ORIGINAL ARTICLE

Early Withdrawal of Aspirin after PCI in Acute Coronary Syndromes

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ABSTRACT

BACKGROUND

Whether potent P2Y12 inhibitor monotherapy without aspirin initiated shortly after successful percutaneous coronary intervention (PCI) is effective and safe for patients with acute coronary syndromes is unclear.

METHODS

We conducted a multicenter, open-label, randomized trial in Brazil involving patients with acute coronary syndromes who had undergone successful PCI. Patients were assigned in a 1:1 ratio within the first 4 days of hospitalization to stop treatment with aspirin and receive potent P2Y12 inhibitor monotherapy (ticagrelor or prasugrel) or to receive dual antiplatelet therapy (aspirin and a potent P2Y12 inhibitor) for 12 months. The two ranked primary outcomes, assessed through 12 months, were a composite of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization (tested for noninferiority, with a noninferiority margin of 2.5 percentage points) and major or clinically relevant nonmajor bleeding (tested for superiority).

RESULTS

A total of 3410 patients were included in the intention-to-treat population (1712 in the monotherapy group and 1698 in the dual antiplatelet therapy group). At 12 months, death from any cause, myocardial infarction, stroke, or urgent revascularization had occurred in 119 patients (Kaplan–Meier estimate, 7.0%) in the monotherapy group and in 93 patients (Kaplan–Meier estimate, 5.5%) in the dual antiplatelet therapy group (absolute risk difference, 1.47 percentage points; 95% confidence interval [CI], −0.16 to 3.10; P=0.11 for noninferiority). Major or clinically relevant nonmajor bleeding had occurred in 33 patients (Kaplan–Meier estimate, 2.0%) in the monotherapy group and in 82 patients (Kaplan–Meier estimate, 4.9%) in the dual antiplatelet therapy group (absolute risk difference, –2.97 percentage points; 95% CI, −4.20 to –1.73). Stent thrombosis occurred in 12 patients in the monotherapy group and in 4 in the dual antiplatelet therapy group.

CONCLUSIONS

Among patients who had undergone successful PCI for acute coronary syndromes, potent P2Y12 inhibitor monotherapy was not found to be noninferior to dual antiplatelet therapy with respect to a composite of death or ischemic events at 12 months. (Funded by the Brazilian Ministry of Health; NEO-MINDSET ClinicalTrials.gov number, NCT04360720.)

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*A full list of NEO-MINDSET Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor for 12 months is the standard antithrombotic treatment for patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI).[1,2] However, this regimen is accompanied by an increase in the risk of bleeding, which is associated with an adverse prognosis.[3,4] Alternative therapeutic approaches have been evaluated to mitigate the risk of hemorrhage while preserving ischemic benefits, with recent evidence supporting the withdrawal of aspirin after 1 to 3 months of dual antiplatelet therapy followed by monotherapy with ticagrelor.[5-9] A substantial proportion of thrombotic and bleeding events occurs in the periprocedural and early post-PCI period,[10-13] and whether an aspirin-free approach with potent P2Y12 inhibitor monotherapy immediately after successful PCI is effective and safe for patients with acute coronary syndromes is unclear.

We designed the NEO-MINDSET trial (Percutaneous Coronary Intervention Followed by Monotherapy Instead of Dual Antiplatelet Therapy in the Setting of Acute Coronary Syndromes) to test the hypothesis that monotherapy with a potent P2Y12 inhibitor shortly after successful PCI would be noninferior to dual antiplatelet therapy with aspirin and a potent P2Y12 inhibitor for the prevention of death or ischemic events and superior to dual antiplatelet therapy in reducing bleeding in patients with acute coronary syndromes treated with contemporary drug-eluting stents.

Methods

Trial Design and Oversight

We conducted this investigator-initiated, multicenter, open-label, randomized trial with blinded outcome adjudication at 50 sites in Brazil. The trial rationale and design have been published previously.[14] The trial protocol (available with the full text of this article at NEJM.org) was approved by the ethics committee at each participating site, and all the patients provided written informed consent. An independent data and safety monitoring board reviewed the unblinded safety data when the trial reached prespecified enrollment milestones (after 400 patients, one third, one half, three fifths, and all the patients in the intention-to-treat population had enrolled and had completed the 30-day follow-up period). Members of a clinical events committee who were unaware of the group assignments adjudicated outcome events, according to prespecified definitions. The trial was designed and led by an academic steering committee and was sponsored by the Brazilian Ministry of Health (Programa de Apoio ao Desenvolvimento Institucional do Sistema Único de Saúde [PROADI-SUS]). Trial operations and statistical analyses were conducted by the Academic Research Organization of Hospital Israelita Albert Einstein.

The first and last authors prepared the initial draft of the manuscript, which was reviewed and approved by all the authors. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The committee members and participating investigators are listed in the Supplementary Appendix, available at NEJM.org.

