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 of 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),

THIS WEEK'S LETTERS

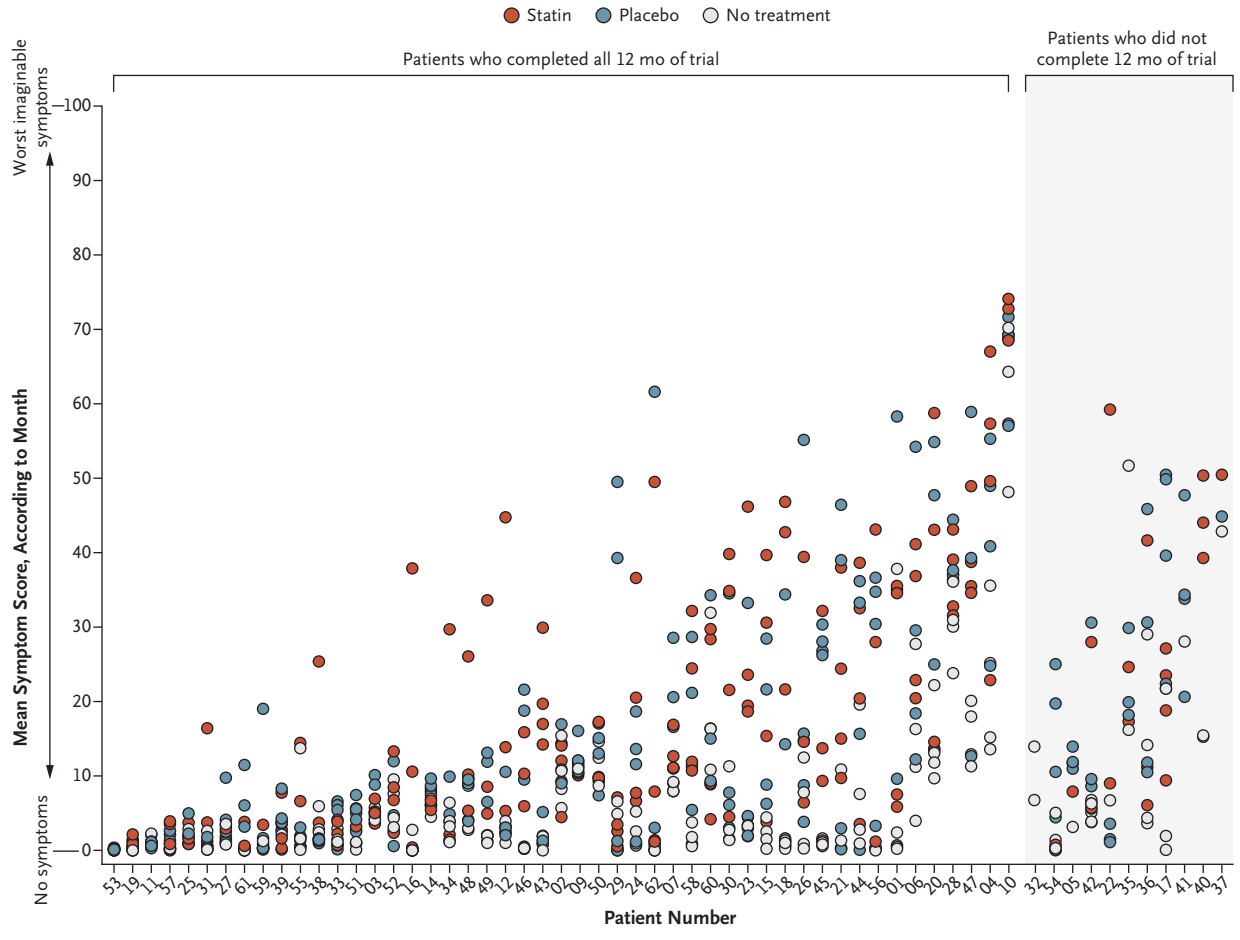


**Figure 1. Symptom Scores for All the Trial Patients.**

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.

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

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# Early Spread of SARS-CoV-2 in the Icelandic Population

**TO THE EDITOR:** Gudbjartsson and colleagues (June 11 issue)[1] reveal important insights into the transmission of SARS-CoV-2. An aspect of their study that merits further exploration is the positive test results in asymptomatic persons in both the population-screening group (in 36 of 7218 persons [0.5%]) and the random-sample population screening group (in 7 of 2012 persons [0.3%]).

Although the authors note that some persons may have been presymptomatic — a recognized issue with cross-sectional testing[2] — another interpretation is that these are false positive results. For example, if a test with a specificity of 99.7% is used, the detection of a positive result in 0.3% of the participants would not be unexpected.

The effect of false positive tests is particularly important when the prevalence of a condition is low.[3] For example, in countries such as Australia, where the estimated prevalence of SARS-CoV-2 is currently less than 0.05%,[4] even a test that is 95.0% sensitive and 99.7% specific would have a positive predictive value of 13.7% (i.e., 86.3% of the positive results would be false positive) (see Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

Population-screening programs typically include a follow-up diagnostic test after an initial positive screening test. There is currently no such option for SARS-CoV-2; consideration must therefore be given to addressing the problem of false positives when testing asymptomatic persons.

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