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Clinical trials

Prasugrel or ticagrelor monotherapy vs dual antiplatelet treatment after percutaneous coronary intervention in acute coronary syndromes: a landmark analysis from the NEO-MINDSET trial

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Abstract

Background and Aims The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention in patients with acute coronary syndrome remains uncertain. This analysis examined the temporal patterns of ischaemic and bleeding risks of early aspirin withdrawal compared with DAPT.

Methods NEO-MINDSET randomized 3410 acute coronary syndrome patients undergoing successful percutaneous coronary intervention with drug-eluting stents within 4 days of hospital admission to either potent $P2Y_{12}$ inhibitor monotherapy (prasugrel or ticagrelor) or standard DAPT (aspirin plus a potent $P2Y_{12}$ inhibitor) for 12 months. This prespecified landmark analysis

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examined early (0–30 days) and late (31–365 days) follow-up events. Co-primary outcomes were (i) the composite of all-cause death, myocardial infarction, stroke, or urgent target-vessel revascularization (ischaemic outcome) and (ii) Bleeding Academic Research Consortium type 2, 3, or 5 bleeding.

Results At 30 days, the composite ischaemic outcome occurred in 3.3% of patients receiving monotherapy vs 1.8% with DAPT (risk difference 1.5%, 95% confidence interval .4% to 2.6%; P = .006). Bleeding occurred in .6% vs 1.5% (risk difference −.8%, 95% confidence interval −1.5% to −.1%; *P* = .018). In the landmark analysis between Days 31 and 365, ischaemic outcome rates were similar between study groups (3.8% each; *P* = .977), while bleeding remained less frequent with monotherapy (1.3% vs 3.5%; risk difference −2.2%, 95% confidence interval −3.2% to −1.1%; *P* < .0001).

Conclusions This prespecified 30-day landmark analysis suggests an excess of ischaemic risk with monotherapy vs DAPT in the first 30 days but not thereafter, whereas an aspirin-free strategy was consistently associated with fewer bleeding events within and after 30 days.

Structured Graphical Abstract

Key Question

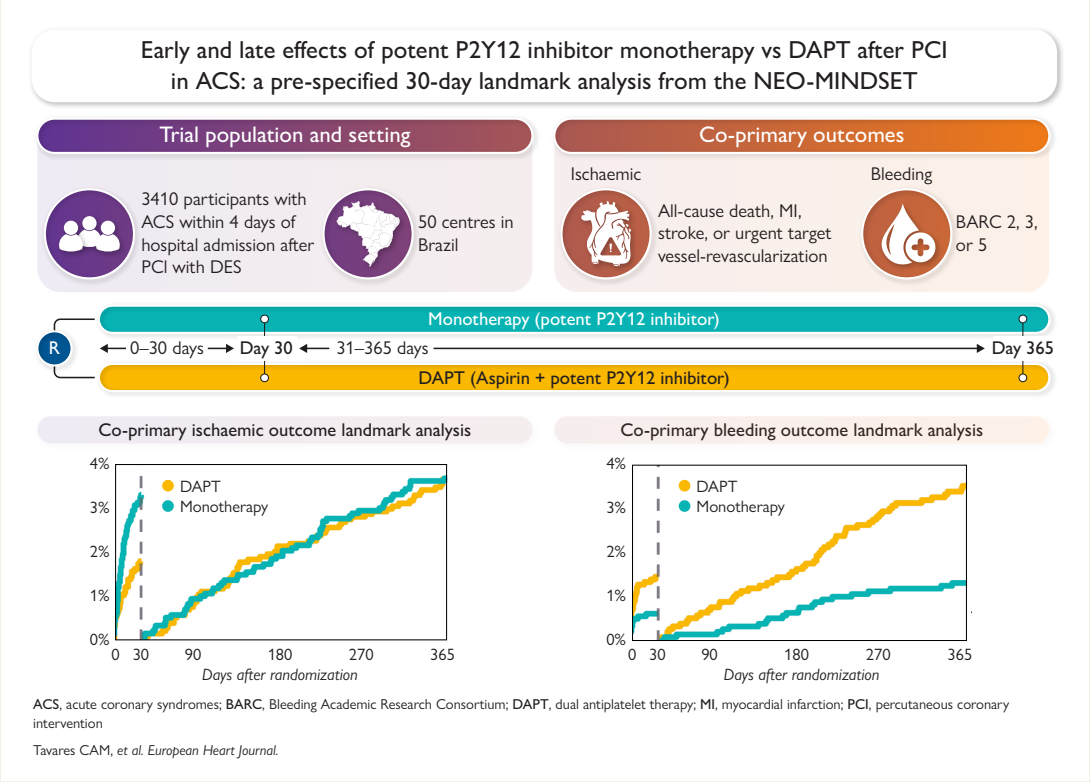
How do ischaemic and bleeding risks differ in early (0–30 days) and late (31–365 days) periods in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI), who receive potent $P2Y_{12}$ inhibitor monotherapy versus dual antiplatelet therapy (DAPT)?

Key Finding

In this pre-specified 30-day landmark analysis of the NEO-MINDSET trial $P2Y_{12}$ inhibitor monotherapy was associated with an increased ischaemic risk within the first 30 days as compared to DAPT. Beyond 30 days, this risk appeared comparable between monotherapy and DAPT. Bleeding events were lower with monotherapy in both time periods.

Take Home Message

These findings may help modulate DAPT after PCI in ACS.



ACS, acute coronary syndromes; BARC, Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention

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Landmark prespecified analysis of the NEO-MINDSET trial comparing the occurrence of the co-primary ischaemic and bleeding outcomes between study groups within the first 30 days and from 31 to 365 days of follow-up. BARC, Bleeding Academic Research Consortium; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; R, randomization.