Trial Population

Patients were eligible for inclusion in the trial if they were at least 18 years of age, had been admitted with an acute coronary syndrome (ST-segment elevation myocardial infarction [STEMI], non–ST-segment elevation myocardial infarction, or unstable angina), and had undergone successful PCI with at least one contemporary drug-eluting stent within the first 4 days of hospitalization. Success of the PCI was determined by the treating physicians at each site. Patients who were undergoing staged PCI were allowed to participate in the trial only if completion of all planned interventional procedures occurred within the 4-day period of hospitalization. The main exclusion criteria were the planned use of dual antiplatelet therapy for less than 12 months, residual coronary-artery stenoses warranting further intervention in the next 12 months, the need for oral anticoagulation, major active or in-hospital bleeding, ischemic stroke within the month before randomization, and a history of intracranial hemorrhage. Details regarding the eligibility criteria are provided in the Supplementary Appendix.

Randomization, Treatment, and Follow-up

At hospital admission, patients received antiplatelet agents according to local practices. After successful PCI with contemporary drug-eluting stents, eligible patients were randomly assigned in a 1:1 ratio in an open-label fashion to stop treatment with aspirin and receive a potent P2Y12 inhibitor alone (monotherapy) or to receive treat-

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ment with aspirin plus a potent P2Y12 inhibitor (dual antiplatelet therapy) for 12 months. Before randomization, the investigators could choose to use either prasugrel or ticagrelor as the potent P2Y12 inhibitor. Randomization was performed with the use of a centralized, automated Web-based system, in blocks of varying sizes, with concealed assignment and with stratification according to trial site.

After randomization, aspirin treatment was immediately discontinued in the monotherapy group and continued at a dose of 81 to 100 mg once daily in the dual antiplatelet therapy group. In patients who had not been receiving treatment with P2Y12 inhibitors and in those who had been receiving clopidogrel before randomization, a loading dose of prasugrel (60 mg) or ticagrelor (180 mg) was administered. In patients who had previously received treatment with prasugrel or ticagrelor, no loading dose was recommended. Maintenance doses were continued through 12 months, with prasugrel administered at a dose of 5 mg or 10 mg once daily and ticagrelor at a dose of 90 mg twice daily, according to the package inserts. P2Y12 inhibitors were provided at no cost to the sites and patients by the coordinating center.

On-site follow-up visits occurred at 1 month (±5 days), 6 months (±15 days), and 12 months (±15 days) after randomization. Telephone contacts occurred at 3, 9, and 13 months (±15 days).

OUTCOMES

The two ranked primary outcomes were a composite of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization and major or clinically relevant nonmajor bleeding. Major or clinically relevant nonmajor bleeding was defined by a Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding event (range, 0 [no bleeding] to 5 [fatal bleeding]).[15,16] Secondary outcomes included death from any cause; death from cardiovascular causes; death from noncardiovascular causes; sudden death within 30 days; myocardial infarction; stroke; invasive coronary intervention; stent thrombosis; BARC type 1, 2, 3, or 5 bleeding events; and net adverse clinical events (a composite of death from any cause, myocardial infarction, stroke, urgent target-vessel revascularization, or a BARC type 2, 3, or 5 bleeding event). Detailed definitions of outcomes are included in the Supplementary Appendix.

STATISTICAL ANALYSIS

We estimated that a sample size of at least 3400 patients would provide the trial with 80% power to determine the noninferiority of potent P2Y12 inhibitor monotherapy to dual antiplatelet therapy with respect to death or ischemic events (myocardial infarction, stroke, or urgent target-vessel revascularization), at a one-sided alpha level of 0.025, under the assumption of an annual event rate of 7.0% in the dual antiplatelet therapy group[17] and a dropout rate of 4.0%. The noninferiority margin for the absolute risk difference was 2.5 percentage points, a margin consistent with that used in previous trials that evaluated strategies for de-escalation of dual antiplatelet therapy after PCI.[8,18] If noninferiority was shown for death or ischemic events, this sample size would also be sufficient to give the trial 88% power to show the superiority of monotherapy to dual antiplatelet therapy with regard to bleeding, under an assumed incidence of bleeding of 5.0% in the monotherapy group and 8.0% in the dual antiplatelet therapy group,[5] at a two-sided alpha level of 0.025.

The two primary outcomes were sequentially evaluated by a hierarchical testing strategy in the intention-to-treat population (all the patients who had undergone randomization, with the exception of three patients who were excluded after randomization). The analysis of the first primary outcome assessed whether potent P2Y12 inhibitor monotherapy would be noninferior to dual antiplatelet therapy with respect to the composite of death or ischemic events. If noninferiority was established, major or clinically relevant nonmajor bleeding, the second primary outcome, would be tested for superiority.

