ORIGINAL ARTICLE

# Aspirin Omission at the Time of Primary Percutaneous Coronary Intervention in STEMI

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## ABSTRACT

### BACKGROUND

The safety of omitting up-front treatment with aspirin during primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) remains unclear.

### METHODS

We conducted a multicenter, open-label, randomized trial in Japan involving patients with STEMI who were undergoing primary PCI. Patients were randomly assigned in a 1:1 ratio before PCI to receive low-dose prasugrel monotherapy or dual antiplatelet therapy (DAPT) with aspirin and low-dose prasugrel for 12 months. The primary outcome was a composite of death from any cause, stroke, or myocardial infarction at 12 months, which was assessed for noninferiority with a prespecified noninferiority margin of 1.50 for the 95% confidence interval of the hazard ratio. The major secondary outcome was major bleeding (defined as a bleeding event of Bleeding Academic Research Consortium [BARC] type 3 [nonfatal major bleeding] or 5 [fatal bleeding]) at 12 months, which was assessed for superiority if noninferiority was established for the primary outcome.

### RESULTS

A total of 2216 patients were included in the full analysis population; 1109 were assigned to receive monotherapy and 1107 to receive DAPT. At 12 months, death from any cause, stroke, or myocardial infarction had occurred in 124 patients (Kaplan–Meier estimate, 11.0%) in the monotherapy group and in 94 patients (Kaplan–Meier estimate, 8.5%) in the DAPT group (hazard ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.75; P=0.40 for noninferiority). Major bleeding had occurred in 61 patients (Kaplan–Meier estimate, 5.6%) in the monotherapy group and in 92 patients (Kaplan–Meier estimate, 8.4%) in the DAPT group (hazard ratio, 0.66; 95% CI, 0.47 to 0.91). The percentages of patients with definite or probable stent thrombosis and serious adverse events appeared to be similar in the two groups.

### CONCLUSIONS

Among patients with STEMI who were undergoing primary PCI, low-dose prasugrel monotherapy initiated before PCI was not noninferior to DAPT for 12 months with respect to a composite of death from any cause, stroke, or myocardial infarction at 12 months. (Funded by Boston Scientific Japan; PREMIUM ClinicalTrials.gov number, NCT05709626.)

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*A complete list of the PREMIUM trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the standard treatment after percutaneous coronary intervention (PCI), with current U.S. and European guidelines recommending at least 12 months of therapy in patients with acute coronary syndromes who are not at high risk for bleeding.[1,2] Although DAPT reduces the risk of recurrent ischemic events, it increases the risk of bleeding, which is associated with poor long-term outcomes.[3]

Recent advances in stent technology and intravascular imaging–guided PCI have reduced the risk of stent-related complications, which has led to a greater proportion of recurrent ischemic events that result from lesions unrelated to stents.[4] In parallel, potent P2Y12 inhibitors have further reduced the risk of ischemic events, albeit at the cost of an increased bleeding risk, which makes the balance between ischemic protection and bleeding risk increasingly challenging.[5,6] Against this background, randomized trials in which abbreviated DAPT (for 1 to 3 months) followed by P2Y12 inhibitor monotherapy was compared with DAPT for 12 months have shown a lower incidence of bleeding with the abbreviated regimen without a substantially higher incidence of ischemic events.[7-11] However, among patients with ST-segment elevation myocardial infarction (STEMI), both ischemic events and bleeding events typically occur early after primary PCI.[12] In the STOPDAPT-3 trial (Short and Optimal Duration of Dual Antiplatelet Therapy-3), patients with acute coronary syndrome or a high risk of bleeding were randomly assigned to receive up-front prasugrel monotherapy or DAPT for 1 month, but the DAPT (control) group received aspirin monotherapy after 1 month.[13]

Data had been lacking from randomized trials in which omission of up-front treatment with aspirin was specifically compared with a standard 12-month regimen of DAPT in patients with STEMI. Accordingly, the PREMIUM trial (Prasugrel Monotherapy Following Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction) was designed to determine whether prasugrel monotherapy initiated at presentation would be noninferior to a 12-month regimen of DAPT with respect to ischemic outcomes while reducing the risk of major bleeding among patients with STEMI who were undergoing primary PCI.

## Methods

### Trial Design and Oversight

Details regarding the rationale and design of the PREMIUM trial have been described previously,[14] and the protocol (along with the statistical analysis plan) is available with the full text of this article at NEJM.org. The PREMIUM trial was an investigator-initiated, multicenter, open-label, randomized trial that was conducted at 69 centers in Japan. The trial was approved by the institutional review board at each participating center and conducted in accordance with the principles of the Declaration of Helsinki. Boston Scientific Japan (the sponsor) had no role in the design of the trial, the selection of sites, the collection of data, the adjudication of clinical events, the statistical analysis, the interpretation of results, the preparation of the manuscript, or the decision to submit the manuscript for publication. All the patients provided written informed consent.

