

Emma Davies Smith<sup>1</sup>, Pamela S. Douglas<sup>2</sup>, Sara McCallum<sup>3</sup>, James Troendle<sup>4</sup>, Marissa Diggs<sup>3</sup>, Sarah Chu<sup>3</sup>, Michael T. Lu<sup>3</sup>, Markella V. Zanni<sup>3</sup>, Steven K. Grinspoon<sup>3</sup>, and Heather J. Ribaud<sup>1</sup>

<sup>1</sup>Harvard T.H. Chan School of Public Health, Boston, MA, USA, <sup>2</sup>Duke University School of Medicine, Durham, NC, USA, <sup>3</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>4</sup>National Institutes of Health, Bethesda, MD, USA

## BACKGROUND

- REPRIEVE demonstrated a 36% reduction (HR=0.64) in **Major Adverse Cardiovascular Events (MACE)** among those randomized (1:1) to pitavastatin versus placebo using a **time-to-first-event (TTFE)** analysis.
- In cardiovascular (CV) trials, TTFE can overemphasize *less severe* events (e.g., MI and stroke) because they occur more often and earlier than *more severe* events (e.g., death).
- The **Win Ratio (WR)** is a novel and increasingly popular alternative comparative statistic which incorporates severity, but depends on follow-up (more severe events will occur with longer follow-up).
- For a single event, WR is closely related to **Hazard Ratio (HR)** when proportional hazards assumption met: **WR=1/HR**.

## Research Questions

1. How do REPRIEVE's primary TTFE findings compare to WR analysis?
2. Does WR change if trial ended at 1 year, 2 years, 8 years of follow-up?
3. What happens when lower severity events are removed from MACE?

## METHODS

- We re-estimated the WR by censoring follow-up at each of 8 years, for two tiered composites: MACE and Hard MACE (Table 2).

### Win Ratio (WR) in 3 Easy Steps

1. Create all pairs featuring one pitavastatin and placebo participant.
  2. For each pair, compare outcomes for each event by tier until a win is declared for either participant.
- **Win conditions:**
- 1) Pitavastatin event or censor time > Placebo event time.
  - 2) Placebo event or censor time > Pitavastatin event time.
- **Tie condition:** No winner across all events.
3. Win Ratio = Pitavastatin wins / Placebo wins.

**WR>1:** Pitavastatin advantage, **WR<1:** Placebo advantage

### Table: Baseline characteristics of REPRIEVE participants.

Demographics	N=7,769
Age, mean	50 years
Female (%)	2,419 (31%)
Non-White (%)	5,065 (65%)
10-year ASCVD risk, median	4.5%
CD4, mean	660 cells/mm <sup>3</sup>

### Table: (Hard) MACE event tiers, by descending severity.

HARD	CV Death*
	*MACE includes death from undetermined cause
	Stroke
	Myocardial Infarction (MI)
	Other CV Events
	Transient ischemic attack, unstable angina, peripheral arterial ischemia
	CV Procedures

**Pitavastatin advantage driven by early, persistent wins on stroke, MI, and CV death among people living with HIV at low-to-moderate CV risk**

## RESULTS

### Year 1

- No advantage for either arm on CV Death and CV Procedures.
- Pitavastatin advantage on Stroke and MI.
- Placebo advantage on Other CV Events.
- WR=1.59 for Hard MACE > WR=1.18 for MACE.

### Year 2 and 3

- Placebo advantage persists for Other CV Events.
- Pitavastatin wins increase across all events.
- WR≈1.9 for Hard MACE > WR≈1.5 for MACE.

### Year 4 and 5

- All placebo advantage diminished.
- Event tier contributions stabilized.