Absolute risk differences and 95% confidence intervals for the two primary outcomes and secondary outcomes at 12 months were estimated with the use of the Kaplan–Meier method and Greenwood standard errors. For all outcomes, Kaplan–Meier estimates at 12 months are reported along with treatment effects, calculated with the use of Cox proportional-hazards models. Data from patients who had not had a primary-outcome event were censored at the last known contact date or 12 months after randomization, whichever occurred first. We assessed for evidence of nonproportional hazards using the Grambsch–Therneau test,[19] and no violation of the proportionality assumption was found. The two primary outcomes were assessed in prespecified subgroups

with the use of Cox proportional-hazards regression models with interaction terms. Because the statistical analysis plan did not include a provision for correction of multiplicity when tests were conducted for secondary outcomes or according to subgroups, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals for secondary outcomes have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. No imputation of missing data was performed. All analyses were performed with the use of R software, version 4.3 (R Foundation for Statistical Computing). The statistical analysis plan is available with the protocol, and additional details regarding the statistical methods are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From October 2020 through October 2023, a total of 3413 patients underwent randomization at 50 sites in Brazil: 1713 were assigned to receive monotherapy and 1700 to receive dual antiplatelet therapy (Fig. 1). After 3 patients were excluded owing to Good Clinical Practice violations, invalid randomization, and withdrawal of consent, the

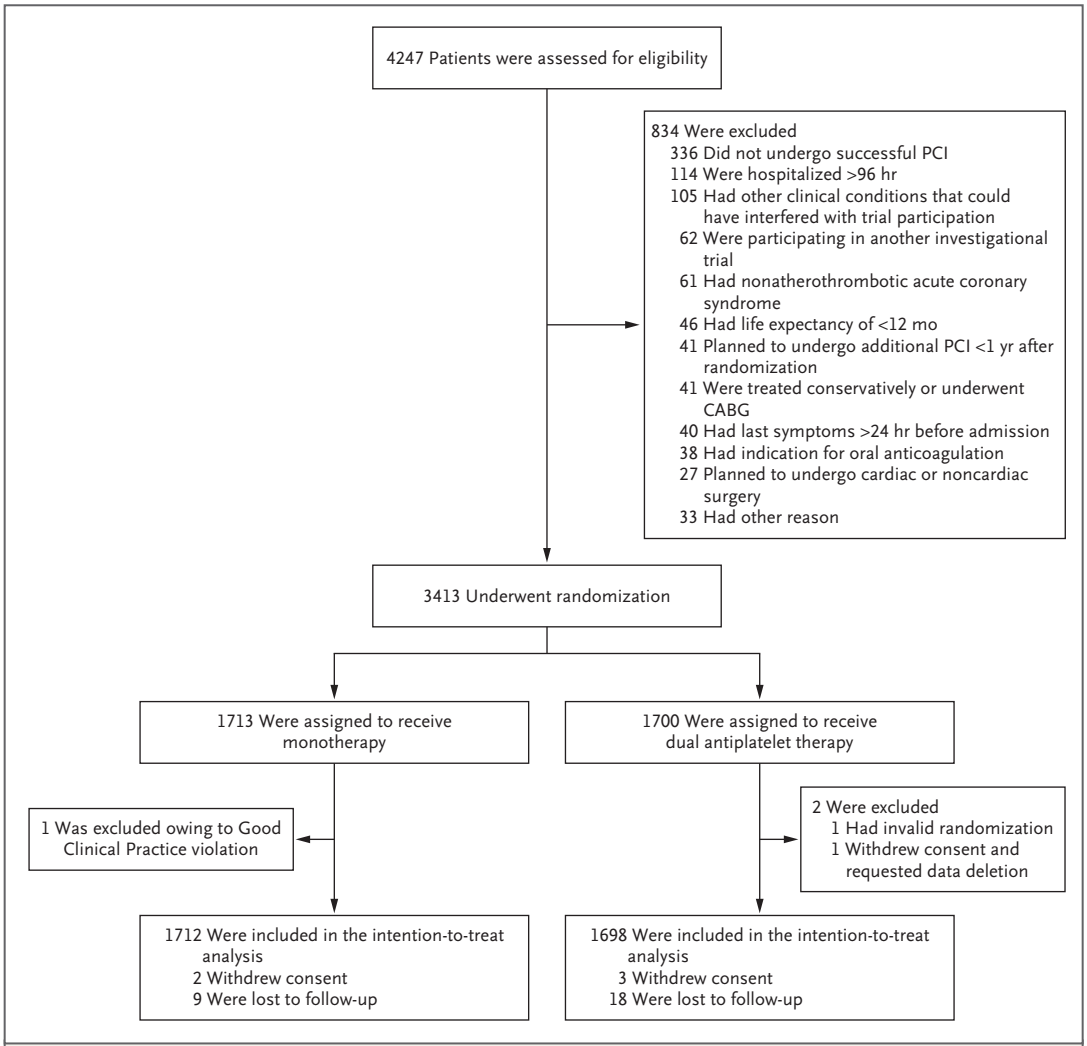


Figure 1. Enrollment, Randomization, and Follow-up.