To ensure patient safety, a prespecified safety trigger was implemented: if the absolute difference between the two treatment groups in the number of definite events of stent thrombosis reached five or more, the independent data and safety monitoring board would review unblinded data and assess whether the trial should continue. In addition, in response to emerging external evidence that suggested a possible early increased risk of stent thrombosis with omission of aspirin,[13] the protocol was amended to include an interim safety analysis after the enrollment of 900 patients. When this enrollment target was reached, the data and safety monitoring board reviewed unblinded safety data while the investigators continued to remain unaware of the treatment-group assignments and ultimately recommended continuation of the trial. A subsequent ad hoc safety review after the enrollment of 1500 patients, performed under the data and safety monitoring board charter, again supported continuation of the trial. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Additional details regarding trial oversight and author responsibilities are provided in the Supplementary Appendix, available at NEJM.org.

### Trial Population

Patients 18 years of age or older were eligible if they presented with STEMI within 12 hours after



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the onset of symptoms, were undergoing primary PCI with planned implantation of a platinum–chromium everolimus-eluting stent (Synergy, Boston Scientific), and were candidates for 12 months of DAPT. Key exclusion criteria were the use of oral anticoagulation, a life expectancy of less than 1 year, and participation in another interventional trial. Additional details regarding the enrollment criteria are provided in Table S1 in the Supplementary Appendix.

### RANDOMIZATION, TREATMENT, AND FOLLOW-UP

After written informed consent had been obtained, patients were randomly assigned in a 1:1 ratio to receive low-dose prasugrel monotherapy or DAPT for 12 months. Randomization was performed before primary PCI; a central Web-based stochastic minimization system was used, with the participating site as the sole balancing factor. Treatment assignments were revealed to the investigators immediately after randomization. In the monotherapy group, patients received prasugrel alone, starting with a 20-mg loading dose before PCI and without aspirin, followed by a once-daily 3.75-mg maintenance dose (the approved loading and maintenance doses in Japan) for 12 months. In the DAPT group, patients received aspirin (at a loading dose of 162 to 200 mg, if they were not already taking aspirin) plus prasugrel (at a loading dose of 20 mg) before PCI, followed by aspirin at a dose of 81 to 100 mg once daily plus prasugrel at a dose of 3.75 mg once daily for 12 months. In patients in the DAPT group who had been assessed as having a high risk of bleeding on the basis of the criteria of the Academic Research Consortium for High Bleeding Risk,[15] aspirin was discontinued at 3 months in accordance with the protocol; P2Y12 inhibitor monotherapy was continued thereafter on the basis of local clinical guidelines.[16]

PCI procedures were performed according to standard practice at each participating center. Intravascular imaging was strongly recommended but not mandated. In patients with multivessel coronary artery disease, staged PCI of nonculprit lesions was permitted within 90 days after randomization while the assigned antiplatelet regimen was maintained. Clinical follow-up was performed at 1, 3, and 12 months. Guideline-directed medical therapy, including lipid-lowering therapy, was strongly encouraged.

### OUTCOMES

The primary outcome was a composite of death from any cause, stroke, or myocardial infarction at 12 months. The major secondary outcome was major bleeding, which was defined as a bleeding event of Bleeding Academic Research Consortium (BARC) type 3 (nonfatal major bleeding) or 5 (fatal bleeding), at 12 months.[17] Other secondary outcomes were death from any cause, death from cardiovascular causes, death from noncardiovascular causes, stroke, myocardial infarction, definite or probable stent thrombosis, BARC bleeding events, coronary revascularization, clinically driven target-lesion revascularization, clinically driven nontarget-lesion revascularization, the patient-oriented composite outcome (a composite of death from any cause, stroke, myocardial infarction, or coronary revascularization), and target-lesion failure (a composite of death from cardiovascular causes, target-vessel myocardial infarction, or clinically driven target-lesion revascularization).

Myocardial infarction was classified as procedural or spontaneous according to Academic Research Consortium-2 definitions.[18] Because cardiac biomarker levels were elevated at presentation, periprocedural myocardial infarction was not applicable to the index PCI. Stent thrombosis (categorized as definite or probable) was defined according to Academic Research Consortium-2 criteria.[18] All the clinical events were adjudicated by an independent clinical events committee whose members were unaware of the treatment assignments. Outcome definitions are provided in Table S2.

### STATISTICAL ANALYSIS

The sample size was calculated on the basis of a noninferiority hypothesis for the primary outcome. Previous registry data suggested that the 12-month incidence of primary-outcome events would be approximately 9.0%.[19] Under the assumption of a conservative event incidence of 7.0% in both groups, a noninferiority margin of 1.50 for the upper boundary of the one-sided 95% confidence interval of the hazard ratio was prespecified.[14] We calculated that a sample of 2258 patients would provide the trial with 80% power at a one-sided alpha level and would allow for 5% attrition.[14] A prespecified blinded assessment of the aggregate event data after the enrollment of approximately 80% of the target sample confirmed the adequacy of the planned sample size. Before