Keywords Acute coronary syndrome • Antiplatelet monotherapy • Aspirin-free

Introduction

Twelve-month dual antiplatelet therapy (DAPT) with aspirin plus a potent $P2Y_{12}$ inhibitor constitutes the default strategy for patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI), though the balance between ischaemic and bleeding risks evolves over time.[1] Importantly, the ischaemic protection afforded by DAPT is accompanied by a cumulative risk of bleeding.[2] This consideration has led to the investigation of shortened DAPT durations and various antiplatelet de-escalation strategies,[3] encompassing the use of single antiplatelet regimens, dose reduction schemes, or switching from a potent to a less potent $P2Y_{12}$ inhibitor.[4,5] Increasing evidence has suggested that de-escalation strategies may not substantially increase ischaemic risk while significantly reducing clinically relevant bleeding.[6–8]

Trials evaluating de-escalation of antiplatelet therapy have predominantly been conducted after an initial interval of 1–6 months of DAPT.[4] Currently, evidence on the ischaemic and bleeding trade-off of initiating single antiplatelet therapy with $P2Y_{12}$ inhibition immediately after PCI in the ACS population remains limited. This timeframe is critical, as the thrombotic risk peaks early after ACS and PCI, declining steeply over time thereafter.[9,10] Similarly, this early phase also carries a substantial burden of haemorrhagic risk, further amplified by the invasive procedure.

The percutaNEOus coronary intervention followed by Monotherapy INstead of Dual antiplatelet therapy in the SETting of acute coronary syndromes (NEO-MINDSET) trial compared very early aspirin withdrawal with potent $P2Y_{12}$ inhibitor monotherapy vs DAPT with aspirin and a potent $P2Y_{12}$ inhibitor in patients with ACS undergoing PCI. The trial did not demonstrate non-inferiority of monotherapy over DAPT for ischaemic events [myocardial infarction (MI), stroke, or urgent target-vessel coronary revascularization] or death at 1 year. Bleeding rates, however, were numerically lower in the monotherapy group compared with DAPT.[11]

The objective of this prespecified analysis of NEO-MINDSET is to explore the ischaemic and haemorrhagic risks during the first 30 days after randomization and from 31 days to 1 year with potent $P2Y_{12}$ inhibitor monotherapy vs DAPT. Understanding the risk–benefit of monotherapy in each period is particularly relevant given the evolving landscape of antiplatelet monotherapy in patients with ACS undergoing PCI and the increasing emphasis on personalized treatment approaches based on individual patient risk profiles.

Methods

Study design and population

NEO-MINDSET was an investigator-initiated, multicentre, open-label, randomized trial conducted in Brazil. The study organization, participating centres, and investigators are listed in Supplementary data online, *Appendices A* and *B*. The study design and main results have been published elsewhere.[11,12] In brief, adults (≥18 years) presenting with ACS [ST-elevation myocardial infarction (STEMI) or non-ST-elevation ACS] who underwent successful PCI with contemporary drug-eluting stents (DES) were eligible, provided all planned interventions had been completed within 4 days of admission. Key exclusion criteria were need for oral anticoagulation, in-hospital or major active bleeding, stroke within 30 days, and previous intracranial haemorrhage (see Supplementary data online, *Table S1*). Patients were randomized within 4 days of hospitalization in a 1:1 ratio to receive either monotherapy with a potent $P2Y_{12}$ inhibitor or DAPT for 1 year. Site investigators selected between ticagrelor (90 mg twice daily) and prasugrel (5 or 10 mg daily) for all participants, irrespective of the study group allocation. Patients not receiving these agents before randomization received loading doses (ticagrelor 180 mg or prasugrel 60 mg), while those already on ticagrelor or prasugrel before randomization continued their current therapy without additional loading.[13] The monotherapy group discontinued aspirin immediately post-randomization. Study treatment continued for 12 months with follow-up extending to 13 months (in-person visits: 1, 6, and 12 months; remote visits: 3, 9, and 13 months).

The study protocol was approved by the ethics committee at each participating site, and written informed consent was obtained from all patients before any study-related procedures. The trial is registered on ClinicalTrials.gov (NCT04360720). The full study protocol and statistical analysis plan are provided in the supplementary data online.

Study outcomes

The two co-primary adjudicated outcomes in this trial were as follows: the composite of all-cause mortality, MI, stroke, or urgent target-vessel revascularization and major or clinically relevant non-major bleeding, defined as Bleeding Academic Research Consortium (BARC) type 2, 3, or 5.[14] Prespecified secondary outcomes included each individual component of the co-primary composites, cardiovascular and non-cardiovascular mortality, stent thrombosis, all bleeding events (BARC 1–5), and net adverse clinical events (all-cause mortality, MI, stroke, urgent target-vessel revascularization, and BARC 2, 3, or 5 bleeding). All events were adjudicated centrally by an independent committee blinded to treatment assignment. Details from the study outcomes are provided in Supplementary data online, *Appendix C*.

Statistical analysis

Categorical variables were expressed as numbers and percentages, while continuous variables were expressed as medians and interquartile ranges (IQRs). A prespecified landmark analysis was performed at 30 days, comparing study groups regarding clinical events occurring during two periods: 0–30 days and 31–365 days post-randomization. For all study outcomes, participants experiencing the event of interest within the first 30 days were excluded from the analysis of the second period. Patients were censored at 365 days or at the date of last known vital status. Incidences of time-to-event outcomes at 30 and 365 days were calculated using Kaplan–Meier estimates. Between-group differences were estimated using Greenwood standard errors and presented as absolute risk differences (ARDs) with 95% confidence intervals (CIs). To explore time-varying treatment effects of monotherapy vs DAPT, daily between-group absolute differences with 95% CIs were plotted throughout each time period for the two co-primary outcomes. This approach corresponds to performing a milestone analysis at each day of follow-up.[15] Cox proportional hazards models were also fitted for both time intervals to estimate hazard ratios with 95% CIs for all outcomes. For the two co-primary outcomes, interaction *P*-values were calculated to compare hazard ratios between the two periods.