The primary analysis was performed in the intention-to-treat population, which included all the patients who had undergone randomization, with the exception of three patients who were excluded after randomization. Patients may have been excluded for more than one reason. CABG denotes coronary-artery bypass graft, GCP Good Clinical Practice, and PCI percutaneous coronary intervention.

intention-to-treat population included 3410 patients: 1712 in the monotherapy group and 1698 in the dual antiplatelet therapy group. A total of 27 patients (0.8%) were lost to follow-up.

The demographic and clinical characteristics of the patients at baseline appeared to be well balanced between the two groups (Table 1). The mean (±SD) age of the patients was 59.6±10.8

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Monotherapy (N=1712)	Dual Antiplatelet Therapy (N=1698)	Total (N=3410)
Age — yr	59.5±10.9	59.8±10.7	59.6±10.8
Female sex — no. (%)	502 (29.3)	497 (29.3)	999 (29.3)
Race — no. (%)†			
White	1169 (68.3)	1167 (68.7)	2336 (68.5)
Black	313 (18.3)	329 (19.4)	642 (18.8)
Mixed race	230 (13.4)	202 (11.9)	432 (12.7)
Body-mass index‡	27.6±4.5	27.5±4.4	27.5±4.5
Medical history			
Hypertension — no. (%)	1093 (63.8)	1090 (64.2)	2183 (64.0)
Diabetes — no. (%)	459 (26.8)	477 (28.1)	936 (27.4)
Dyslipidemia — no. (%)	464 (27.1)	452 (26.6)	916 (26.9)
Smoking — no./total no. (%)			
Current	597/1654 (36.1)	588/1635 (36.0)	1185/3289 (36.0)
Previous	376/1654 (22.7)	390/1635 (23.9)	766/3289 (23.3)
Previous myocardial infarction — no. (%)	171 (10.0)	162 (9.5)	333 (9.8)
Previous PCI — no. (%)	142 (8.3)	142 (8.4)	284 (8.3)
Previous coronary-artery bypass graft — no. (%)	30 (1.8)	26 (1.5)	56 (1.6)
Previous heart failure — no. (%)	61 (3.6)	63 (3.7)	124 (3.6)
Qualifying index event — no. (%)			
STEMI	1058 (61.8)	1061 (62.5)	2119 (62.1)
NSTEMI	527 (30.8)	512 (30.2)	1039 (30.5)
Unstable angina	127 (7.4)	125 (7.4)	252 (7.4)
High bleeding risk — no. (%)§	339 (19.8)	335 (19.7)	674 (19.8)
Multivessel coronary artery disease — no. (%)	777 (45.4)	719 (42.3)	1496 (43.9)
Antiplatelet therapy before randomization — no./total no. (%)			
Aspirin	1641/1711 (95.9)	1656/1696 (97.6)	3297/3407 (96.8)
Clopidogrel	1442/1711 (84.3)	1439/1696 (84.8)	2881/3407 (84.6)
Ticagrelor	136/1710 (8.0)	129/1696 (7.6)	265/3406 (7.8)
Prasugrel	99/1710 (5.8)	98/1696 (5.8)	197/3406 (5.8)
No. of days from admission to first PCI (IQR)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)
No. of days from admission to randomization (IQR)	2.0 (2.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)

* Plus–minus values are means ±SD. NSTEMI denotes non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.
† Race or ethnic group was determined by the investigator.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 15 patients.
§ High bleeding risk was determined by the Bleeding Academic Research Consortium (BARC) risk score, which is binary and is defined as at least a 4% risk of a BARC type 3 or 5 bleeding event at 1 year or at least a 1% risk of intracranial hemorrhage at 1 year.

years, 29.3% of the patients were women, and 27.4% had diabetes. Of the patients who underwent randomization, 62.1% had STEMI at admission. A total of 19.8% patients were at high bleeding risk according to the Academic Research Consortium definition (≥4% risk of a BARC type 3 or 5 bleeding event at 1 year or ≥1% risk of intracranial hemorrhage at 1 year)[20] and 43.9% had multivessel coronary artery disease. Information on procedural characteristics and on the representativeness of the trial population is provided in Tables S1 and S2, respectively, in the Supplementary Appendix. Before undergoing randomization, most patients were receiving treatment with aspirin (96.8%) and clopidogrel (84.6%).