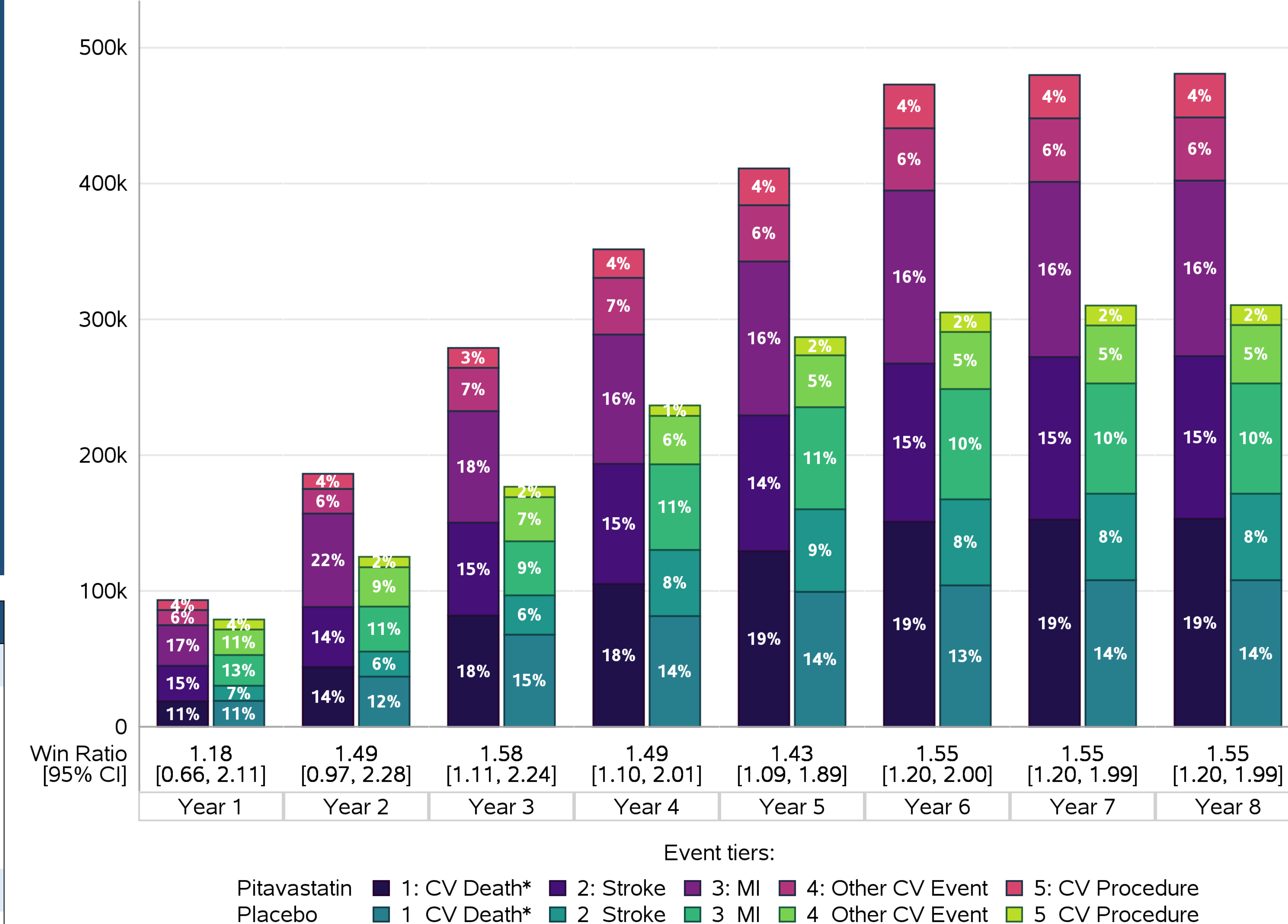
### Year 6 to 8

- MACE WR stabilized at 1.55 (95% CI: 1.20 to 1.99).
- Hard MACE WR stabilized at 1.65 (95% CI: 1.27 to 2.27).

## CONCLUSIONS

- Pitavastatin advantage over placebo was early and persistent for CV Death, Stroke, and MI and increased over time for all events.
- Early but diminishing placebo advantage on less severe CV events led to large differences in WR for MACE vs Hard MACE.
- Reciprocal of WR at 8 years (1/1.55=0.645) approximately equals TTFE HR=0.64, demonstrating strong agreement with REPRIEVE's primary findings.

Number of pairs resulting in a win



**Figure: Wins by Event Tier and Arm for MACE, Censoring at Each Follow-up Year** N=3,888 Pitavastatin and N=3,881 Placebo participants were compared, resulting in 15,089,328 total pairs. Win Ratio with CI shown on the y-axis. Bar labels show proportion of all wins by event tier and arm. \*CV Death includes death of undetermined cause.

**Table: Win ratio breakdown by year for Hard MACE across 15,089,328 pairs.**

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 8
<b>CV</b>	Pitavastatin wins	3,693	14,463	24,826	31,421	46,717	58,266
	Placebo wins	3,697	14,438	21,333	24,737	36,668	41,094
<b>Stroke</b>	Pitavastatin wins	26,246	44,302	68,491	88,570	100,228	120,111
	Placebo wins	11,341	18,466	28,896	48,925	61,082	64,203
<b>MI</b>	Pitavastatin wins	29,726	68,925	82,508	95,554	113,570	129,407
	Placebo wins	22,504	33,191	39,966	63,321	75,303	81,478
<b>Total</b>	Pitavastatin wins	59,665	127,690	175,825	215,545	260,515	307,784
	Placebo wins	37,542	66,095	90,195	136,983	173,053	186,775
<b>Win Ratio (95% CI)</b>		1.59 (0.74, 3.43)	1.93 (1.13, 3.31)	1.95 (1.24, 3.08)	1.57 (1.06, 2.33)	1.51 (1.06, 2.13)	1.65 (1.20, 2.27)