Prespecified subgroup analyses included the following: ACS presentation type [unstable angina vs non-ST-elevation myocardial infarction (NSTEMI) vs STEMI], sex, age (≥70 vs <70 years), diabetes mellitus, body mass index (≥27 vs <27 kg/m^2), prior MI, prior stroke, multivessel disease, multivessel PCI, vascular access (femoral vs radial), index PCI strategy (single vs staged procedure), and choice of $P2Y_{12}$ inhibitor (prasugrel vs ticagrelor). Sensitivity analyses complemented the primary analysis: (i) more restrictive composite outcomes were assessed, comprising MI, stroke, or all-cause death for ischaemic events; BARC type 3 or 5 bleeding for bleeding events; and a modified net adverse clinical event endpoint combining all these ischaemic and bleeding outcomes; and (ii) landmark analyses were performed at 7, 14, and 21 days, with daily between-group absolute differences illustrated graphically.

No specific power analysis was performed for this 30-day landmark analysis; the rationale and sample size calculation for the main analysis were reported previously.[12] All analyses followed the intention-to-treat principle, analysing participants according to their randomized treatment assignment regardless of actual treatment received, without imputation of missing data. Statistical analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria). All *P*-values are two-sided without adjustment for multiple tests and should be considered exploratory.

Table 1 Key clinical and procedural characteristics of the study population

Characteristic	All patients (*N* = 3410)	Monotherapy (*N* = 1712)	DAPT (*N* = 1698)
Age (years)	60 (52–67)	60 (52–67)	60 (53–67)
≥70 years	600 (17.6)	306 (17.9)	294 (17.3)
Female sex	999 (29.3)	502 (29.3)	497 (29.3)
Non-White race	1074 (31.5)	543 (31.7)	531 (31.3)
Body mass index (kg/m^2)	27.0 (24.5–29.8) [3395]	27.0 (24.6–29.8) [1704]	26.9 (24.5–29.9) [1691]
Hypertension	2183 (64.0)	1093 (63.8)	1090 (64.2)
Diabetes	936 (27.4)	459 (26.8)	477 (28.1)
Dyslipidaemia	916 (26.9)	464 (27.1)	452 (26.6)
Prior myocardial infarction	333 (9.8)	171 (10.0)	162 (9.5)
Current smoker	1185/3289 (36.0)	597/1654 (36.1)	588/1635 (36.0)
ARC high bleeding risk	674 (19.8)	339 (19.8)	335 (19.7)
ACS presentation			
STEMI	2119 (62.1)	1058 (61.8)	1061 (62.5)
NSTEMI	1039 (30.5)	527 (30.8)	512 (30.2)
Unstable angina	252 (7.4)	127 (7.4)	125 (7.4)
No. of days from admission to first PCI	1 (0–2) [3408]	1 (0–2) [1711]	1 (0–2) [1697]
No. of days from admission to randomization	2 (1–3)	2 (2–3)	2 (1–3)
Angiographic characteristics			
Any radial access	2910/3406 (85.4)	1465/1709 (85.7)	1445/1697 (85.2)
Multivessel disease	1496 (43.9)	777 (45.4)	719 (42.3)
Number of implanted stents	[3404]	[1709]	[1695]
One	2101 (61.7)	1050 (61.4)	1051 (62.0)
Two	846 (24.9)	425 (24.9)	421 (24.8)
Three or more	457 (13.4)	234 (13.7)	223 (13.2)
Treated vessel	[3407]	[1710]	[1697]
Left main coronary artery	33 (1.0)	20 (1.2)	13 (.8)
Left anterior descending artery	2009 (59.0)	1010 (59.1)	999 (58.9)
Right coronary artery	1360 (39.9)	677 (39.6)	683 (40.2)
Circumflex artery	788 (23.1)	393 (23.0)	395 (23.3)
Other	78 (2.3)	44 (2.6)	34 (2.0)
Aspirin	3297/3407 (96.8)	1641/1711 (95.9)	1656/1696 (97.6)
Clopidogrel	2881/3407 (84.6)	1442/1711 (84.3)	1439/1696 (84.8)
Ticagrelor	265/3406 (7.8)	136/1710 (8.0)	129/1696 (7.6)
Prasugrel	197/3406 (5.8)	99/1710 (5.8)	98/1696 (5.8)
RAS inhibitors	2598 (76.2)	1310 (76.5)	1288 (75.9)
Beta-blocker	2216 (65.0)	1116 (65.2)	1100 (64.8)
Diuretics[a]	419 (12.3)	213 (12.4)	206 (12.1)
Statins	3192 (93.6)	1614 (94.3)	1578 (92.9)
$P2Y_{12}$ post-randomization			
Prasugrel	2364 (69.3)	1192 (69.6)	1172 (69.0)

Continued

Table 1 *Continued*

Characteristic	All patients (*N* = 3410)	Monotherapy (*N* = 1712)	DAPT (*N* = 1698)
Ticagrelor	981 (28.8)	480 (28.0)	501 (29.5)
P2Y$_{12}$ loading dose administered[b]	2964 (86.9)	1486 (86.8)	1478 (87.0)

Data are presented as *n* (%) or median (interquartile range). [*N*] indicates the number analysed where data were missing.
ARC, Academic Research Consortium; NSTEMI, non-ST-elevation myocardial infarction; RAS, renin–angiotensin system; STEMI, ST-elevation myocardial infarction.
[a]Thiazides, loop diuretics, or mineralocorticoid receptor antagonists.
[b]For participants not receiving the selected P2Y$_{12}$ inhibitor (ticagrelor or prasugrel) prior to randomization, a loading dose was recommended.