The median time from hospitalization to randomization was 2 days. After randomization, prasugrel was administered to 1192 patients (69.6%) in the monotherapy group and to 1172 patients (69.0%) in the dual antiplatelet therapy group. Ticagrelor was administered to 480 patients (28.0%) in the monotherapy group and to 501 patients

Table 2. Primary and Secondary Efficacy Outcomes (Intention-to-Treat Population).*

Outcome	Monotherapy (N=1712)	Dual Antiplatelet Therapy (N=1698)	Risk Difference (95% CI)	Hazard Ratio (95% CI)
	no. of patients (%)†		*percentage points*	
Primary Outcomes‡				
Death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization	119 (7.0)	93 (5.5)	1.47 (–0.16 to 3.10)	1.28 (0.98 to 1.68)
Major or clinically relevant nonmajor bleeding§	33 (2.0)	82 (4.9)	–2.97 (–4.20 to –1.73)	0.40 (0.26 to 0.59)
Secondary Outcomes				
Death from any cause	62 (3.6)	50 (3.0)		1.24 (0.85 to 1.79)
Death from cardiovascular causes	42 (2.5)	34 (2.0)		1.23 (0.78 to 1.93)
Death from noncardiovascular causes	20 (1.2)	16 (1.0)		1.25 (0.65 to 2.40)
Sudden death within 30 days	2 (0.1)	3 (0.2)		0.66 (0.11 to 3.97)
Stroke	20 (1.2)	15 (0.9)		1.33 (0.68 to 2.60)
Myocardial infarction	45 (2.7)	31 (1.9)		1.45 (0.92 to 2.30)
Invasive coronary intervention	43 (2.6)	26 (1.6)		1.65 (1.01 to 2.69)
Urgent target-vessel revascularization	22 (1.3)	12 (0.7)		1.83 (0.90 to 3.69)
Definite or probable stent thrombosis	12 (0.7)	4 (0.2)		2.99 (0.97 to 9.28)
BARC bleeding event				
Type 1 to 5	75 (4.5)	150 (9.0)		0.49 (0.37 to 0.64)
Type 1	45 (2.7)	76 (4.6)		0.58 (0.40 to 0.84)
Type 2	21 (1.3)	50 (3.0)		0.41 (0.25 to 0.69)
Type 3	11 (0.7)	33 (2.0)		0.33 (0.17 to 0.65)
Type 5	1 (0.1)	2 (0.1)		0.50 (0.05 to 5.48)
Net adverse clinical events¶	145 (8.5)	166 (9.9)		0.86 (0.69 to 1.08)

* The intention-to-treat population included all the patients who underwent randomization, with the exception of three patients who were excluded after randomization. Hazard ratios are shown for the primary outcomes and for secondary outcomes. The widths of the 95% confidence intervals for secondary outcomes have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.
† Percentages were calculated as Kaplan–Meier estimates of the incidence of the outcome at 12 months after randomization.
‡ The primary outcomes are listed in order of the prespecified hierarchical testing. For the first primary outcome (a composite of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization), the upper limit of the 95% confidence interval for the absolute between-group difference did not indicate noninferiority (P=0.11). Since noninferiority was not shown, the second primary outcome (major or clinically relevant nonmajor bleeding) was not tested for superiority.
§ Major or clinically relevant nonmajor bleeding was defined as a BARC type 2, 3, or 5 bleeding event.
¶ Net adverse clinical events were a composite of death from any cause, myocardial infarction, stroke, urgent target-vessel revascularization, or a BARC type 2, 3, or 5 bleeding event.

(29.5%) in the dual antiplatelet therapy group. Details on the use of antiplatelet agents during the trial are available in Table S3.

PRIMARY OUTCOMES

At 12 months, death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization had occurred in 119 patients (Kaplan–Meier estimate, 7.0%) in the monotherapy group and in 93 patients (Kaplan–Meier estimate, 5.5%) in the dual antiplatelet therapy group (hazard ratio, 1.28; 95% confidence interval [CI], 0.98 to 1.68), for an absolute difference in risk of 1.47 percentage points (95% CI, −0.16 to 3.10), which did not meet the prespecified criterion for noninferiority (P=0.11) (Table 2 and Fig. 2). Because noninferiority was not shown for the first hierarchical primary outcome, formal testing of superiority with respect to major or clinically relevant nonmajor bleeding was not performed.