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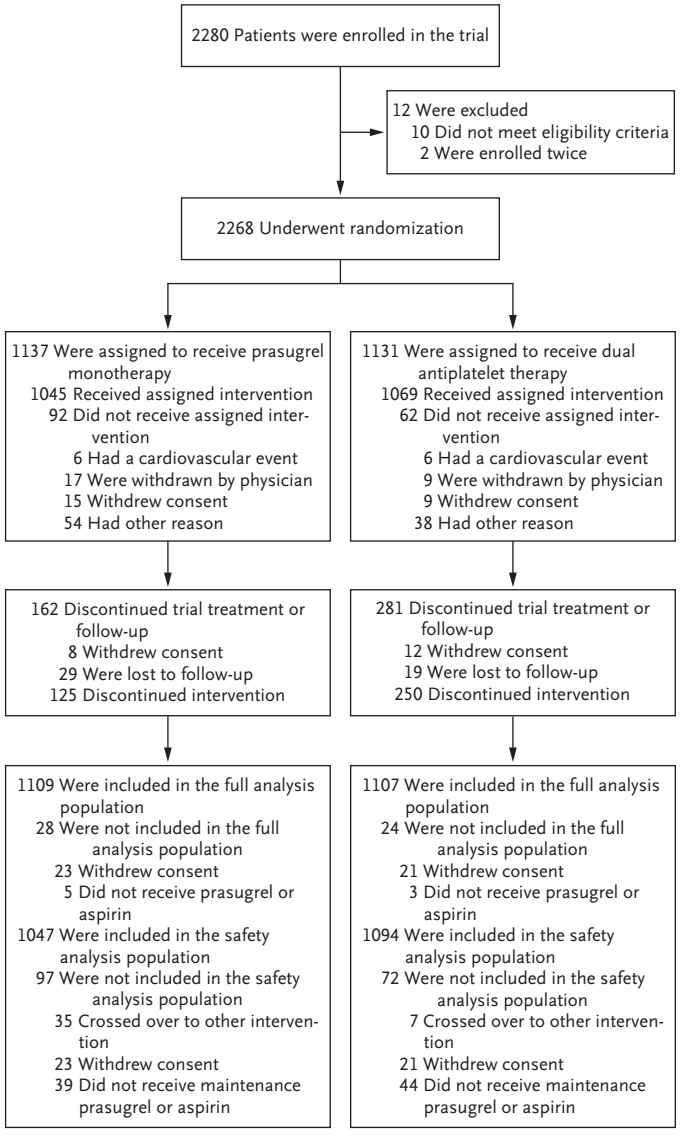



**Figure 1. Enrollment, Randomization, and Follow-up.**

The primary analysis was performed on the basis of the intention-to-treat principle in the full analysis population, which included all the patients who had undergone randomization and received at least one dose of prasugrel or aspirin. The safety analysis population was defined according to the treatment each patient actually received; therefore, patients who crossed over were included in the group corresponding to the treatment they actually received.

the database lock, while the investigators remained unaware of the treatment-group–specific outcome data, the significance level for the noninferiority analysis was prospectively revised from a one-sided alpha level of 0.05 to a more-stringent one-sided alpha level of 0.025.[14] This change was undertaken in order to align the primary analysis with established methodologic guidance for noninferiority trials.[20] No formal interim efficacy analyses were performed.

The primary analysis was performed in the full analysis population, which included all the patients who had undergone randomization and received at least one dose of prasugrel or aspirin, according to the intention-to-treat principle. Time-to-event outcomes were analyzed with Cox proportional-hazards models and Kaplan–Meier methods, with results reported as hazard ratios and 95% confidence intervals. The per-protocol analysis population included patients who had adhered at least 80% of the time to the treatment regimen to which they were randomly assigned; this percentage was based on the adherence to treatment with prasugrel or aspirin, whichever percentage was lower, and was calculated from prospectively obtained medication records. The safety analysis population included patients who received at least one dose of any treatment.

Noninferiority was established if the upper boundary of the two-sided 95% confidence interval of the hazard ratio was less than 1.50. If noninferiority was established, the superiority of prasugrel monotherapy over DAPT with respect to BARC type 3 or 5 bleeding would be tested according to a prespecified sequential testing strategy. A complementary competing-risk analysis of the major secondary outcome in which death was treated as a competing event was performed. Prespecified 30-day landmark and subgroup analyses of the primary and major secondary outcomes were performed with Cox models. The widths of the confidence intervals for the secondary and subgroup analyses were not adjusted for multiplicity and should not be used to infer treatment effects. As prespecified, missing data were not imputed, and analyses were based on available data. The proportional-hazards assumption was assessed with Schoenfeld residual tests and was not violated.