Table 2 Study outcomes from randomization to Day 30

Outcome	Kaplan–Meier estimate, % (*N* of participants with events)		Absolute risk difference, % (95% CI)	*P*-value	Hazard ratio (95% CI)
	Monotherapy	DAPT			
Co-primary outcomes					
Ischaemic[a]	3.3 (57)	1.8 (31)	1.5 (.4 to 2.6)	.006	1.84 (1.19 to 2.85)
Bleeding[b]	.6 (11)	1.5 (25)	−.8 (−1.5 to −.1)	.018	.44 (.21 to .89)
Secondary outcomes					
Death					
From any cause	1.6 (28)	1.1 (18)	.6 (−.2 to 1.4)	.144	1.55 (.86 to 2.80)
From cardiovascular causes	1.4 (24)	.8 (14)	.6 (−.1 to 1.3)	.108	1.71 (.88 to 3.30)
From non-cardiovascular causes	.2 (4)	.2 (4)	.0 (−.3 to .3)	.997	1.00 (.25 to 3.99)
Myocardial infarction	1.4 (24)	.5 (9)	.9 (.2 to 1.6)	.009	2.66 (1.24 to 5.73)
Stroke	.7 (12)	.4 (6)	.4 (−.1 to .8)	.160	1.99 (.75 to 5.31)
Urgent target-vessel revascularization	.6 (11)	.3 (5)	.4 (−.1 to .8)	.135	2.19 (.76 to 6.32)
Stent thrombosis	.5 (9)	.2 (3)	.4 (−.1 to .8)	.084	2.99 (.81 to 11.06)
Bleeding (BARC type)					
Types 1–5	1.5 (26)	3.1 (52)	−1.6 (−2.6 to −.5)	.003	.49 (.31 to .79)
Type 1	.9 (15)	1.6 (27)	−.7 (−1.5 to .0)	.061	.55 (.29 to 1.04)
Type 2	.2 (4)	.7 (11)	−.4 (−.9 to .0)	.068	.36 (.11 to 1.13)
Type 3	.4 (6)	.8 (13)	−.4 (−.9 to .1)	.104	.46 (.17 to 1.20)
Type 5	.1 (1)	.1 (1)	.0 (−.2 to .2)	.996	.99 (.06 to 15.88)
Net adverse clinical events[c]	3.8 (65)	3.1 (52)	.7 (−.5 to 2.0)	.243	1.24 (.86 to 1.79)

BARC, Bleeding Academic Research Consortium.
[a]All-cause death, myocardial infarction, stroke, or urgent target-vessel revascularization.
[b]BARC type 2, 3, or 5.
[c]Composite of myocardial infarction, stroke, urgent target-vessel revascularization, BARC 2, 3, or 5 bleeding, or all-cause death.

Results

A total of 3413 participants were randomized across 50 Brazilian centres between October 2020 and October 2023. After excluding three participants due to one randomization error, one participant who withdrew consent, and one participant due to a major violation of good clinical practice, 3410 participants comprised the intention-to-treat population. The median age was 60 years, and 29.3% were women. The index ACS presentation was STEMI in 62.1%, NSTEMI in 30.5%, and unstable angina in 7.4% of cases. The median time from hospital admission to randomization was 2 days (IQR 1–3 days), while the median interval from hospital admission to first PCI was 1 day (IQR 0–2 days). Only one stent was implanted in 2101 (61.7%) of participants, with the left anterior descending artery being the most frequently treated vessel (59.0%). Most participants received renin–angiotensin system (RAS) inhibitors (*n* = 2598, 76.2%) and statins (*n* = 3192, 93.6%) (*Table 1*).