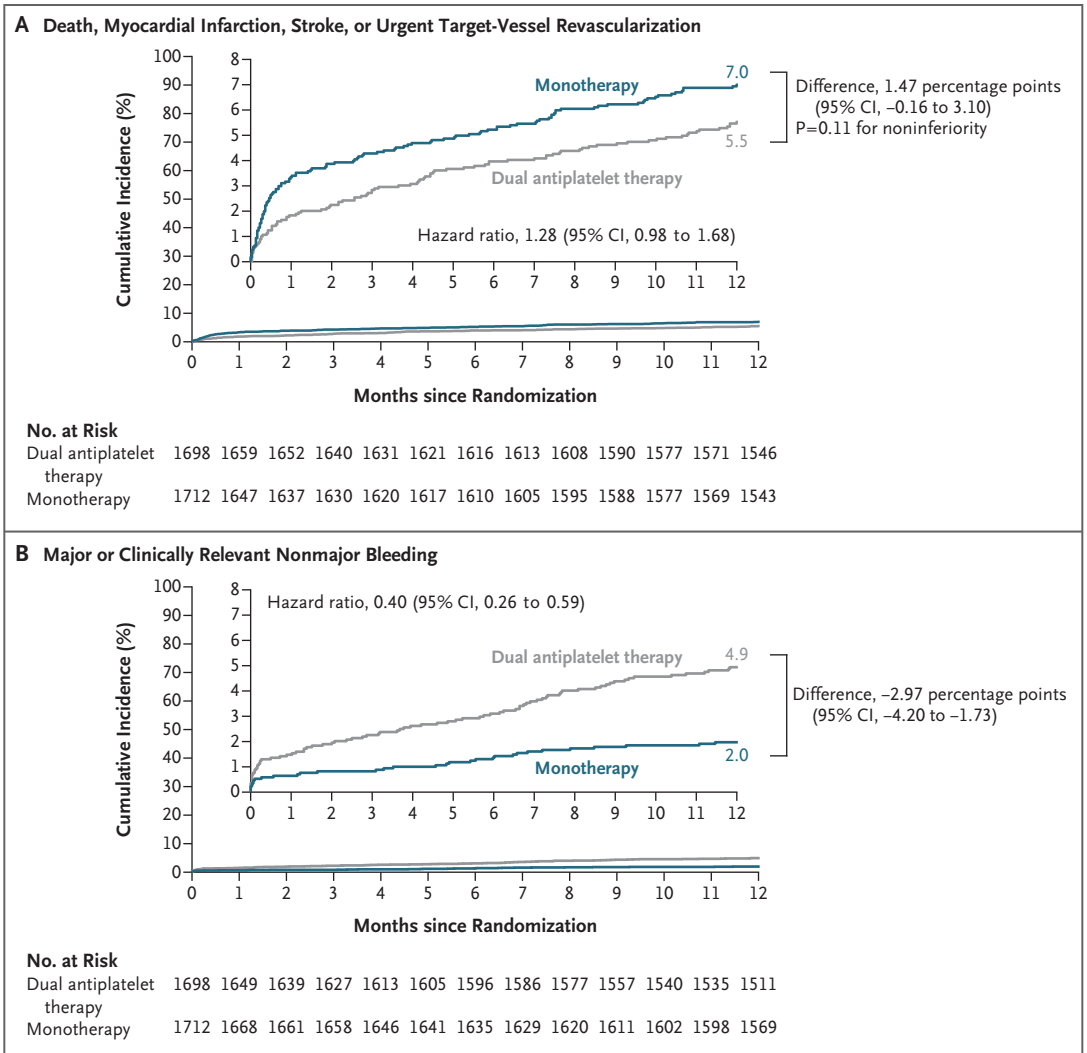
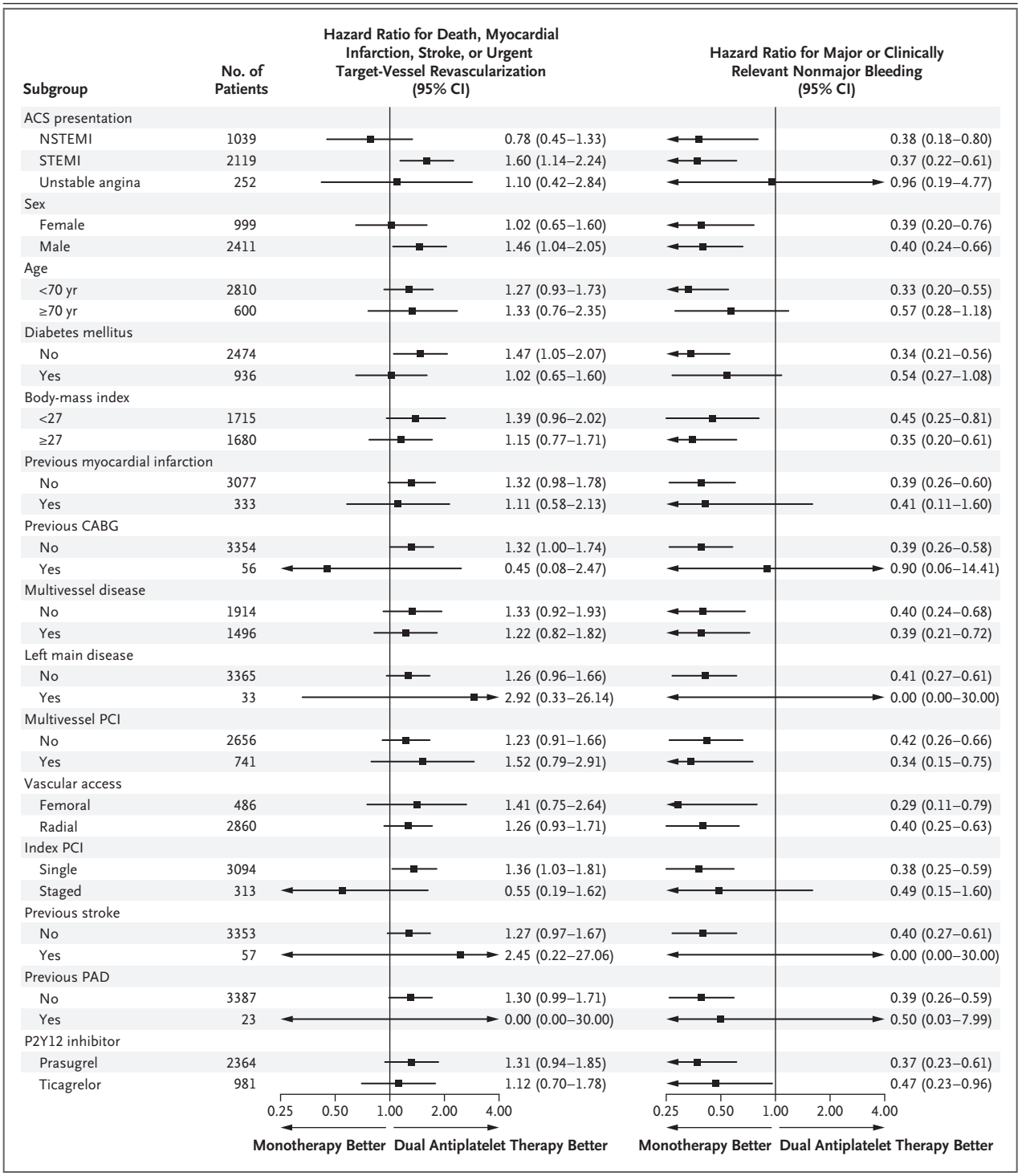


