CORRESPONDENCE

Trial Update of Pitavastatin to Prevent Cardiovascular Events in HIV Infection

TO THE EDITOR: The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) (Aug. 24 issue)[1] was a global trial that assessed pitavastatin calcium as compared with placebo to prevent major adverse cardiovascular events (MACE) among participants with HIV infection who were at low-to-moderate predicted cardiovascular risk. In this trial, MACE was defined as a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause. The trial was designed to detect a hazard ratio of 0.70 with 85% power in the intention-to-treat population on the basis of an estimated 288 primary-outcome events.

In March 2023, the trial was stopped early for efficacy by the data and safety monitoring board during a planned interim analysis that was performed after the occurrence of 225 events (78% of the estimated number) on the basis of follow-up data through December 2022.

At that time, the participants in the pitavastatin group had a 35% reduction in MACE as compared with the placebo group, without any unanticipated safety effects. The participants were advised to continue to receive their assigned treatment until a final trial visit between April and August 2023; the trial data were unblinded in November 2023. At the final trial visit, 13 participants (4 in the pitavastatin group and 9 in the placebo group) had started to receive a nonstudy statin since the trial cutoff. This report updates the published analysis with final data regarding efficacy and safety outcomes, including all participant follow-up (Fig. 1). Additional details are provided in Section 1 in the Supplementary Appendix and in the protocol, available with the full text of this letter at NEJM.org.

Of the 7769 participants who were enrolled, 82% completed the trial (Fig. S1 in the Supplementary Appendix). A first MACE had occurred in 257 participants (89% of the estimated number) over a median of 5.6 years of follow-up, totaling 32 more events than had been described in the primary report. All efficacy and safety findings were consistent with those in the primary report (Tables S1 and S2). The estimated rate of the first MACE was 4.95 per 1000 person-years (95% confidence interval [CI], 4.07 to 6.03) in the pitavastatin group and 7.77 per 1000 person-years (95% CI, 6.64 to 9.08) in the placebo group (hazard ratio, 0.64; 95% CI, 0.48 to 0.84) (Fig. 1 and Fig. S3). Nonproportional hazard assumptions were not violated. Effects that were consistent with those in the primary report were seen for secondary outcomes (including the occurrence of a first MACE or death from any cause) and in
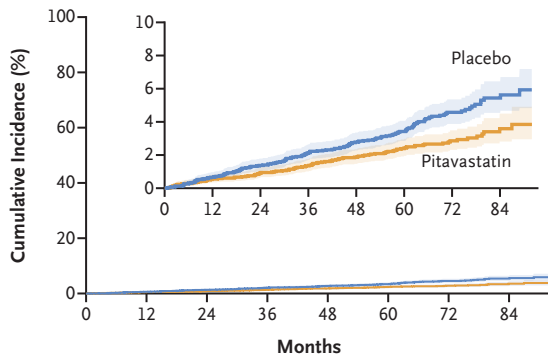
A Estimated Treatment Effect

| Subgroup	Pitavastatin (N=3888)	Placebo (N=3881)	Hazard Ratio (95% CI)	
	no./1000 person-yr (no. of events)			
Primary outcome and supporting analyses				
First MACE	**4.95 (100)**	**7.77 (157)**		**0.64 (0.48–0.84)**
First confirmed MACE	3.91 (79)	6.18 (125)		0.63 (0.48–0.84)
First MACE (as-treated analysis)	4.56 (83)	6.33 (113)		0.72 (0.54–0.95)
First MACE (per-protocol analysis)	4.73 (88)	6.92 (129)		0.68 (0.52–0.90)
First hard MACE	2.91 (59)	4.93 (100)		0.59 (0.43–0.82)
Secondary outcomes and supporting analyses				
First MACE or death	9.31 (188)	12.02 (243)		0.77 (0.64–0.94)
First MACE or death including vital status follow-up	9.27 (193)	12.23 (255)		0.76 (0.63–0.91)
Death from any cause	6.18 (126)	6.99 (143)		0.88 (0.70–1.12)
Individual components of MACE				
First cardiac ischemia or myocardial infarction	1.48 (30)	2.65 (54)		0.56 (0.36–0.87)
First cerebrovascular event (stroke or TIA)	1.53 (31)	2.46 (50)		0.62 (0.40–0.97)
First peripheral arterial ischemia	0.10 (2)	0.15 (3)		0.67 (0.11–4.02)
Death from cardiovascular causes	0.69 (14)	0.98 (20)		0.70 (0.35–1.38)
Death from cardiovascular or undetermined causes	1.72 (35)	2.54 (52)		0.67 (0.44–1.03)
First cardiac catheterization or revascularization	1.08 (22)	1.77 (36)		0.62 (0.36–1.05)
First peripheral arterial revascularization	0.00 (0)	0.29 (6)		0.00 (0.00–0.54)