## RESULTS

### PATIENTS

From April 2023 through December 2024, a total of 2268 patients underwent randomization (Fig. 1). After the exclusion of 8 patients who did not receive the assigned treatment and 44 patients who



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**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.***

| Characteristic | Monotherapy (N=1109) | DAPT (N=1107) |
|---|---|---|
| Age — yr | 68.8±12.7 | 69.9±12.3 |
| Male sex — no. (%) | 855 (77.1) | 843 (76.2) |
| Median body-mass index (IQR)† | 23.9 (21.6–26.2) | 23.6 (21.5–26.1) |
| Medical history — no. (%) | | |
| Hypertension | 841 (75.8) | 826 (74.6) |
| Diabetes mellitus | 448 (40.4) | 406 (36.7) |
| Dyslipidemia | 763 (68.8) | 739 (66.8) |
| Current smoking | 384 (34.6) | 382 (34.5) |
| Previous myocardial infarction — no. (%) | 45 (4.1) | 35 (3.2) |
| Previous percutaneous coronary intervention — no. (%) | 59 (5.3) | 48 (4.3) |
| Chronic kidney disease — no. (%)‡ | 480 (43.3) | 519 (46.9) |
| Left ventricular ejection fraction <50% — no./total no. (%) | 469/1057 (44.4) | 475/1064 (44.6) |
| High risk of bleeding — no./total no. (%)§ | 376/1098 (34.2) | 410/1091 (37.6) |
| Killip class III or IV — no. (%)¶ | 95 (8.6) | 86 (7.8) |
| Percutaneous mechanical circulatory support — no./total no. (%)‖ | 150/1093 (13.7) | 152/1084 (14.0) |
| Antiplatelet therapy before randomization — no. (%) | | |
| Aspirin | 58 (5.2) | 66 (6.0) |
| P2Y12 inhibitor | 38 (3.4) | 30 (2.7) |
| Antiplatelet therapy after randomization — no. (%) | | |
| Aspirin, loading dose | 23 (2.1) | 1059 (95.7) |
| Prasugrel, loading dose | 1106 (99.7) | 1103 (99.6) |
| Median time from arrival at the hospital to randomization (IQR) — min | 42.7 (26.5–62.7) | 43.8 (27.5–65.2) |

* Plus–minus values are means ±SD. Patients were assigned to receive low-dose prasugrel monotherapy or dual antiplatelet therapy (DAPT) with aspirin and low-dose prasugrel. IQR denotes interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing in 1 patient in the monotherapy group.
‡ Chronic kidney disease was defined by an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 $m^2$ of body-surface area, which was based on the equation recommended by the Japanese Society of Nephrology.
§ A high risk of bleeding was defined as meeting at least one major criterion or at least two minor criteria according to the Academic Research Consortium for High Bleeding Risk.
¶ Classes of the Killip classification system range from I to IV, with higher classes indicating greater severity of heart failure.
‖ Percutaneous mechanical circulatory support included intraaortic balloon pumps, extracorporeal membrane oxygenation, and microaxial flow pumps. Patients who received more than one device were counted only once.

withdrew consent and requested deletion of their data, the full analysis population included 1109 patients in the monotherapy group and 1107 patients in the DAPT group. Treatment adherence of at least 80% was observed in 1018 patients (91.8%) in the monotherapy group and, in the DAPT group, in 912 patients (82.4%) for aspirin and 951 patients (85.9%) for prasugrel. At 12 months, clinical follow-up data were available for 97.8% of the patients; 48 patients (2.2%) were lost to follow-up.

The demographic, clinical, and index procedural characteristics of the two groups appeared to be balanced at baseline (Table 1 and Table S3). The mean (±SD) age of the patients was 69.4±12.5 years, 76.6% of the patients were men, 38.5% had diabetes, and 35.9% met the criteria for a high risk of bleeding. The repre-



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**Table 2. Primary and Secondary Outcomes.**

| Outcome | Monotherapy (N=1109) | DAPT (N=1107) | Hazard Ratio (95% CI) |
|---|---|---|---|
| | *no. of patients (%)** | | |
| **Primary outcome** | | | |
| Death from any cause, stroke, or myocardial infarction | 124 (11.0) | 94 (8.5) | 1.34 (1.02–1.75)† |
| **Major secondary outcome** | | | |
| BARC type 3 or 5 bleeding‡§ | 61 (5.6) | 92 (8.4) | 0.66 (0.47–0.91) |
| **Other secondary outcomes‡** | | | |
| Death from any cause | 74 (6.6) | 69 (6.3) | 1.08 (0.78–1.49) |
| Death from cardiovascular causes | 50 (4.5) | 47 (4.3) | 1.07 (0.72–1.59) |
| Death from noncardiovascular causes | 24 (2.2) | 22 (2.1) | 1.10 (0.62–1.96) |
| Stroke | 28 (2.5) | 21 (1.9) | 1.34 (0.76–2.36) |
| Myocardial infarction | 31 (2.9) | 14 (1.3) | 2.24 (1.19–4.21) |
| Periprocedural | 9 (0.8) | 2 (0.2) | 4.52 (0.98–20.91) |
| Spontaneous | 22 (2.1) | 13 (1.2) | 1.71 (0.86–3.39) |
| Definite or probable stent thrombosis | 15 (1.4) | 16 (1.5) | 0.94 (0.46–1.89) |
| BARC bleeding event§ | | | |
| Type 2, 3, or 5 | 74 (6.8) | 107 (9.8) | 0.68 (0.51–0.92) |
| Type 2 | 14 (1.3) | 18 (1.7) | 0.78 (0.39–1.56) |
| Type 3 | 57 (5.2) | 89 (8.2) | 0.63 (0.45–0.88) |
| Type 5 | 5 (0.5) | 4 (0.4) | 1.25 (0.34–4.65) |
| Any coronary revascularization | 72 (6.8) | 50 (4.6) | 1.46 (1.02–2.09) |
| Clinically driven revascularization of the target lesion | 22 (2.1) | 23 (2.1) | 0.96 (0.53–1.72) |
| Clinically driven revascularization of nontarget lesions | 51 (4.9) | 32 (2.9) | 1.62 (1.04–2.52) |
| Patient-oriented composite outcome¶ | 167 (14.9) | 128 (11.5) | 1.33 (1.06–1.67) |
| Target-lesion failure‖ | 77 (7.0) | 69 (6.2) | 1.12 (0.81–1.55) |