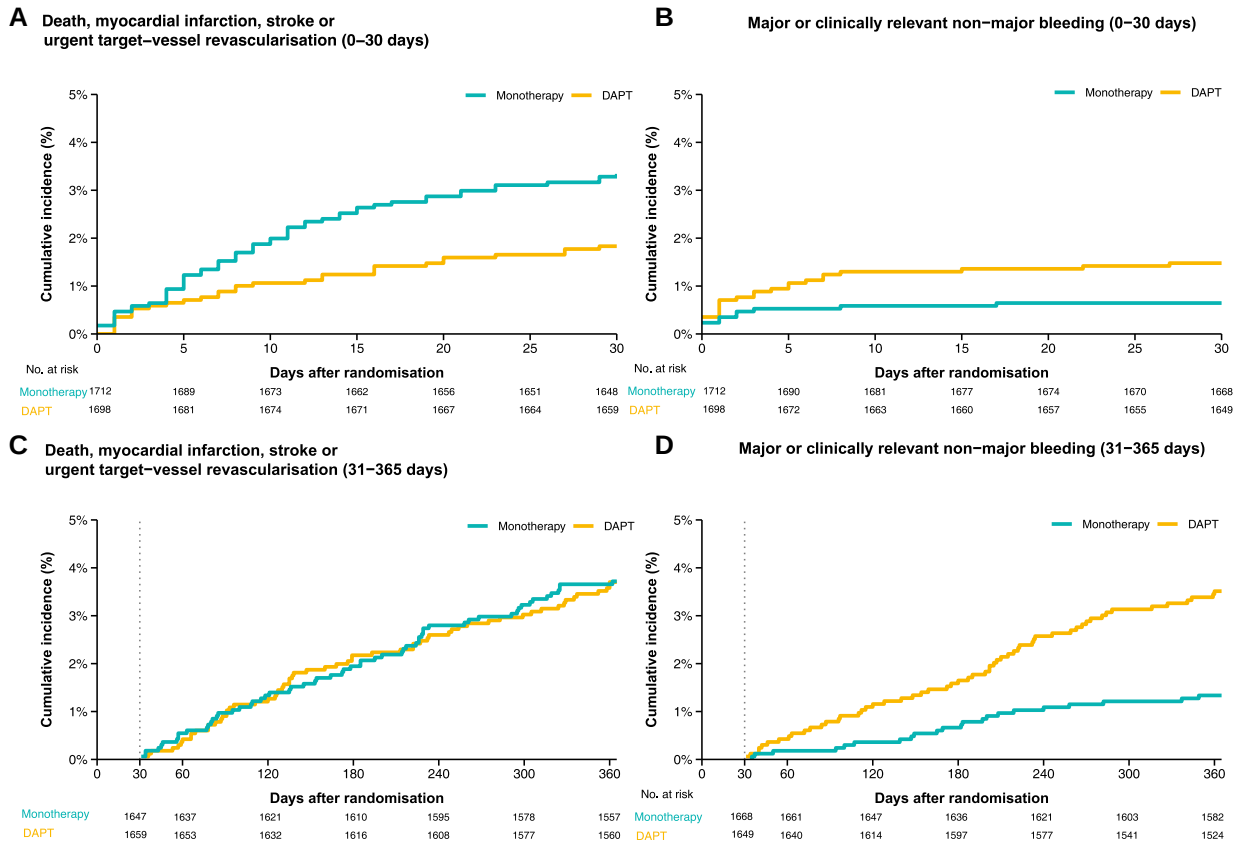

Figure 1 Kaplan–Meier curves for co-primary outcomes within 30 days of randomization and from 31 to 365 days. Kaplan–Meier cumulative incidence curves showing the cumulative probability of experiencing the co-primary outcomes during follow-up. (*A*) Myocardial infarction, stroke, urgent target-vessel revascularization, or death (co-primary ischaemic outcome) from randomization to 30 days. (*B*) Major or clinically relevant non-major bleeding (co-primary bleeding outcome) from randomization to 30 days. (*C*) The co-primary ischaemic outcome from Days 31 to 365 using landmark analysis. (*D*) The co-primary bleeding from Days 31 to 365 using landmark analysis. The blue line represents patients assigned to monotherapy, and the yellow line represents those assigned to dual antiplatelet therapy. Numbers at risk are shown below each panel at specified time intervals. For landmark analyses (panels *C* and *D*), only patients who were event-free at Day 30 were included, with follow-up time reset to begin at Day 31. The dotted vertical line at Day 30 in panels *C* and *D* indicates the landmark timepoint

Detailed baseline demographic, clinical, and angiographic characteristics in the 0–30-day analysis and in the subsequent landmark assessments for each co-primary outcome were generally comparable (see Supplementary data online, *Table S2*).

Clinical outcomes within the first 30 days

Clinical outcomes occurring from randomization to 30 days are summarized in *Table 2*. At 30 days, the co-primary composite outcome of MI, stroke, urgent target-vessel revascularization, or death occurred in 57 participants (3.3%) receiving monotherapy and in 31 (1.8%) receiving DAPT (Kaplan–Meier estimates), yielding a between-group ARD of 1.5% (95% CI .4% to 2.6%; $P = .006$). The co-primary bleeding outcome occurred in 11 participants (.6%) in the monotherapy group and in 25 (1.5%) in the DAPT group, with an ARD of −.8% (95% CI −1.5% to −.1%; $P = .018$). Kaplan–Meier survival curves for the co-primary outcomes are illustrated in *Figure 1A* and for the co-primary bleeding outcome in *Figure 1B*. The temporal evolution of ARDs between treatment groups, based on Kaplan–Meier estimates, is depicted in *Figure 2A* (ischaemic outcome) and *Figure 2B* (bleeding outcome). Estimates for net adverse clinical events at 30 days were numerically higher in the monotherapy group (*Table 2* and Supplementary data online, *Figures S1* and *S2*).

Clinical outcomes from 31 to 365 days

Between Days 31 and 365, no differences were observed in the occurrence of the co-primary composite outcome of MI, stroke, urgent target-vessel revascularization, or death among treatment groups [3.8% of each group (ARD .0%, 95% CI −1.3% to 1.3%; $P = .977$)]. In contrast, bleeding events were less frequent among patients receiving monotherapy compared with those receiving DAPT during this time period (1.3% vs 3.5%), corresponding to an ARD of −2.2% (95% CI −3.2% to −1.1%; $P < .001$). Comparison of hazard ratios between the two landmark periods yielded *P*-values for interaction of .035 for the co-primary ischaemic outcome and .74 for the co-primary bleeding outcome.

