

end points were the rate of increase between day 0 and day 15 in neutralizing-antibody titers against the original D614 strain and the beta, B.1.617.2 (delta), and B.1.1.529 (omicron) BA.1 variants; the geometric mean of anti-spike (anti-S1) IgG levels; and interferon- γ - and interleukin-2-secreting CD4+ T-cell response against the original strain and the omicron variant in each randomized group.

Among the 247 participants who underwent randomization between December 8, 2021, and January 14, 2022, a total of 24 participants were excluded, mainly owing to preexisting immunity against SARS-CoV-2. The per-protocol population included 223 participants: 76 in the MVD614 group, 71 in the MVB.1.351 group, and 76 in the BNT162b2 group (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The mean age of the participants was 40.6 years, and 40% were women. The baseline characteristics of the participants did not differ among the trial groups (Table S1).

The percentage of participants who had an increase in the neutralizing-antibody titer by a factor of at least 10 between day 0 and day 15 for the original strain was 55% (95% confidence interval [CI], 43 to 67) in the MVD614 group, 76% (95% CI, 64 to 85) in the MVB.1.351 group, and 63% (95% CI, 51 to 74) in the BNT162b2 group. For the beta variant, the corresponding percentages were 45% (95% CI, 33 to 57), 85% (95% CI, 74 to 92), and 51% (95% CI, 40 to 63).

The MVB.1.351 vaccine elicited higher neutralizing-antibody titers than the other vaccines against the original strain and against the beta, delta, and omicron BA.1 variants (Fig. 1 and Table S2). The geometric mean titer of anti-S1 increased from 277.1 binding antibody units (BAU) per milliliter at day 0 to 1875.1 BAU per milliliter at day 15 in the MVD614 group, from 206.8 to 2240.8 BAU per milliliter in the MVB.1.351 group, and from 253.6 to 2405.4 BAU per milliliter in the BNT162b2 group (Table S3). The MVB.1.351 vaccine also induced high levels

of specific polyfunctional CD4+ type 1 helper T-cell response (Figs. S3 and S4). The reactogenicity profiles of the three booster vaccines did not differ among the trial groups (Table S4).

Over the short term, heterologous boosting with the beta-adjuvanted MVB.1.351 vaccine resulted in a higher neutralizing-antibody response against the beta variant as well as against the original strain and the delta and omicron BA.1 variants than did the mRNA vaccine BNT162b2 or the MVD614 formulation. The use of new vaccines that contain beta spike protein may be an interesting strategy for broader protection against SARS-CoV-2 variants.

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CT or Invasive Coronary Angiography in Stable Chest Pain

TO THE EDITOR: Ten years ago, the Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT-II) trial evaluated

whether the use of coronary computed tomographic (CT) angiography led to shorter emergency department stays than usual testing among

patients with symptoms suggestive of acute coronary syndrome without changes on electrocardiography or an elevated troponin level.¹ One question that was raised at the time was not whether a particular test was better than another but whether any further diagnostic testing was indicated.²

The report by the Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease (DISCHARGE) Trial Group (April 28 issue)³ compels us to consider the issue further. Among the patients in this trial (56% of whom were women), the incidences of major adverse cardiovascular events and typical angina were low. The question that was investigated should not have been whether coronary CT angiography or invasive coronary angiography leads to better outcomes but whether clinical evaluation with judicious noninvasive stress testing is a better choice to identify the few patients with coronary artery disease who may then benefit from intensive lifestyle and pharmacologic interventions (“optimal medical therapy”). Multiple trials have shown no benefit of revascularization as compared with optimal medical therapy.^{4,5} The DISCHARGE trial shows again that the risk of cardiac events among middle-aged persons with stable or non-anginal chest pain is very low, and no kind of coronary angiography is associated with improved outcomes.

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TO THE EDITOR: The DISCHARGE trial compared coronary CT angiography with invasive coronary

angiography as the initial diagnostic investigation in patients with chest discomfort and low-to-intermediate pretest probability of coronary plaque. With respect to the secondary outcome of angina, there was no substantial difference between the groups, despite similar medical therapy prescribed in both groups and a significantly higher frequency of revascularization procedures in the group that underwent invasive coronary angiography.

Although invasive angiography, as compared with medical therapy, has been shown to reduce the severity of angina,^{1,2} it has been postulated by means of a new blinded, sham-procedure, controlled trial that this may be a placebo effect,³ with perceived revascularization proposed as the mechanism. However, the results of the DISCHARGE trial suggest that symptomatic relief may be attributable to anatomical assessment, and whether coronary CT angiography may help alleviate a patient's symptoms is worthy of further investigation.

In addition, given the low prevalence of obstructive epicardial plaque in each trial group (approximately 25%), angina may be attributable to coronary causes beyond epicardial stenosis, such as microvascular angina or coronary vasospasm.⁴ Neither of these conditions would be detected on coronary CT angiography or standard invasive coronary angiography, a fact that highlights the need for coronary investigation beyond epicardial vessels.