* The percentages were calculated as Kaplan–Meier estimates of the incidence of the outcome at 12 months after randomization (day 360).
† P=0.40 for noninferiority.
‡ The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer treatment effects.
§ Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding indicates clinically relevant bleeding; type 2 indicates overt bleeding for which medical attention is warranted, type 3 nonfatal major bleeding, and type 5 fatal bleeding.
¶ The patient-oriented composite outcome was defined as a composite of death from any cause, any stroke, any myocardial infarction, or any coronary revascularization.
‖ Target-lesion failure was defined as a composite of death from cardiovascular causes, target-vessel myocardial infarction, or clinically driven target-lesion revascularization.

sentativeness of the trial population is provided in Table S4.

Before randomization, 5.6% of the patients had been receiving aspirin and 3.1% had been receiving a P2Y12 inhibitor. Randomization was performed soon after patients arrived at the hospital and before PCI, with a median time from arrival at the hospital to randomization of 43.3 minutes. After randomization, a loading dose of prasugrel was administered in 99.7% of the patients overall, and a loading dose of aspirin in 95.7% of the patients in the DAPT group. Radial-artery access was used in 92.3% of the patients with available data, and intravascular imaging in 98.6% of the patients undergoing PCI. Multivessel coronary artery disease was present in 41.8% of the patients with available angiographic data, and staged PCI was performed in 23.4% of the



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patients; the characteristics of the lesions were similar in the two groups (Table S5). Antiplatelet regimens and cardiovascular medications are shown in Table S6. In accordance with the protocol-defined strategy for patients with a high risk of bleeding, aspirin was discontinued after 3 months in 305 patients (27.6%) in the DAPT group.

### PRIMARY AND MAJOR SECONDARY OUTCOMES

At 12 months, death from any cause, stroke, or myocardial infarction (the primary outcome) had occurred in 124 patients (Kaplan–Meier estimate, 11.0%) in the monotherapy group and in 94 patients (Kaplan–Meier estimate, 8.5%) in the DAPT group (hazard ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.75; P=0.40 for noninferiority) (Table 2 and Fig. 2A). The upper boundary of the 95% confidence interval of the hazard ratio exceeded the prespecified noninferiority margin of 1.50; therefore, noninferiority was not established.

Major bleeding (a bleeding event of BARC type 3 or 5, the major secondary outcome) at 12 months had occurred in 61 patients (Kaplan–Meier estimate, 5.6%) in the monotherapy group and in 92 patients (Kaplan–Meier estimate, 8.4%) in the DAPT group (hazard ratio, 0.66; 95% CI, 0.47 to 0.91) (Table 2 and Fig. 2B). Sources of major bleeding are shown in Table S7. Because noninferiority was not shown for the primary outcome, formal superiority testing for the major secondary outcome was not performed.

The results of the competing-risk analysis were consistent with those of the main analysis (Fig. S1). The results of prespecified 30-day landmark analyses showed that most of the excess in the risk of a primary-outcome event with monotherapy and most of the excess in the risk of a major bleeding event with DAPT occurred within 30 days after randomization, although additional events occurred after that time (Fig. S2). Prespecified subgroup analyses of the primary and major secondary outcomes are shown in Figure 3.