Hazard Ratio axis: 0.0 0.1 0.2 0.4 0.7 1.0 1.4 2.0

← Pitavastatin Better   Placebo Better →

B First MACE

Cumulative Incidence (%) vs Months (0–84)

Placebo / Pitavastatin

Cumulative Incidence of Event (%)

Placebo	0.00	0.66	1.38	2.14	2.78	3.42	4.58	5.44
Pitavastatin	0.00	0.56	0.95	1.35	1.88	2.43	2.86	3.59

No. at Risk

Placebo	3881	3693	3510	3369	3191	2785	1492	698
Pitavastatin	3888	3653	3485	3382	3225	2681	1351	511

C First MACE or Death

Cumulative Incidence (%) vs Months (0–84)

Placebo / Pitavastatin
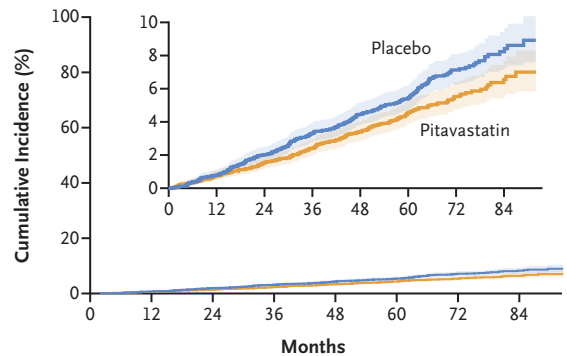
Cumulative Incidence of Event (%)

Placebo	0.00	0.80	2.03	3.33	4.47	5.42	7.14	8.24
Pitavastatin	0.00	0.77	1.58	2.41	3.40	4.57	5.54	6.57

No. at Risk

Placebo	3881	3693	3510	3369	3191	2693	1492	551
Pitavastatin	3888	3653	3485	3382	3225	2681	1351	511

Figure 1. Treatment Effect of Pitavastatin on Major Adverse Cardiovascular Events.

Shown is the incidence of major adverse cardiovascular events (MACE) among trial participants with HIV infection in the pitavastatin group and the placebo group and the estimated treatment effect, according to stratified Cox proportional-hazards analysis (Panel A). The primary outcome of the trial is shown in bold at the top of the graph. In addition to the previously reported outcome measures, a supportive outcome measure that was limited to the hard clinical end points of myocardial infarction, stroke, and cardiovascular death (hard MACE) is presented. Cox proportional-hazards models were stratified according to sex at birth and the CD4 count at screening. Also shown are the cumulative incidence of a primary-outcome event (first MACE) (Panel B) and a key secondary outcome (first MACE or death from any cause) (Panel C). In Panels B and C, the insets show the data on an expanded y axis. Aside from the primary result, the widths of the confidence intervals have not been adjusted for multiplicity and therefore may not be used in place of hypothesis testing. TIA denotes transient ischemic attack.

supportive analyses of the primary outcome and a sensitivity analysis accounting for missing data, as well as for individual MACE components and events within prespecified subgroups (Figs. S3 through S6). In a post hoc analysis, the number of patients who would need to be treated with pitavastatin to prevent one primary-outcome event was 100 (Fig. S10).

Thus, among a group of participants with HIV infection who were at low-to-moderate predicted cardiovascular risk, pitavastatin reduced the incidence of MACE over a follow-up of 5.6 years with an acceptable safety profile. Revised treatment guidelines incorporating data from REPRIEVE that recommend statin therapy in this patient population were recently announced.[2]

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1. Grinspoon SK, Fitch KV, Zanni MV, et al. Pitavastatin to prevent cardiovascular disease in HIV infection. N Engl J Med 2023; 389:687-99.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Rockville, MD: NIH Office of AIDS Research, February 2024 (https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv).

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CAR T-Cell Therapy in Autoimmune Disease

TO THE EDITOR: In the case series presented by Müller et al. (Feb. 22 issue),[1] CD19-targeting chimeric antigen receptor (CAR) T-cell therapy in patients with systemic lupus erythematosus (SLE) resulted in prompt clinical and serologic remission. In contrast, in patients with Scl70+ systemic sclerosis, serologic remission after CAR T-cell therapy was not as complete. This observation is discrepant with the case of a patient with systemic sclerosis that we recently presented.[2] In the case series, CAR T cells disappeared within a few weeks, whereas the third-generation CD19 CAR T cells that we administered were still detectable at 11 months. It is notable that autoantibodies against Scl70 in our patient not only gradually decreased but eventually disappeared 15 months after therapy (Fig. 1). The protocols that we used were slightly different in several aspects from those used in the case series, including the number of infused CAR T cells. In addition, mycophenolate had been continued initially after CAR T-cell therapy in our patient but was finally discontinued 7 months later owing to a favorable disease course. Together, the cases suggest that CAR T-cell therapy must be tailored and is not a "one size fits all" solution for autoimmunity. In patients with systemic sclerosis, persistence of CAR T cells for more than a few weeks may be required for the eventual disappearance of autoantibodies.

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