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TO THE EDITOR: The findings from the DISCHARGE trial are not unexpected. On the basis of the pretest probability, the intended trial population had to be at intermediate risk, but a low-risk population, with a predominance of female patients (56%) and a high percentage of patients (>85%) with nonanginal chest pain or atypical angina, was ultimately enrolled. These patient characteristics contribute to the explanation of the lower-than-expected annual incidence of major adverse cardiovascular events (the primary outcome). Indeed, the observed incidence of a primary-outcome event in the control group is almost equivalent to the expected incidence in the experimental group after accounting for the estimated treatment effect. For these reasons, the trial might not be sufficiently powered to address the question of risk stratification in patients at intermediate risk. In such a low-risk setting, it is very unlikely that any diagnostic test, even the most accurate, will be able to show superiority in terms of prevention of cardiovascular events unless a very large randomized trial is undertaken.

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TO THE EDITOR: The DISCHARGE trial involved patients with an intermediate pretest probability of coronary artery disease (CAD). I share the concerns of the editorialist¹ regarding the authors' choice of a scoring system to calculate pretest probability and their inclusion of many patients (>35%) with nonanginal chest pain. The trial used a pretest probability calculator that was developed by Haase et al. for the Collaborative Meta-Analysis of Cardiac CT (COME-CCT) Consor-

Table 1. Pretest Probability of Coronary Artery Disease among Women with Nonanginal Chest Pain.

Age	Pretest Probability	
	Genders et al. ³	DISCHARGE Trial*
	<i>percent</i>	
35 yr	5.3	14
45 yr	8.0	18
55 yr	11.7	23
65 yr	16.9	29

* Data were obtained from Section S7 in the Supplementary Appendix of the article by the Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease (DISCHARGE) Trial Group.

tium.² The results derived with this calculator (Section S7 of the Supplementary Appendix in the article) for women with nonanginal chest pain are much higher than the pretest probability estimates reported by Genders et al. (Table 1).³

Haase et al. compared coronary CT angiography with invasive angiography for the diagnosis of CAD, with stratification according to the pretest probability estimates in the study by Genders et al., and reported that “up to a pretest probability of 40%, pretest probability predictions overestimated true CAD prevalence by about 10 percentage points.”² A calculator based on data from the study by Haase et al. would therefore be expected to provide pretest probability estimates that were lower than those of Genders et al., not higher. Can the authors please explain this apparent paradox?

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THE AUTHORS REPLY: Redberg and Jeon, as well as the editorialist Loscalzo, raise an important question of whether a strategy of optimal medical therapy without any testing is appropriate in patients with stable chest pain whose characteristics suggest a low risk of obstructive CAD. The DISCHARGE trial is a step in that direction. All the patients in the DISCHARGE trial had a clinical indication for invasive coronary angiography according to European guidelines at the time that the trial was conducted, and the incidence of major procedure-related complications was lower with the CT-first strategy than with the invasive coronary angiography strategy. In a patient cohort with a similar rate of obstructive CAD (25.4%), the Scottish Computed Tomography of the Heart (SCOT-HEART) trial showed that the incidence of fatal and nonfatal myocardial infarction was lower with CT than with standard care that included judicious noninvasive stress testing.¹ A logical next step would be to test whether a strategy of optimal medical therapy without any testing is as good as CT for the management of stable chest pain.

Baumann et al. say correctly that symptom relief at follow-up in the DISCHARGE trial may be attributable to medical treatment after anatomical assessment by CT. We agree that there is a need to investigate imaging techniques beyond coronary angiography to detect and quantify microvascular angina or coronary vasospasm.²

Danzi and Piccolo comment on the high percentage of women (56%) in the DISCHARGE trial, which is a strength of the trial that addresses the underrepresentation of female patients in previous trials. The incidence of major adverse cardiovascular events at a median of 3.5 years was lower than expected, and the trend in the time-to-event curve suggests that a longer follow-up of 5 or 6 years would be important to address reduction of the risk of major adverse cardiovascular events with the use of CT, because it is unlikely there will be another large, randomized trial comparing CT with invasive coronary angiography.

Gibbons highlights the importance of CAD pretest probability assessment. In the DISCHARGE trial, the mean calculated pretest probability of obstructive CAD (37.7%) was higher than the observed prevalence (25.7%). This difference is probably due to differences in the base rate of obstructive CAD³ between the DISCHARGE trial

Table 1. A Comparison of the Pretest Probabilities of Obstructive CAD Derived with the COME-CCT Consortium and CAD Consortium Calculators in the Four Chest-Pain Groups.*