Figure 2. Cumulative Incidence of the Primary Outcomes According to Treatment Group.

The ranked primary outcomes were a composite of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization (Panel A) and major or clinically relevant nonmajor bleeding, defined by a Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding event (Panel B). Both primary outcomes were assessed in the intention-to-treat population. The hazard ratio is shown for monotherapy as compared with dual antiplatelet therapy. BARC bleeding types range from 0 (no bleeding) to 5 (fatal bleeding). The insets show the same data on an expanded y axis. CI denotes confidence interval.

Major or clinically relevant nonmajor bleeding had occurred in 33 patients (Kaplan–Meier estimate, 2.0%) in the monotherapy group and in 82 patients (Kaplan–Meier estimate, 4.9%) in the dual antiplatelet therapy group (hazard ratio, 0.40; 95% CI, 0.26 to 0.59), for an absolute difference in risk of –2.97 percentage points (95% CI, –4.20 to –1.73). Results for the two primary outcomes appeared to be similar across prespecified subgroups (Fig. 3).



SECONDARY OUTCOMES

At 12 months, the incidence of death from any cause, according to Kaplan–Meier estimates, was 3.6% in the monotherapy group and 3.0% in the dual antiplatelet therapy group (hazard ratio, 1.24; 95% CI, 0.85 to 1.79). The Kaplan–Meier estimate of the percentage of patients who died from cardiovascular causes was 2.5% in the monotherapy group and 2.0% in the dual antiplatelet therapy group (hazard ratio, 1.23; 95% CI, 0.78 to 1.93). In the monotherapy group, definite or probable stent thrombosis had occurred in 12 patients — 10 with subacute stent thrombosis (occurring 24 hours to 30 days after stent placement) and 2 with late stent thrombosis (occurring >30 days to <1 year after stent placement). In the dual antiplatelet therapy group, definite or probable stent thrombosis had occurred in 4 patients; 1 with acute stent thrombosis (occurring <24 hours after stent placement), 2 with subacute stent thrombosis, and 1 with late stent thrombosis (Table S4). Other secondary outcomes are summarized in Table 2.

At 12 months, the Kaplan–Meier estimate of the percentage of patients with any bleeding event (BARC type 1 to 5) was 4.5% in the monotherapy group and 9.0% in the dual antiplatelet therapy group. Details on the site of bleeding are provided in Table S5. The Kaplan–Meier estimate of the percentage of patients with net adverse clinical events was 8.5% in the monotherapy group and 9.9% in the dual antiplatelet therapy group (hazard ratio, 0.86; 95% CI, 0.69 to 1.08) (Fig. S1).

Figure 3 (facing page). Subgroup Analyses of the Primary Outcomes.

Shown are the hazard ratios for the primary outcomes (the composite of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization and major or clinically relevant nonmajor bleeding [BARC type 2, 3, or 5 bleeding events]) in prespecified subgroups of patients. The confidence intervals in the subgroup analyses have not been adjusted for multiplicity and therefore should not be interpreted as representing hypothesis tests of effects within the subgroups. The body-mass index is the weight in kilograms divided by the square of the height in meters. Data are missing for 15 patients for BMI, 12 for left main disease, 13 for multivessel disease, 64 for vascular access, and 3 for index PCI. ACS denotes acute coronary syndromes, NSTEMI non–ST-segment elevation myocardial infarction, PAD peripheral artery disease, and STEMI ST-segment elevation myocardial infarction.

Serious adverse events had occurred in 161 patients (9.4%) in the monotherapy group and in 177 patients (10.4%) in the dual antiplatelet therapy group (Table S6).