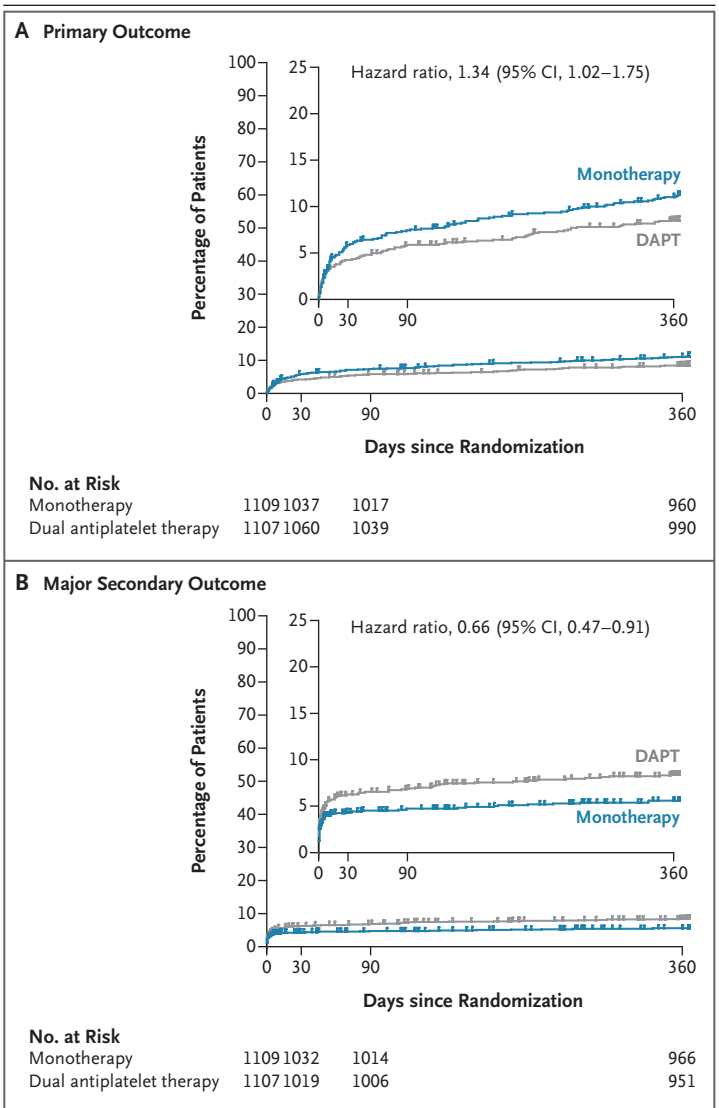



**Figure 2. Primary and Major Secondary Outcomes.**

Panel A shows the incidence of a composite of death from any cause, stroke, or myocardial infarction (the primary outcome). Panel B shows the incidence of major bleeding (the major secondary outcome), which was defined as a bleeding event of Bleeding Academic Research Consortium type 3 (nonfatal major bleeding) or 5 (fatal bleeding). In each panel, the inset shows the same data on an expanded y axis. DAPT denotes dual antiplatelet therapy.

### OTHER SECONDARY OUTCOMES

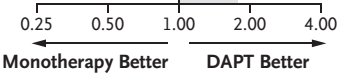
At 12 months, death from any cause had occurred in 6.6% of the patients in the monotherapy group and in 6.3% of those in the DAPT group (hazard ratio, 1.08; 95% CI, 0.78 to 1.49) (Table 2 and Fig. S3). Stroke had occurred in 2.5% and 1.9% of the patients, respectively (hazard ratio, 1.34; 95% CI, 0.76 to 2.36). Myocardial infarction had occurred in 2.9% and 1.3% of the patients (hazard ratio, 2.24; 95% CI, 1.19 to 4.21), inclusive of periprocedural and spontaneous myocardial infarctions (Table 2 and Fig. S4). Definite or probable stent thrombosis had occurred in 1.4% and 1.5% of the patients (hazard ratio, 0.94; 95% CI, 0.46 to 1.89), and any coronary revascularization in 6.8% and 4.6% (hazard ratio, 1.46;



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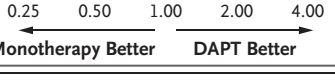
**A Primary Outcome**

| Subgroup | Monotherapy (no. of patients with event/total no. of patients) | DAPT (no. of patients with event/total no. of patients) | Hazard Ratio (95% CI) |
|---|---|---|---|
| All patients | 124/1109 | 94/1107 | 1.34 (1.02–1.75) |
| Age | | | |
| <75 yr | 56/692 | 33/647 | 1.62 (1.05–2.49) |
| ≥75 yr | 68/417 | 61/460 | 1.25 (0.88–1.77) |
| Sex | | | |
| Male | 87/855 | 57/843 | 1.53 (1.10–2.14) |
| Female | 37/254 | 37/264 | 1.05 (0.67–1.66) |
| Body-mass index | | | |
| <25 | 93/697 | 68/710 | 1.42 (1.04–1.94) |
| ≥25 | 30/411 | 26/397 | 1.12 (0.67–1.90) |
| Diabetes mellitus | | | |
| Yes | 57/448 | 40/406 | 1.31 (0.88–1.97) |
| No | 67/661 | 54/701 | 1.34 (0.93–1.91) |
| Chronic kidney disease | | | |
| eGFR <60 ml/min/1.73 m$^2$ | 77/480 | 66/519 | 1.29 (0.93–1.79) |
| eGFR ≥60 ml/min/1.73 m$^2$ | 47/629 | 28/588 | 1.59 (1.00–2.54) |
| Left ventricular ejection fraction | | | |
| ≤40% | 51/272 | 35/261 | 1.46 (0.95–2.24) |
| >40% to <50% | 19/197 | 16/214 | 1.33 (0.68–2.58) |
| ≥50% | 50/588 | 35/589 | 1.44 (0.94–2.22) |
| Smoking status | | | |
| Current | 31/384 | 24/382 | 1.30 (0.76–2.21) |
| Past or never | 93/725 | 70/725 | 1.35 (0.99–1.85) |
| Killip classification | | | |
| Class I | 75/874 | 57/878 | 1.34 (0.95–1.89) |
| Class II or III | 36/181 | 26/180 | 1.41 (0.85–2.33) |
| Class IV | 13/54 | 11/49 | 1.09 (0.49–2.43) |
| Multivessel disease | | | |
| Yes | 75/466 | 43/451 | 1.74 (1.20–2.54) |
| No | 49/643 | 51/656 | 0.98 (0.66–1.46) |
| Complex percutaneous coronary intervention | | | |
| Yes | 36/242 | 18/233 | 1.97 (1.12–3.48) |
| No | 88/867 | 76/874 | 1.18 (0.87–1.61) |
| Final TIMI flow | | | |
| 0–2 | 46/266 | 35/269 | 1.37 (0.88–2.12) |
| 3 | 73/804 | 54/794 | 1.35 (0.95–1.92) |




