

CORRESPONDENCE

N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects

TO THE EDITOR: Statins are often discontinued because of side effects,^{1,2} even though some blinded trials have not shown an excess of symptoms with statins as compared with placebo.^{3,4} Patients who had previously discontinued statins because of side effects that occurred within 2 weeks after the initiation of treatment were enrolled in a double-blind, three-group, n-of-1 trial to test whether symptoms would be induced by a statin or placebo. Details of the trial methods are provided in Section S2 in the Supplementary Appendix (available with the full text of this letter at NEJM.org); the trial protocol and statistical analysis plan are also available at NEJM.org.

The patients received four bottles containing atorvastatin at a dose of 20 mg, four bottles containing placebo, and four empty bottles; each bottle was to be used for a 1-month period according to a random sequence. The patients used a smartphone application to report symptom intensity daily. Symptom scores ranged from 0 (no symptoms) to 100 (worst imaginable symptoms). If the patients determined that their symptoms were unacceptably severe, they could discontinue the tablets for that month.

The primary end point was symptom intensity as assessed with the use of the nocebo ratio (i.e., the ratio of symptom intensity induced by taking placebo to the symptom intensity induced by taking a statin). This ratio was calculated as the symptom intensity with placebo minus the symptom intensity with neither statin nor placebo, divided by the symptom intensity with a statin minus the symptom intensity with neither statin nor placebo.

From June 2016 through March 2019, a total of 60 patients underwent randomization. The screening data, the baseline characteristics of the

patients, and a diagram showing screening, randomization, intervention, and follow-up are provided in Sections S1 through S3 in the Supplementary Appendix. A total of 49 patients completed all 12 months of the trial.

The original primary end-point analysis showed a nocebo ratio of 2.2 (95% confidence interval [CI], -62.3 to 66.7). This value was high and had a wide confidence interval because in some of the patients the value of the symptom intensity with statins minus the symptom intensity with neither statin nor placebo was unexpectedly small or negative. An independent statistician therefore recommended a different analysis (see Section S2 in the Supplementary Appendix) in which individual patient data were pooled before calculation of the ratio. This analysis showed a nocebo ratio of 0.90. Among all 60 patients, the mean symptom intensity was 8.0 during no-tablet months (95% CI, 4.7 to 11.3), 15.4 during placebo months (95% CI, 12.1 to 18.7; $P < 0.001$ for the comparison with no-tablet months), and 16.3 during statin months (95% CI, 13.0 to 19.6; $P < 0.001$ for the comparison with no-tablet months and $P = 0.39$ for the comparison with placebo months) (Fig. 1). Adverse events are listed in Section S4 in the Supplementary Appendix.

Six months after completion of the trial, 30 of the patients (50%) had successfully restarted statins, 4 planned to do so, and 1 could not be contacted. The remaining 25 patients were not receiving statins and were not planning to restart statins. The reasons given by these 25 patients for not planning to restart statins are listed in Section S3 in the Supplementary Appendix.

In patients who had discontinued statin therapy because of side effects, 90% of the symptom burden elicited by a statin challenge was also