Age†	Typical Angina		Atypical Angina		Nonanginal Chest Pain‡		Other Chest Pain‡	
	Women	Men	Women	Men	Women	Men	Women	Men
	<i>% with COME-CTT Consortium calculator – % with CAD Consortium calculator (percentage-point difference)</i>							
35 yr	30.9–27.5 (3.4)	51.6–59.1 (–7.5)	14.5–9.6 (4.9)	29.4–28.9 (0.5)	13.9–5.3 (8.6)	28.3–17.7 (10.6)	11.7–5.3 (6.4)	24.7–17.7 (7.0)
45 yr	37.8–36.7 (1.1)	59.0–68.9 (–9.9)	18.9–14.0 (4.9)	36.1–38.4 (–2.3)	18.1–8.0 (10.1)	34.9–24.8 (10.1)	15.4–8.0 (7.4)	30.8–24.8 (6.0)
55 yr	45.0–47.1 (–2.1)	66.1–77.3 (–11.2)	24.2–20.0 (4.2)	43.3–48.9 (–5.6)	23.2–11.7 (11.5)	42.0–33.6 (8.4)	20.0–11.7 (8.3)	37.6–33.6 (4.0)
65 yr	52.5–57.7 (–5.2)	72.5–83.9 (–11.4)	30.2–27.7 (2.5)	50.7–59.4 (–8.7)	29.1–16.9 (12.2)	49.5–43.7 (5.8)	25.4–16.9 (8.5)	44.9–43.7 (1.2)
75 yr	59.9–67.7 (–7.8)	78.2–88.9 (–10.7)	37.0–37.0 (0.0)	58.2–69.2 (–11.0)	35.8–23.8 (12.0)	56.9–54.4 (2.5)	31.6–23.8 (7.8)	52.4–54.4 (–2.0)

* The pretest probabilities, expressed as percentages, are shown for the four types of chest pain, stratified according to sex and five age groups. Typical angina was considered if the following three criteria were fulfilled: retrosternal chest discomfort, precipitation by exertion, and prompt relief (within 30 seconds to 10 minutes) by rest or nitroglycerin. Patients who met two, one, or none of these three criteria were classified as having atypical angina, nonanginal chest pain or discomfort, and other chest pain or discomfort, respectively. Because all the trial patients were symptomatic with stable chest pain, the category of “other chest pain” was used for patients who did not have any of the three criteria as described. The Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease (DISCHARGE) trial used the calculator developed by the Collaborative Meta-Analysis of Cardiac CT (COME-CCT) Consortium to assess the pretest probability of obstructive coronary artery disease (CAD); the development of this calculator was based on data from 4416 patients with stable chest pain referred for invasive coronary angiography.⁴ The development of the CAD Consortium calculator was based on data from 2260 patients referred for invasive coronary angiography.⁵

† The results are shown for age in 10-year intervals for the purpose of the comparison between the COME-CCT Consortium calculator used in the DISCHARGE trial and the CAD Consortium calculator.

‡ In the CAD Consortium, the categories of “nonanginal chest pain” and “other chest pain” that were used in the original classification by Diamond and Forrester (<https://fpnotebook.com/cv/exam/DmndAndFrstrCstnPnPrdctnRl.htm>) were merged into a single category labeled “nonspecific chest pain,” whereas in the DISCHARGE trial, these types of pain were analyzed as separate categories.

cohort (25.7%) and the independent COME-CCT Consortium cohort (49.2%); the pretest probability calculator that was used in the DISCHARGE trial was developed by the COME-CCT Consortium.⁴ A comparison between the COME-CCT Consortium and the CAD Consortium calculators⁵ is provided in Table 1, which shows that in patients with typical angina and men with atypical angina, the COME-CCT calculator reduces overestimation while the CAD Consortium calculator is more accurate in patients with non-anginal or other chest pain. The editorialist asked why a pretest probability of obstructive CAD of 10 to 60% was chosen as the inclusion range; our rationale was that CT is most accurate in this intermediate risk range.⁴

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

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Single-Dose Amphotericin B for Cryptococcal Meningitis

TO THE EDITOR: Jarvis et al. (March 24 issue)¹ showed that a regimen that included a single dose of liposomal amphotericin B (10 mg per kilogram of body weight) followed by 14 days of treatment with flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day) was noninferior to the current treatment recommended by the World Health Organization (WHO) for cryptococcal meningoencephalitis, with fewer adverse events. The need for better treatment regimens for cryptococcosis is urgent, because the estimated global rate of death associated with the condition is 181,000 cases per year.² The trial results are consistent with the pharmacodynamic properties of amphotericin B and could have a substantial effect on clinical practice. We believe that the main issue here is not whether liposomal amphotericin B works in single-dose regimens but rather whether it can be made available (and affordable) in places where it is needed most, including Latin America, Africa, and Southeast Asia. Liposomal amphotericin B — not to mention 5-fluorocytosine — is

scarce in most of these places. Only four countries in sub-Saharan Africa have access to liposomal amphotericin B,³ and it is unavailable in most public health systems in Latin America.⁴ It is time for scientists, politicians, and members of industry to work together to make this treatment available for the benefit of global public health.

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