for three MASH comorbidities — **cardiovascular diseases (CVD), type 2 diabetes (T2D), and obesity** — from which patients may die due to associated complications. In addition, patients may die from **age- and sex-specific background mortality**.
- Natural-history transition rates for standard of care (SoC) came **from a meta-analysis of placebo arms in prior RCTs**; resmetirom effects were applied as relative-risk multipliers taken from **MAESTRO-MASH trial**, modifying the same baseline transitions. Background (non-liver) mortality was included so patients could also die from other causes.
- **Time-to-event construction:** for each endpoint (F4, DCC, HCC, LT, liver-related death), the event time was the first cycle a patient entered that state. If a patient never entered the state, they were censored at the last modeled cycle; **if a patient died of non-liver causes before the endpoint, they were censored at that death time for that endpoint.**
- **Composite advanced complication** was defined as the **first occurrence** of F4, DCC, HCC, or LT after baseline; non-liver deaths (due to CVD, T2D, Obesity, and background mortality) were treated as competing risks (not events), and liver-related death was analyzed separately because it typically follows advanced disease and would otherwise double-count events.
- **Primary statistical analysis: Cox proportional hazards models from baseline** compared resmetirom vs SoC for each endpoint, reporting HRs with 95% CIs using robust standard errors; **non-liver deaths were treated as censoring events**. (HR < 1 means lower instantaneous risk of that complication over time).
- **Competing-risk reporting (absolute risks):** We estimated cumulative incidence functions (Aalen–Johansen) for each endpoint, treating non-liver death as a competing event. Absolute risk and absolute risk reduction (ARR = SoC − Resmetirom) were reported at 5, 10 years, and lifetime (simulated until death from any cause). For interpretability, ARR was scaled to a 10,000-patient cohort (events prevented). Number-needed-to-treat (NNT = 1/ARR as a proportion) was also reported, except when the ARR 95% CI included 0.
- **HRs** include 95% CIs **from robust SEs**; ARRs include bootstrap 95% CIs to reflect simulation and sampling variability.

Results

Risk of advanced liver complications

- Resmetirom reduced the risk of advanced liver outcomes versus SoC across all endpoints. (FIGURE 1)

Competing-risk cumulative incidence resmetirom vs SoC

- TABLE 1 summarizes the results of a statistical analysis projecting the clinical benefits of resmetirom. The table presents the ARR and the NNT for several critical endpoints.

Lifetime ARR

- Over a lifetime, In 10,000 sampled patient cohort, treating with resmetirom instead of SoC is projected to meaningfully reduce lifetime disease burden—preventing 1,380 (95% CI 1240–1,510) cirrhosis cases, 259 (179-346) decompensations, 248 (168-335) HCCs, 221 (145-303) transplants, and 614 (496-720) liver-related deaths—indicating substantial postponement of advanced events and downstream complications.

Lifetime progression free from baseline

- Baseline, death-counted event-free survival showed durable separation favoring resmetirom (FIGURE 2):
  - **Cirrhosis-free survival** (event = first incidence if cirrhosis or any death): SoC median ≈ 7 y vs ≈20 y with resmetirom
  - **At 10 years** the cohort was event-free in 46% (SoC) vs 65% (resmetirom); i.e., cumulative event (F4 or death) 53.6% vs 34.9%.
  - Event breakdown at 10 y: F4 first in 45.1% (SoC) vs 23.8% (resmetirom); death first in 8.5% vs 11.1%; no event in 46.4% vs 65.1%.
  - DCC-free, HCC-free, and transplant-free survival (event = endpoint or any death) also favored resmetirom over the lifetime horizon with visibly higher curves and non-overlapping CIs around 5–10 years.