Clinical outcomes for the 31–365-day analysis period are presented in *Table 3*, with corresponding Kaplan–Meier survival curves shown in

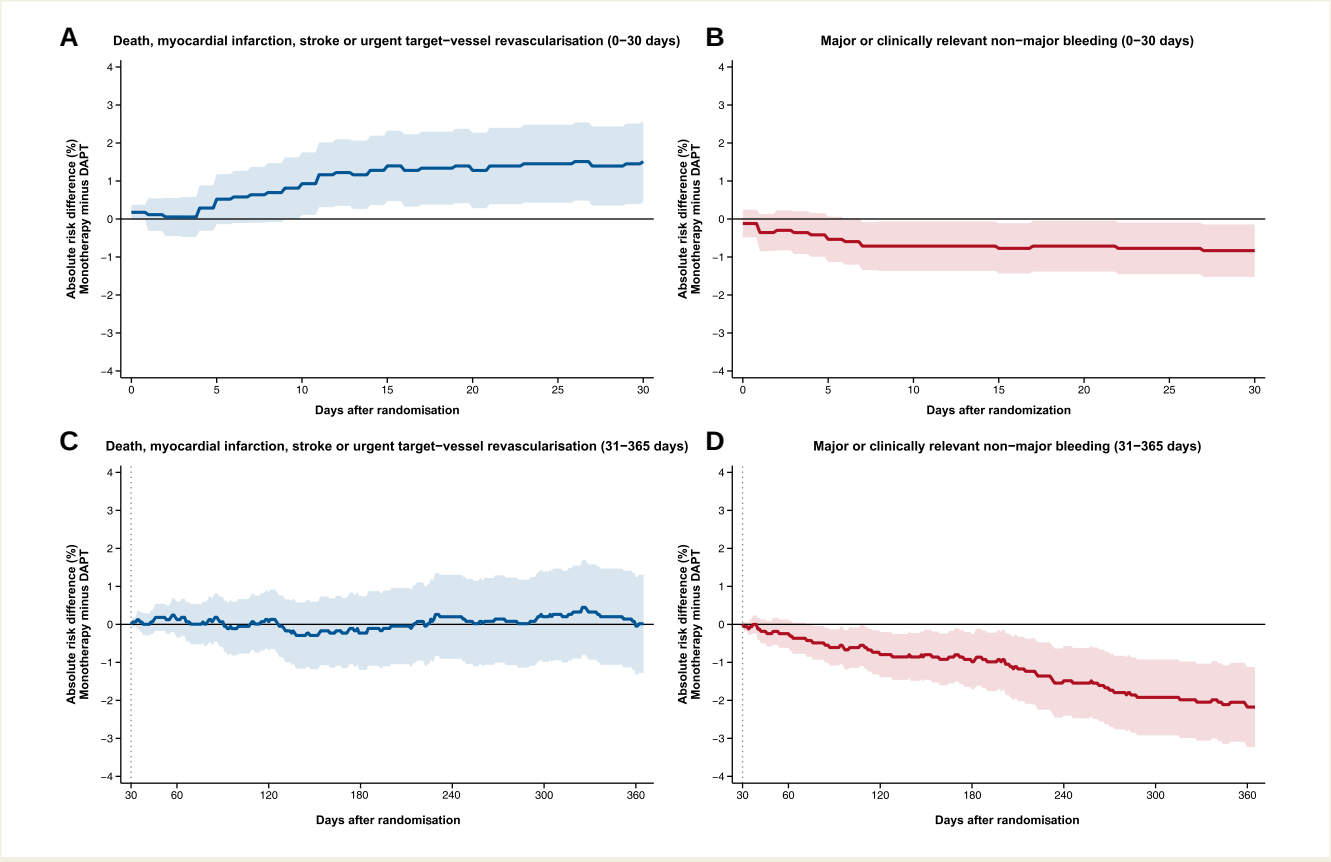

Figure 2 Absolute risk differences between monotherapy and dual antiplatelet therapy for ischaemic and bleeding events before and after 30 days. Graphic display of time-dependent absolute risk differences between monotherapy and dual antiplatelet therapy for the primary ischaemic and bleeding endpoints. The absolute risk difference is calculated as the difference in Kaplan–Meier estimates (monotherapy minus dual antiplatelet therapy) iteratively for each study day, with positive values indicating higher risk with monotherapy and negative values indicating higher risk with dual antiplatelet therapy. (*A*) Composite of myocardial infarction, stroke, urgent target-vessel revascularization, or death (ischaemic co-primary outcome) during the first 30 study days. (*B*) Major or clinically relevant non-major bleeding (bleeding co-primary outcome) during the first 30 days. (*C*) Ischaemic co-primary outcome analyses from Days 31 to 365. (*D*) Bleeding co-primary outcome from Days 31 to 365. The solid lines represent the point estimates of absolute risk differences over time, with light shaded areas indicating 95% confidence intervals

Figure 1C (ischaemic outcome) and *Figure 1D* (bleeding outcome). The daily evolution of cumulative between-group differences in Kaplan–Meier estimates is illustrated in *Figure 2C* (ischaemic outcome) and *Figure 2D* (bleeding outcome). Net adverse clinical events during this period are shown in Supplementary data online, *Figures S3* and *S4*. As bleeding hazards accumulated over time, the between-group difference favoured the monotherapy group during late follow-up. The temporal pattern of secondary ischaemic and bleeding outcomes is shown in Supplementary data online, *Figures S5* and *S6*. Most MIs observed during follow-up were type 1. Detailed MI data by study group and landmark period are presented in Supplementary data online, *Table S3*.