**B Major Secondary Outcome**

| Subgroup | Monotherapy (no. of patients with event/total no. of patients) | DAPT (no. of patients with event/total no. of patients) | Hazard Ratio (95% CI) |
|---|---|---|---|
| All patients | 61/1109 | 92/1107 | 0.66 (0.47–0.91) |
| Age | | | |
| <75 yr | 26/692 | 40/647 | 0.61 (0.37–0.99) |
| ≥75 yr | 35/417 | 52/460 | 0.73 (0.48–1.13) |
| Sex | | | |
| Male | 41/855 | 63/843 | 0.64 (0.43–0.95) |
| Female | 20/254 | 29/264 | 0.70 (0.40–1.24) |
| Body-mass index | | | |
| <25 | 42/697 | 70/710 | 0.60 (0.41–0.88) |
| ≥25 | 19/411 | 22/397 | 0.84 (0.45–1.55) |
| Diabetes mellitus | | | |
| Yes | 18/448 | 35/406 | 0.46 (0.26–0.81) |
| No | 43/661 | 57/701 | 0.79 (0.53–1.18) |
| Chronic kidney disease | | | |
| eGFR <60 ml/min/1.73 m$^2$ | 35/480 | 57/519 | 0.66 (0.43–1.01) |
| eGFR ≥60 ml/min/1.73 m$^2$ | 26/629 | 35/588 | 0.69 (0.41–1.14) |
| Left ventricular ejection fraction | | | |
| ≤40% | 22/272 | 35/261 | 0.60 (0.35–1.02) |
| >40% to <50% | 13/197 | 17/214 | 0.83 (0.40–1.71) |
| ≥50% | 21/588 | 37/589 | 0.56 (0.33–0.96) |
| Smoking status | | | |
| Current | 17/384 | 30/382 | 0.56 (0.31–1.01) |
| Past or never | 44/725 | 62/725 | 0.70 (0.48–1.04) |
| Killip classification | | | |
| Class I | 34/874 | 55/878 | 0.62 (0.40–0.95) |
| Class II or III | 15/181 | 20/180 | 0.74 (0.38–1.44) |
| Class IV | 12/54 | 17/49 | 0.58 (0.28–1.21) |
| Multivessel disease | | | |
| Yes | 33/466 | 50/451 | 0.63 (0.41–0.98) |
| No | 28/643 | 42/656 | 0.68 (0.42–1.09) |
| Complex percutaneous coronary intervention | | | |
| Yes | 18/242 | 24/233 | 0.71 (0.38–1.30) |
| No | 43/867 | 68/874 | 0.63 (0.43–0.93) |
| Final TIMI flow | | | |
| 0–2 | 25/266 | 33/269 | 0.74 (0.44–1.25) |
| 3 | 32/804 | 56/794 | 0.56 (0.36–0.87) |






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**Figure 3 (facing page). Subgroup Analyses of the Primary and Major Secondary Outcomes.**

Shown are the hazard ratios for the primary outcome (Panel A) and major secondary outcome (Panel B) in prespecified subgroups of patients. The confidence intervals have not been adjusted for multiplicity and therefore should not be interpreted as presenting hypothesis tests of effects within the subgroups. Data were missing for body-mass index (the weight in kilograms divided by the square of the height in meters) in 1 patient in the monotherapy group, for left ventricular ejection fraction in 52 patients in the monotherapy group and in 43 patients in the DAPT group, and for final Thrombolysis in Myocardial Infarction (TIMI) flow in 39 patients in the monotherapy group and in 44 patients in the DAPT group. Classes of the Killip classification system range from I to IV, with higher classes indicating greater severity of heart failure. Grades of the TIMI flow grading system range from 0 to 3, with higher grades indicating better coronary blood flow. The shaded areas indicate the 95% confidence intervals of the hazard ratio for the overall population. The term eGFR denotes estimated glomerular filtration rate.

95% CI, 1.02 to 2.09). Clinically driven revascularization of the target lesion had occurred in 2.1% of the patients in both groups (hazard ratio, 0.96; 95% CI, 0.53 to 1.72) (Table 2 and Fig. S5). The results of other secondary outcomes are shown in Table 2. The results in the per-protocol and safety analysis populations were generally consistent with those of the main analysis (Tables S8 and S9).

### SAFETY

Serious adverse events were reported in 180 patients (17.2%) in the monotherapy group and in 181 patients (16.5%) in the DAPT group. Other common or important adverse events are summarized in Table S10.