TABLE 1. ARR and NNT for liver-related outcomes for resmetirom vs SoC

Endpoint	5 y ARR	5 y NNT	10 y ARR	10 y NNT	Lifetime[2] ARR	Lifetime NNT
F4	6.4%	16	10.1%	10	13.8%	7
DCC	0.24%	omitted[1]	0.82%	122	2.59%	39
HCC	0.11%	omitted	0.84%	119	2.48%	40
LT	0.21%	476	0.62%	161	2.21%	45
Liver related death	0.31%	omitted	1.32%	76	6.14%	16

1 - ARR 95% CI includes 0 2 – Mean time to death: 23.2 $_{y\ resmetirom}$ vs 22.2 $_{y\ SoC}$

FIGURE 1. Endpoint-specific KM curves (95% CI) with non-liver death censored

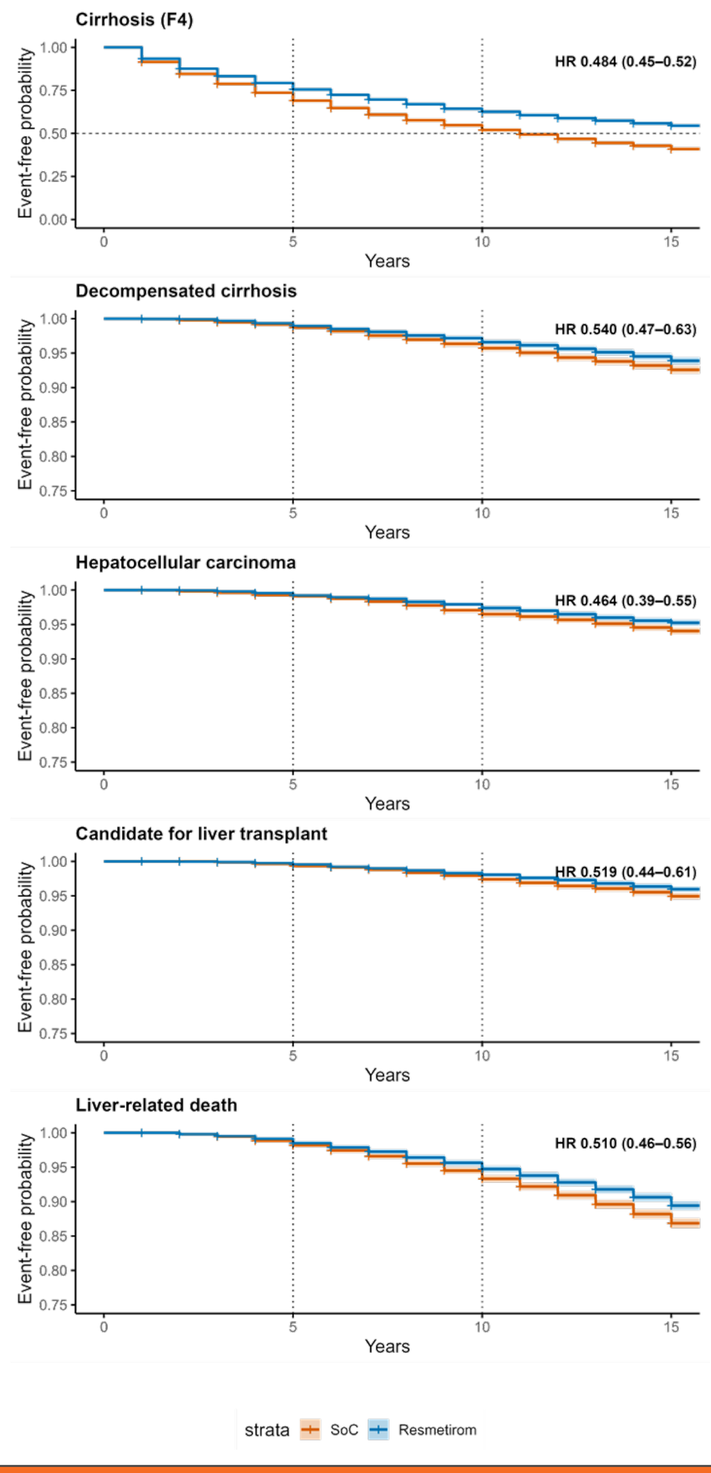
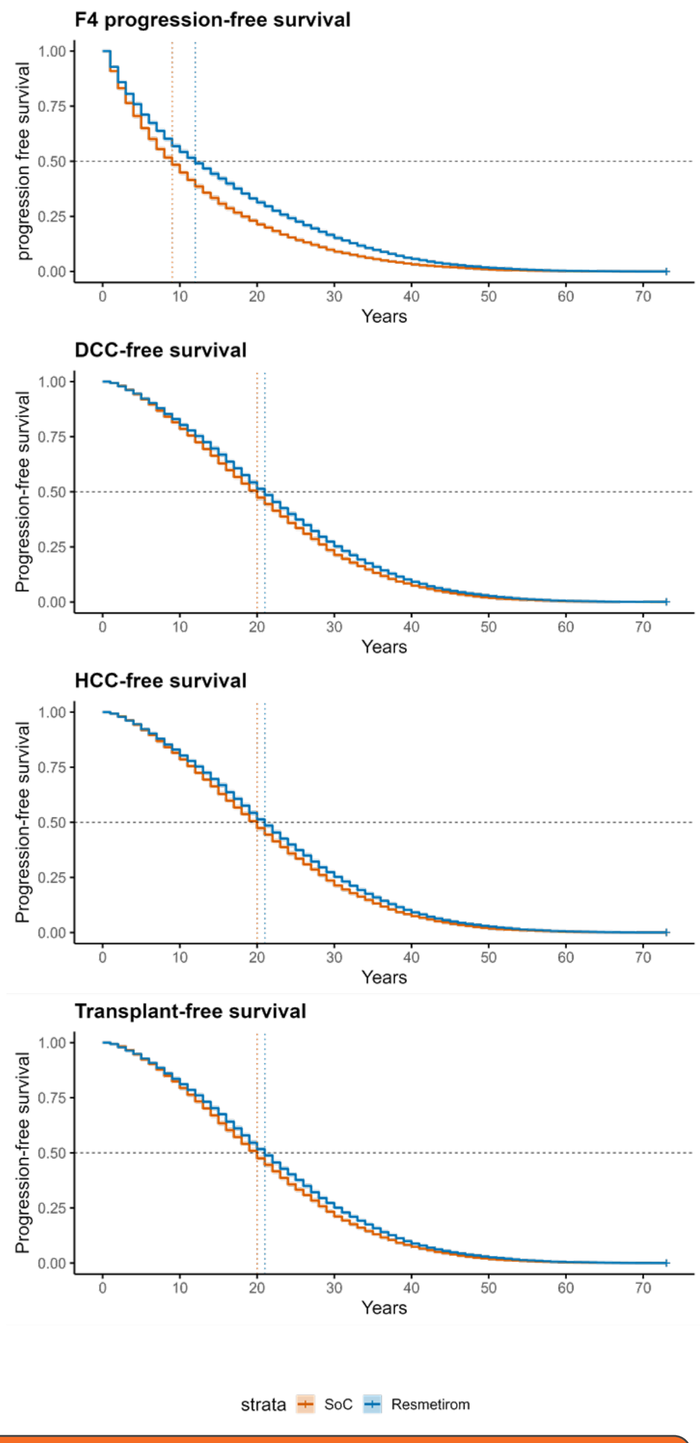


