identify reinfections and infections in these cohorts, and Table S2 presents the demographic characteristics of the persons in the cohorts. The median date of previous PCR-confirmed infection was June 21, 2020 (interquartile range, May 24 to August 20, 2020). Kaplan–Meier curves show the cumulative incidence of reinfection among persons with previous PCR-confirmed infection (previous-infection cohort) as compared with that of infection among antibody-negative persons (antibody-negative cohort) (Fig. 1). At 42 days of follow-up, the cumulative incidence was 0.27% (95% confidence interval [CI], 0.22 to 0.32) in the previous-infection cohort and 3.44% (95% CI, 3.27 to 3.61) in the antibody-negative cohort for the beta variant and 0.03% (95% CI, 0.02 to 0.06) and 1.35% (95% CI, 1.25 to 1.46), respectively, for the alpha variant.

Incidence rates of infection with the beta variant were estimated at 4.34 cases per 10,000 person-weeks (95% CI, 3.64 to 5.19) in the previous-infection cohort and at 56.25 cases per 10,000 person-weeks (95% CI, 53.50 to 59.14) in the antibody-negative cohort. With regard to the alpha variant, the corresponding incidence rates were 0.53 cases per 10,000 person-weeks (95% CI, 0.32 to 0.89) and 22.44 cases per 10,000 person-weeks (95% CI, 20.73 to 24.30). The efficacy of natural infection against reinfection, which was derived by comparing the incidence rate in both cohorts, was estimated at 92.3% (95% CI, 90.3 to 93.8) for the beta variant and at 97.6% (95% CI, 95.7 to 98.7) for the alpha variant. Details are provided in Table S3.

Additional analyses comparing the incidence of reinfection among antibody-positive persons with the incidence of infection among antibody-negative persons or adjusting for differences in testing frequency across the cohorts, for the varying phase of the pandemic, or for competing risks of variant infections and death were all consistent with the main study results. However, the efficacies were slightly lower overall (Section S2).

Protection by previous SARS-CoV-2 infection against reinfection with the beta variant was observed, even 1 year after the primary infection, but protection was slightly lower than that against the alpha variant and wild-type virus circulating in Qatar.[3-5] These findings give some insights into the hypothesis that natural immunity may provide protection against known variants of concern.

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Maintenance or Discontinuation of Antidepressants in Primary Care

TO THE EDITOR: In the 52-week trial of discontinuation of antidepressant medication conducted by Lewis et al. (Sept. 30 issue),[1] relapse risk was significantly higher in the discontinuation group than in the maintenance group. We suggest that this finding may have been confounded

by symptoms of antidepressant withdrawal. The effects of acute withdrawal can last 6 weeks, and the effects of postacute antidepressant withdrawal syndrome may last from several months to years.[2,3] Because withdrawal symptoms may overlap with primary depression, patients who have these symptoms may have higher scores on depression-rating scales.[2]A meta-analysis has indicated that more than half of persons who attempt to discontinue antidepressants have withdrawal effects and that a similar proportion of those who have withdrawal effects describe them as severe.[3] In the results reported by Lewis et al.,[1] the frequency of new or worsened drug-withdrawal symptoms was higher in the discontinuation group than it was in the maintenance group at weeks 12, 26, and 39, suggesting that withdrawal effects have a role in the primary outcome.

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TO THE EDITOR: In their randomized, placebo-controlled trial in which participants in primary care stopped or continued to take antidepressants, Lewis et al. provided limited information regarding the severity and duration of the episodes they classified as depressive relapses. Apart from a transient increase in distress in the discontinuation group at weeks 12 and 26 of the study, the aggregate scores on the Patient Health Questionnaire 9-item version (PHQ-9), which are both sensitive and specific for the diagnosis of depression,[1] did not differ significantly from scores in the general population.[2] This pattern of transient increase and subsequent normalization can also be seen in scores on the Generalized Anxiety Disorder Assessment 7-item version (GAD-7) and the 12-Item Short-Form Health Survey (SF-12) mental health scores as well as on the Global Rating Questionnaire. Because 59% of patients in the discontinuation group were unblinded and 71% correctly guessed the group to which they had been assigned (as compared with 29% and 47%, respectively, in the maintenance group), these seemingly fleeting increases in distress might be better explained as a short-term failure of outcome expectancy than as a true relapse of depression.[3,4]

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THE AUTHORS REPLY: The ANTLER trial provided evidence of withdrawal symptoms over the medium and longer term after antidepressant discontinuation. The trial also provided evidence of an increased relapse rate in the group assigned to discontinue antidepressants. Some overlap between new and worsening symptoms of withdrawal and depressive relapse is possible. Liang et al. suggest that this overlap leads to an apparent increase in depressive relapse. However, the opposite is just as likely — namely, that an increase in depressive symptoms might lead to an increase in "new and worsening" symptoms that are recorded as withdrawal symptoms. Although

it is likely that these two conditions will remain difficult to separate, we plan further analyses to explore these possibilities. Withdrawal symptoms can only occur in the discontinuation group, but participants reported some new and worsening symptoms while continuing to take antidepressants. We found no evidence that the hazard ratio for relapse varied across the 12-month follow-up period, whereas one would expect withdrawal symptoms to cluster around the time after the medication was terminated. We found that the difference in withdrawal symptoms between the groups was largest at 12 weeks.

Kuschpel inquires about the severity of relapses in our trial. In addition to our prespecified definition of relapse, we used internationally agreed-upon International Classification of Diseases, version 10, criteria for relapse of depression and found similar results to those in our primary analysis (see Table S11 in the Supplementary Appendix, available with the full text of our article at NEJM.org). We recorded relapses that may have occurred at any time in the 3 months preceding the assessment and may have resolved by the time the participant was assessed on our secondary outcomes, such as the PHQ-9. We therefore would have expected a smaller between-group difference regarding secondary outcomes because they only assessed how the participant was feeling at the time of the assessment. Our finding that people in the discontinuation group were more likely to guess their allocation could be due to the clinical effect of discontinuation and is not, in our view, an indication that our findings were invalid.

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Since publication of their article, the authors report no further potential conflict of interest.

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Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension

TO THE EDITOR: In a trial involving elderly patients with hypertension, Zhang et al. (Sept. 30 issue)[1] found that intensive treatment (systolic blood-pressure target, 110 to <130 mm Hg) resulted in a lower incidence of cardiovascular events and stroke than standard treatment (target, 130 to <150 mm Hg). However, the use of antihypertensive drugs was imbalanced between the two groups. For example, at 42 months, hydrochlorothiazide was used more in the intensive-treatment group (280 patients) than in the standard-treatment group (102 patients).

A recent systematic review[2] showed that use of calcium-channel blockers led to a higher risk of major cardiovascular events than use of diuretics (risk ratio, 1.05) but to a lower risk than use of beta-blockers (risk ratio, 0.84) or angiotensin-converting–enzyme inhibitors (risk ratio, 0.90). Use of calcium-channel blockers also led to a lower risk of myocardial infarction than use of angiotensin-receptor blockers (risk ratio, 0.82).

Given that several lines of evidence have shown that these drugs affect the cardiovascular system independent of blood pressure,[3,4] the type of antihypertensive drug used can bias trial results. We wonder whether the authors could provide a subgroup analysis with the type of antihypertensive drug as a variable.

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No potential conflict of interest relevant to this letter was reported.

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