## DISCUSSION

In this randomized trial involving patients with STEMI who were undergoing primary PCI, omission of up-front treatment with aspirin and treatment with low-dose prasugrel monotherapy was not noninferior to standard DAPT, although it appeared to be associated with fewer major bleeding events. The results of the landmark analysis suggest that the clinical trade-off between ischemic protection and avoidance of bleeding is established early after STEMI but continues to evolve beyond the first month. These findings suggest that combined platelet inhibition with aspirin and a P2Y12 inhibitor remains critical for ischemic protection in the initial phase after STEMI, even with contemporary PCI.

The temporal pattern of ischemic protection reflects the trial design. Unlike previous trials, in which patients underwent randomization after an uneventful period of DAPT after successful PCI,[7-11] patients in the PREMIUM trial underwent randomization before PCI, with a median time from arrival at the hospital to randomization of 43 minutes. In the NEO-MINDSET trial (Percutaneous Coronary Intervention Followed by Monotherapy Instead of Dual Antiplatelet Therapy in the Setting of Acute Coronary Syndromes), randomization occurred later — a median of 2 days after hospitalization.[21] Notwithstanding this difference in timing, both the PREMIUM trial and the NEO-MINDSET trial consistently showed an increased risk of myocardial infarction; these findings suggest that aspirin-free strategies may be unsafe when they are implemented too early after STEMI.

Several findings may explain the between-group difference in ischemic outcomes in our trial. Stent thrombosis was infrequent, and the incidence appeared to be similar in the two groups — results that probably reflect the use of contemporary PCI with newer-generation drug-eluting stents and routine intravascular imaging–guided optimization. By contrast, the incidence of periprocedural and spontaneous myocardial infarction appeared to be higher with monotherapy than with DAPT. One possible mechanism to explain this difference is that, during staged PCI, omission of aspirin may have amplified platelet activation after procedural plaque disruption, which may have led to periprocedural myocardial infarction. The continued divergence of the Kaplan–Meier curves with respect to spontaneous myocardial infarction may reflect persistent vulnerability of untreated or nonculprit plaques. This interpretation is supported by pathological and intravascular imaging studies showing plaque rupture throughout the coronary tree and repeated cycles of rupture and healing that contribute to disease progression and subsequent revascularization.[22,23] This mechanism is consistent with the higher incidence of clinically driven revascularization of nontarget lesions in the monotherapy group,



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without a difference in the incidence of target-lesion revascularization.

Omission of aspirin was associated with a lower incidence of major bleeding than DAPT, a finding that is consistent with the results seen in previous trials involving early discontinuation of aspirin.[7-11] The early separation of the event curves suggests that continued aspirin exposure contributed to bleeding after PCI. Although radial-artery access was used in 92.3% of the patients, BARC type 3 or 5 bleeding occurred in 8.4% of the patients in the DAPT group, a higher incidence than that seen in previous trials,[7-11,21] including the STEMI cohort of the NEO-MINDSET trial, in which the incidence was 2.5%.[24] This finding probably reflects the higher bleeding risk in the trial population and the fact that randomization occurred at the time of presentation. Of note, gastrointestinal bleeding accounted for a substantial proportion of the major bleeding events, despite the use of proton-pump inhibitors in approximately 90% of the patients in the DAPT group, which suggests that routine gastroprotection does not eliminate the risk of aspirin-associated gastrointestinal bleeding. Although aspirin was discontinued at 3 months in patients with a high risk of bleeding who had been assigned to the DAPT group, the lower incidence of major bleeding with prasugrel monotherapy remained clinically apparent and underscores the bleeding risk associated with aspirin during both the early and later periods after STEMI.

Our results should be interpreted in light of several limitations. First, the open-label design may have introduced bias, although all the clinical outcomes were adjudicated by an independent committee whose members were unaware of the treatment-group assignments. Second, the trial was conducted in Japan with low-dose prasugrel, which may limit generalizability to other health care systems in which standard doses of prasugrel or ticagrelor are commonly used. However, pharmacodynamic studies have shown effective platelet inhibition with this regimen in Japanese patients.[25] Moreover, the incidence of myocardial infarction in the control group of our trial was similar to the 1.2% incidence in the STEMI cohort of the NEO-MINDSET trial,[24] despite the fact that our trial involved a higher-risk population. The increased incidence of myocardial infarction with early omission of aspirin in both our trial and the NEO-MINDSET trial suggests that the finding is unlikely to be explained solely by the dose of prasugrel or regional practice patterns. Third, the occurrence of BARC type 2 bleeding (overt bleeding for which medical attention is warranted) may have been incompletely ascertained because it relies more on patient reporting and site-level documentation than does BARC type 3 or 5 bleeding. Fourth, the trial was not powered to assess individual clinical outcomes, including myocardial infarction and stent thrombosis.

Among patients with STEMI who were undergoing primary PCI, low-dose prasugrel monotherapy initiated at presentation, before PCI, was not noninferior to DAPT with respect to a composite of death from any cause, stroke, or myocardial infarction at 12 months.

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