Subgroup and sensitivity analyses

The treatment effects were generally consistent across prespecified subgroups for the co-primary outcomes when assessed one at time (see Supplementary data online, *Figures S7–S10*). Sensitivity analyses of exploratory modified composite clinical endpoints confirmed the primary findings. For the composite of MI, stroke, or all-cause death, the absolute between-group difference (monotherapy minus DAPT) was 1.6% (95% CI .5 to 2.6; $P = .004$) at 30 days and −.2% (95% CI −1.5 to 1.0; $P = .720$) from Days 31 to 365. For BARC type 3 or 5 bleeding, the corresponding differences were −.4% (95% CI −.9 to .1; $P = .121$) at 30 days and −1.0% (95% CI −1.6 to −.4; $P = .002$) from Days 31 to 365 (see Supplementary data online, *Table S4*). Additional landmark analyses shortening the 30-day period to 21, 14, and 7 days are shown in Supplementary data online, *Figures S11–S13*. Visual inspection of the absolute between-group difference curves suggested that the ischaemic risk difference appeared to stabilize after 14–21 days, while the bleeding difference continued to accrue beyond this timepoint, favouring monotherapy.

Discussion

This prespecified analysis of the NEO-MINDSET trial examined the temporal effects of potent P2Y$_{12}$ inhibitor monotherapy in comparison with DAPT after PCI with DES in patients with ACS. The principal finding is that very early aspirin withdrawal was associated with an excess in ischaemic risk compared with DAPT, predominantly clustered within the first 30 days post-randomization. This pattern was observed across all the individual components of the composite ischaemic outcome. Beyond 30 days, the risk of thrombotic events seemed similar between

Table 3 Study outcomes from 31 to 365 days

Outcome	Kaplan–Meier estimate, % (*N* of participants with events)		Absolute risk difference, % (95% CI)	*P*-value	Hazard ratio (95% CI)
	Monotherapy	DAPT			
Co-primary outcomes					
Ischaemic[a]	3.8 (62)	3.8 (62)	.0 (−1.3 to 1.3)	.977	1.01 (.71 to 1.43)
Bleeding[b]	1.3 (22)	3.5 (57)	−2.2 (−3.2 to −1.1)	<.0001	.38 (.23 to .62)
Secondary outcomes					
Death					
From any cause	2.0 (34)	1.9 (32)	.1 (−.8 to 1.1)	.817	1.06 (.65 to 1.72)
From cardiovascular causes	1.1 (18)	1.2 (20)	−.1 (−.8 to .6)	.738	.90 (.47 to 1.70)
From non-cardiovascular causes	1.0 (16)	.7 (12)	.2 (−.4 to .9)	.455	1.33 (.63 to 2.81)
Myocardial infarction	1.3 (21)	1.3 (22)	−.1 (−.8 to .7)	.887	.96 (.53 to 1.74)
Stroke	.5 (8)	.5 (9)	−.1 (−.6 to .4)	.807	.89 (.34 to 2.30)
Urgent target-vessel revascularization	.7 (11)	.4 (7)	.3 (−.3 to .8)	.352	1.56 (.61 to 4.03)
Stent thrombosis	.2 (3)	.1 (1)	.1 (−.1 to .4)	.319	2.99 (.31 to 28.76)
Bleeding (BARC type)					
Types 1–5	3.0 (49)	6.1 (98)	−3.1 (−4.6 to −1.7)	<.0001	.48 (.34 to .68)
Type 1	1.8 (30)	3.0 (49)	−1.2 (−2.3 to −.1)	.027	.60 (.38 to .95)
Type 2	1.0 (17)	2.4 (39)	−1.4 (−2.2 to −.5)	.003	.43 (.24 to .76)
Type 3	.3 (5)	1.2 (20)	−.9 (−1.5 to −.3)	.002	.25 (.09 to .66)
Type 5	.0 (0)	.1 (1)	−.1 (−.2 to .1)	.317	NA
Net adverse clinical events[c]	4.9 (80)	7.0 (114)	−2.1 (−3.7 to −.5)	.011	.69 (.52 to .92)

BARC, Bleeding Academic Research Consortium.
[a]Myocardial infarction, stroke, urgent target-vessel revascularization, or all-cause death.
[b]BARC type 2, 3, or 5.
[c]Composite of myocardial infarction, stroke, urgent target-vessel revascularization, BARC 2, 3, or 5 bleeding, or all-cause death

study groups. While monotherapy appeared to reduce bleeding events consistently throughout the 1-year follow-up, our findings do not support very early aspirin discontinuation and suggest that at least 30 days of DAPT might be needed (*Structured Graphical Abstract*).

Several de-escalation trials have shown that shortening DAPT duration after PCI was not associated with an excessive ischaemic risk while reducing bleeding complications.[6,7,16–21] While it is known that most thrombotic events occur within the first 3 months after ACS, there are no clear guidelines for a defined number of days or weeks to split phases for predominance of ischaemic or bleeding risks. As trials have progressively shown that short DAPT strategies are associated with a positive trade-off between ischaemic and bleeding risks, the safety of potent $P2Y_{12}$ inhibitor monotherapy in the first 30 days after PCI was unclear, although this concept was supported by a small feasibility study.[22] Furthermore, most de-escalation trials selected populations that were event-free during the first months after ACS, which might affect the risks and benefits observed thereafter.[23]

Only two trials have stopped aspirin before the first month following PCI with DES.[3,24] In the T-PASS study, discontinuation of aspirin at a median of 16 days with subsequent ticagrelor monotherapy was both non-inferior and superior for net adverse clinical events (MI, definite or probable stent thrombosis, stroke, major bleeding, and all-cause death) compared with DAPT at 1 year. BARC bleeding types 2, 3 and 5 were reported in 2.0% of the monotherapy group and 4.5% of the DAPT group, while a composite ischaemic outcome occurred in 1.5% and 2.2%, respectively. At 30 days, these outcomes occurred in .9% and .8% and in .2% and .2% of study groups, respectively—strikingly lower than what was observed in our study. The STOPDAPT-3 trial included 6002 patients with ACS undergoing PCI (75% of the study population) or at high bleeding risk and compared 1-month prasugrel-based monotherapy (3.75 mg/day) vs 1-month DAPT with prasugrel (3.75 mg/day). Importantly, almost all participants stopped aspirin at the index PCI procedure. At 1 month, thrombotic events occurred in 4.1% in the monotherapy group and 3.7% in the DAPT group, while BARC bleeding type 3 or 5 occurred in 4.5% and 4.7%, respectively—much higher than what was observed in this landmark analysis at 30 days.