DISCUSSION

The NEO-MINDSET trial was designed to assess the efficacy and safety of an aspirin-free approach after PCI, with potent P2Y12 inhibitor monotherapy initiated immediately after successful PCI in patients with acute coronary syndromes. A hierarchical testing strategy was prespecified so that between-group differences with respect to death or ischemic events were assessed for noninferiority before those for bleeding events. Noninferiority of monotherapy to dual antiplatelet therapy with regard to the composite primary outcome of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization through 12 months of follow-up was not shown; therefore, no formal assessment of bleeding events was performed. Hemorrhagic events were observed somewhat less frequently in the monotherapy group than in the dual antiplatelet therapy group.

Previous small, single-group studies showed the feasibility of P2Y12 inhibitor monotherapy shortly after PCI in patients with acute or chronic coronary syndromes.[21-23] A recent randomized trial assessed the efficacy and safety of early monotherapy with prasugrel (3.75 mg once daily) as compared with dual antiplatelet therapy in patients undergoing PCI who had acute coronary syndromes or were at high bleeding risk.[24] In that trial, monotherapy was not shown to be superior to dual antiplatelet therapy with respect to major bleeding, and it was associated with a possible excess incidence of coronary events, including stent thrombosis, within the first 30 days after the initiation of treatment.

Our trial evaluated monotherapy with a full dose of prasugrel (10 mg once daily in most patients) or ticagrelor (90 mg twice daily) administered immediately after successful PCI, exclusively in patients with acute coronary syndromes. The median time from hospitalization to randomization, and thus the timing of aspirin withdrawal in the monotherapy group, was 2 days after admission. The results of this trial suggest that the immediate discontinuation of aspirin is associated with an increased risk of ischemic events, especially during the first weeks after PCI.

Overall, subacute stent thrombosis occurred in 10 patients assigned to monotherapy and in 2 patients assigned to dual antiplatelet therapy. After the first 30 days, the observed incidence of ischemic events appeared to be similar in the groups, a finding consistent with that in previous trials.[7,8] The prothrombotic state in the first weeks after an acute coronary event indeed justifies the need for an enhanced degree of platelet inhibition, which is achieved with the combination of two antiplatelet agents acting synergistically on key pathways of platelet activation.[25] On the other hand, bleeding events appeared to occur more often among patients in the dual antiplatelet therapy group than among those in the monotherapy group at 12 months of follow-up. In contrast to the incidence of death or ischemic events, the cumulative incidence curves for hemorrhagic complications appeared to diverge progressively throughout the entire follow-up period.

We included patients across the entire spectrum of acute coronary syndromes, but most had STEMI as their qualifying index event. Of note, in our trial, no eligibility restrictions were established according to the coronary-artery morphologic features of the patients or the complexity of PCI, and nearly half the patients presented with multivessel coronary artery disease. Conversely, we excluded patients at high bleeding risk, such as those using oral anticoagulants and those with a history of hemorrhagic events. Excluding patients at high bleeding risk may have contributed to the lower-than-expected incidence of bleeding, even though the incidence of bleeding reported in our study is in line with that in more recent trials comparing P2Y12 inhibitor monotherapy with dual antiplatelet therapy.[26]

Before randomization, investigators in this trial could choose to use either prasugrel or ticagrelor as the P2Y12 inhibitor on the basis of the package insert and their own preferences. Prasugrel was the most commonly used agent in our trial (in nearly 70% of patients), which differs from most previous trials that evaluated P2Y12 monotherapy predominantly with the use of clopidogrel or ticagrelor.[5-7,18,27,28] In this trial, treatment effects appeared to be similar regardless of the potent P2Y12 inhibitor administered; however, subgroup analyses were not sufficiently powered to draw definitive conclusions and can be interpreted only as hypothesis-generating. No apparent interaction was observed for ischemic or bleeding events across all other prespecified subgroups during the 12-month follow-up period.

Our trial has limitations that merit consideration. The open-label nature of the trial may have introduced bias in the ascertainment of events. However, all outcome events were adjudicated in a blinded manner by an independent clinical events committee. The observed incidence of ischemic and bleeding events was lower than initially anticipated. Most enrolled patients had STEMI, low hemorrhagic risk, and low atherosclerotic burden and had undergone angiography-guided single-vessel PCI, so the results may not be applicable to patients at higher risk or those who receive treatment according to other interventional strategies. Finally, the choice of the potent P2Y12 inhibitor was made at the discretion of the investigator, although this selection was made before randomization and the type of potent P2Y12 inhibitors used was evenly balanced between the trial groups.

Among patients with acute coronary syndromes, an aspirin-free strategy that involved potent P2Y12 inhibitor monotherapy initiated shortly after successful PCI with contemporary drug-eluting stents was not found to be noninferior to dual antiplatelet therapy with respect to the composite primary outcome of death from any cause, myocardial infarction, stroke, or urgent target-vessel revascularization.

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