FIGURE 2. Progression free survival to different advanced liver complications with Resmetirom vs SoC



CONCLUSION

- **This microsimulation modeling showed that resmetirom consistently reduces the risk of progressing to advanced liver complications and delays progression to F4 within the first decade, translating into possible meaningful lifetime reductions in F4, DCC, HCC, LT, and liver-related death compared to SoC, at the population level.**
- **Per 10,000 MAESTRO-like patients, resmetirom is projected to prevent ~138 F4 cases, 26 DCC, 25 HCC, 22 transplants, and 61 liver-related deaths versus SoC—indicating meaningful postponement of advanced complications at a population level.**
- **Fewer F4/DCC/HCC/LT events may lead to fewer hospital admissions,, procedures, and transplant demand—areas with high cost and constrained capacity—supporting earlier identification and treatment in appropriate non-cirrhotic MASH (F2–F3).**
- **Like any modeling study, this projection—calibrated to MAESTRO-NASH and published data and reliant on simplified disease-transition assumptions may produce long-horizon absolute risks that differ from real-world experience**

ABBREVIATIONS

ARR: Absolute risk reduction; **CI:** Confidence interval; **DCC:** Decompensated cirrhosis; **F4:** Cirrhosis (fibrosis stage 4); **HCC:** Hepatocellular carcinoma; **HR:** Hazard ratio; **KM:** Kaplan–Meier survival estimator; **LT:** Liver transplant; **MASH:** Metabolic dysfunction–associated steatohepatitis; **RCT:** Randomized controlled trial; **RMST:** Restricted mean survival time; **SoC:** Standard of care; **TTE:** Time-to-event.

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