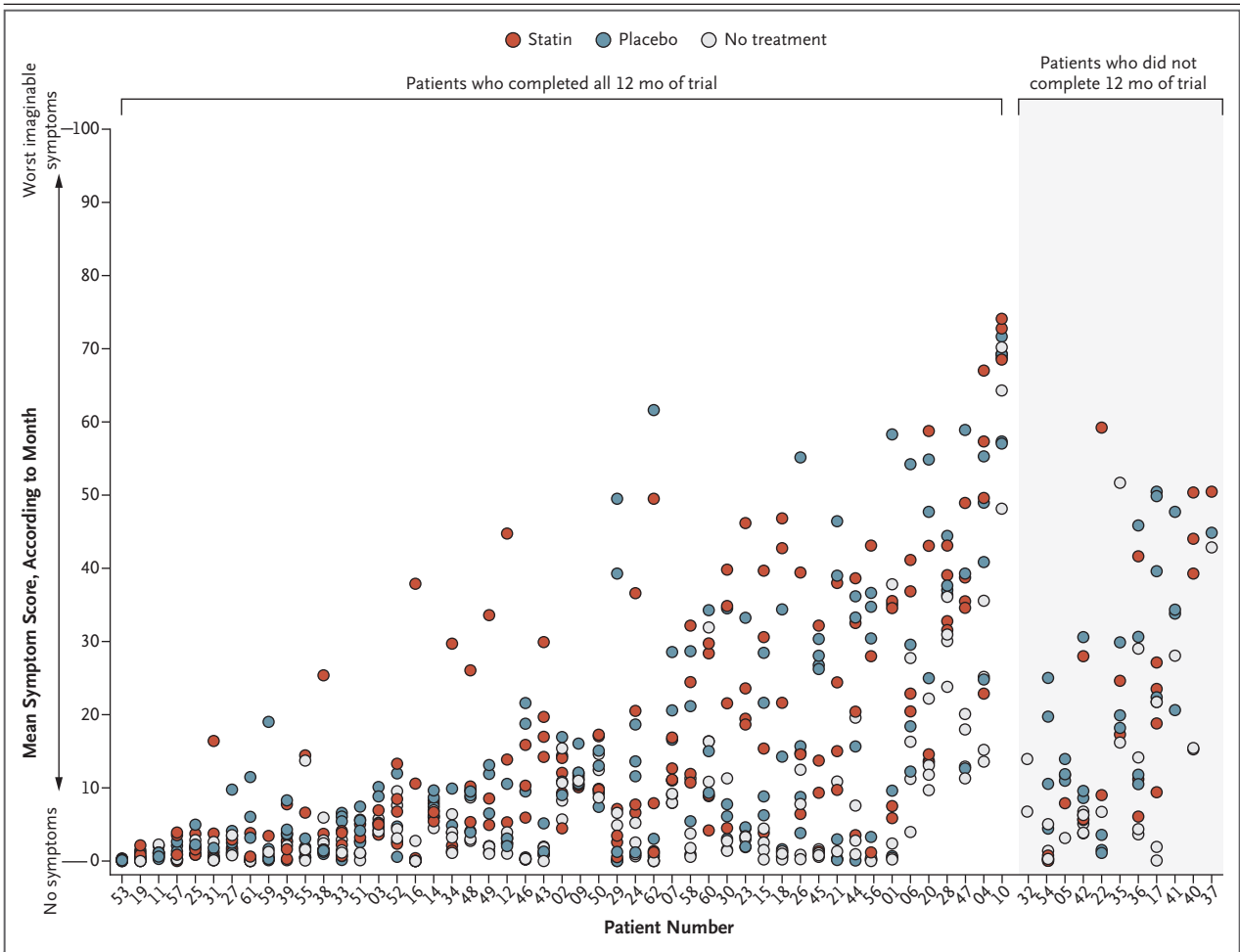


Figure 1. Symptom Scores for All the Trial Patients.

Shown are mean symptom scores for the 49 patients who completed all 12 months of the trial (left) and those for the 11 patients who did not complete all 12 months (right). Each circle represents a single month for each patient. Symptoms were reported daily, and the mean symptom score was calculated for the month regardless of whether the patient discontinued the assigned bottle at any time during that month.

elicited by placebo. Half the trial patients were able to successfully restart statins.

Frances A. Wood, M.Phil.
 James P. Howard, Ph.D.
 Judith A. Finegold, Ph.D.
 Alexandra N. Nowbar, M.B., B.S.
 David M. Thompson, Ph.D.
 Ahran D. Arnold, M.B., B.S.
 Christopher A. Rajkumar, M.B., B.S.
 Susan Connolly, Ph.D.
 Imperial College London
 London, United Kingdom
 research@cardiologists.london

Jaimini Cegla, M.R.C.P.
 Imperial College Healthcare NHS Trust
 London, United Kingdom
 Chris Stride, Ph.D.
 Sheffield University Management School
 Sheffield, United Kingdom
 Peter Sever, F.R.C.P.
 Imperial College London
 London, United Kingdom
 Christine Norton, Ph.D.
 King's College London
 London, United Kingdom

Simon A.M. Thom, M.D.
 Matthew J. Shun-Shin, Ph.D.
 Darrel P. Francis, Ph.D.

Imperial College London
 London, United Kingdom

Ms. Wood and Dr. Howard contributed equally to this letter.

The views expressed in this letter are those of the authors and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

Supported by a grant (PG/15/7/31235) from the British Heart Foundation; a grant (212183/Z/18/Z, to Dr. Howard) from the Wellcome Trust; a grant (MR/S021108/1, to Dr. Rajkumar) from the Medical Research Council; the National Institute for Health Research Imperial Biomedical Research Centre; and the Imperial Clinical Trials Unit.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on November 15, 2020, at NEJM.org.

1. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy — European Atherosclerosis Society Consensus Panel statement on assessment, aetiology and management. *Eur Heart J* 2015;36:1012-22.
2. Stulc T, Češka R, Gotto AM Jr. Statin intolerance: the clinician's perspective. *Curr Atheroscler Rep* 2015;17:69.
3. Finegold JA, Manisty CH, Goldacre B, Barron AJ, Francis DP. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *Eur J Prev Cardiol* 2014;21:464-74.
4. Gupta A, Thompson D, Whitehouse A, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. *Lancet* 2017;389:2473-81.

DOI: 10.1056/NEJMc2031173

Correspondence Copyright © 2020 Massachusetts Medical Society.