Comparing NEO-MINDSET with T-PASS and STOPDAPT-3 is not straightfoward due to differences in aspirin withdrawal timing, $P2Y_{12}$ inhibitor selection and dosing, and patient ethnicity. Our requirement for PCI completion within 96 h created a distinct study population: higher STEMI representation with less complex coronary anatomy (as complex cases often require staged procedures) and exclusion of patients with

early access-site bleeding complications. These selection criteria may have influenced our observed outcome rates relative to other trials.

Our landmark analysis from Days 31 to 365 demonstrated findings that appeared to be consistent with prior trials of abbreviated DAPT after the 1-month mark. The observed between-group differences—~0% for ischaemic events and 2% absolute reduction for bleeding—align generally with $P2Y_{12}$ monotherapy trials after 1-month DAPT in ACS populations. Comparable differences were reported in STOPDAPT-2 ACS (ischaemic: +.9%; bleeding: −.6%), ULTIMATE-DAPT (ischaemic: −.1%; bleeding: −2.5%), and TARGET-FIRST (ischaemic: ~0%; bleeding: −3.0%) although study definitions for ischaemic and bleeding composite outcomes differed.[18,19,25]

Furthermore, among patients with atrial fibrillation and ACS or recent PCI, the addition of aspirin to oral anticoagulation and $P2Y_{12}$ inhibitor therapy beyond 30 days was not associated with reduced ischaemic risk while bleeding risk was increased, as shown in a 30-day landmark analysis from the AUGUSTUS trial.[26] Because bleeding events occurred more frequently in patients receiving DAPT compared with those with monotherapy in both examined periods, when assessing the composite of both ischaemic and bleeding events (net adverse clinical events), absolute differences were less pronounced in the first weeks after ACS than those observed for the co-primary ischaemic outcome alone. However, although net adverse clinical event analyses are useful for balancing ischaemic–bleeding trade-offs, they do not account for the differential long-term prognostic implications of individual components; thus, decisions regarding DAPT duration should weigh both timing and the relative clinical impact of ischaemic and bleeding events.

This analysis provides important information about the optimal timing for potent $P2Y_{12}$ inhibitor monotherapy after ACS. Between-group differences for ischaemic events or death seemed to be predominant within the first month after randomization and attenuated in later periods. These data support current American College of Cardiology/American Heart Association guidelines recommending Class I maintenance of DAPT during the first month post-ACS.[27] However, our analyses suggest that further refinement of this duration warrants prospective investigation. While most of the excess ischaemic risk with $P2Y_{12}$ inhibitor monotherapy appeared to accrue within the first 14 days, the optimal transition point to monotherapy appears to lie somewhere between 14 days and shortly after 30 days.

Limitations

Several limitations warrant consideration. First, as a secondary analysis without adjustment for multiple comparisons, the reported *P*-values should be interpreted as exploratory and hypothesis-generating. Second, landmark analyses inherently select event-free survivors, potentially introducing survivorship bias that may underestimate risk in the subsequent period and influence the appearance of time-varying effects. Third, the open-label design may have introduced event reporting bias, particularly for subjective endpoints. Fourth, while the 30-day landmark was chosen based on established patterns of heightened early ischaemic risk following ACS, this timepoint remains somewhat arbitrary given the non-monotonic decline in risk during the first month, and alternative cut-offs could have been chosen as shown in the *post hoc* exploratory analyses.[28] Fifth, *a priori* weights were not assigned to individual ischaemic and bleeding events to quantify the risk–benefit trade-off of early aspirin withdrawal; establishing such weights remains a fundamental challenge in cardiovascular trials as the relative importance of ischaemic vs bleeding events varies by patient values and clinical context. Sixth, selection bias may have influenced our findings, as evidenced by the relatively low 1-year mortality rate compared with broader registry data.[29–31] The requirement for randomization within 96 h of PCI and exclusion of patients with prolonged hospitalizations, need for oral anticoagulants, or unsuccessful procedures likely selected for a lower-risk population, potentially limiting generalizability to more complex ACS presentations or those with early complications. Finally, the $P2Y_{12}$ inhibitor selection was done at investigator discretion to reflect real-world practice, precluding direct ticagrelor–prasugrel comparisons.

Conclusions

Very early aspirin withdrawal after PCI for ACS is associated with increased rates of ischaemic events or death compared with DAPT within the first 30 days, whereas this difference attenuates thereafter up to 1 year. Bleeding events were less frequent with monotherapy throughout the 1-year follow-up period. Given the excess ischaemic risk observed with monotherapy during the early post-procedural period, these findings do not support very early aspirin discontinuation following PCI. Transitioning DAPT to potent $P2Y_{12}$ inhibitor monotherapy appears to be a safe strategy after 30 days from stenting for ACS, though the optimal minimum duration of DAPT remains to be determined.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

Deidentified data from this study are available upon reasonable request for specific research purposes. Investigators seeking access must submit a brief study protocol or rationale outlining their proposed analyses, which will be subject to review and approval by the steering committee. Following committee approval, data will be provided according to the mechanisms outlined in the proposal. Additionally, approval from Brazilian regulatory agencies is required before data can be shared.

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Ethical Approval

Ethical approval was obtained at each participating site.

Pre-registered Clinical Trial Number

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