SUPPLEMENTARY DATA

SUPPLEMENTARY METHODS 1. INCLUSION AND EXCLUSION CRITERIA

1.1 Inclusion criteria (all of the following):

- Age ≥ 18 years.
- Patients discharged alive after an index acute coronary syndrome (ACS) hospitalization.
- Patients discharged on dual antiplatelet therapy (DAPT) for at least 12 months, combining low-dose aspirin (75–100 mg/day) and a $P2Y_{12}$ receptor inhibitor, either clopidogrel or ticagrelor.

1.2 Exclusion criteria (any of the following):

- Age < 18 years.
- Subjects who died during the index admission.
- Hypersensitivity or contraindication to ticagrelor, clopidogrel or aspirin.
- Patient discharged without a $P2Y_{12}$ inhibitor, or on prasugrel-based DAPT.
- Need for chronic oral anticoagulation therapy at hospital discharge, or use of strong cytochrome P-450 3A inhibitors or inducers at any time.
- History of major bleeding within 6 months before the index admission.
- History of brain arteriovenous malformation, or previous intracranial hemorrhage (ICH) at any time.
- Cancer diagnosis within the 3 years preceding the qualifying admission.
- Known severe liver disease.
- Failure to obtain informed consent from participants.
- Any condition or diagnosis which in the opinion of the investigator would make patients less likely to be prescribed a more potent antiplatelet agent (e.g., frailty, dementia…).
- Patients lost-to follow-up, or with missing data for any reasons.
- Diagnosis other than ACS at hospital discharge (i.e., acute myocarditis, Takotsubo syndrome, pulmonary embolism, acute aortic syndrome…).
- Index myocardial infarction (MI) secondary to an ischemic imbalance (namely type 2 MI according to the third universal definition) in instances of myocardial injury with necrosis.

SUPPLEMENTARY METHODS 2. ADDITIONAL INFORMATION ON METHODS

2.1 Definition of Study Endpoints

Major Adverse Cardiac Events (MACE). Composite of all-cause mortality, non-fatal MI, non-fatal stroke, urgent target lesion revascularization (uTLR), or definite stent thrombosis (ST) up to 1 year after ACS.

- **All-cause mortality:** broken down by three broad categories according to the cause of death
  - **Cardiovascular (CV) death**, defined as cardiac and vascular death. Cardiac death includes any fatal event due to proximate cardiac cause due to MI, sudden cardiac (including unwitnessed) death, heart failure, or those related to cardiac procedures. Vascular death includes deaths from noncoronary vascular causes, such as cerebrovascular disease, bleeding of cardiovascular origin, pulmonary embolism, or other vascular causes (e.g., peripheral artery disease, and acute aortic syndromes).
  - **Non-cardiovascular death**, defined as those deaths with a specific cause that is not thought to be CV in nature.
  - **Unknown death**, deaths of undetermined cause are defined as a death not attributable to any other category because of the absence of any relevant source documents following a complete and thorough clinical investigation. Such fatal events are classified, by consensus, as "CV death" for endpoint determination.
- **Myocardial infarction**: defined according to the Third Universal definition of MI as the occurrence of a spontaneous MI due to a primary coronary event related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries, leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis (type 1), or MI caused by either PCI (type 4a), stent restenosis (type 4c), or cardiac surgery (type 5).
- **Stroke**: defined in the presence of symptoms, pathological or neuroimaging evidence of acute newly onset focal neurologic deficit last for more than 24 hours, resulting from a presumed sudden abnormality of the blood supply after excluding other non-ischemic reasons.
- **Urgent target lesion revascularization**: any clinically-driven, non-elective repeated percutaneous or surgical revascularization of the target lesion performed for restenosis or other related complication.
- **Definite stent thrombosis**: defined in the presence of symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation of stent thrombosis, according to the Academic Research Consortium (ARC) classification.

2.2 Exposure and Outcome Ascertainment

Exposure Ascertainment

Medication adherence was measured at regular time intervals after hospital discharge, irrespective of clinical status, using relevant information extracted from a centralized Electronic Drug Prescription and Dispensation Registry (EDPR) that connects doctor's offices and pharmacies in real time. This database serves as an electronic prescription monitoring tool, which provides instant access to the patient's medication fill history. For the present analysis, DAPT exposure was defined by a prescription fill in the EDPR for clopidogrel or ticagrelor within first 7 days after hospital admittance. Adherence was calculated based on prescription fill dates and days' supply assuming an intended 12-month course of DAPT. To this end, we estimated the cumulative drug exposure for ticagrelor and clopidogrel from the date of hospital admission until time of death, drug discontinuation, drug switching, or censoring, establishing DAPT adherence status (as a time-varying categorical covariate) at different time points throughout the study period according to the "on-treatment" principle (i.e., based on the $P2Y_{12}$ inhibitor actually received, or that previously discontinued before that time point). Accordingly, medication adherence was estimated as a continuous scale covariate by means of the **medication possession ratio (MPR)**,[1] defined as the proportion of a time period where a medication supply is available divided by the total number of days in the observation time period (expressed as a percentage), according to the formula bellow:

$$\text{MPR (\%)} = \left(\frac{\text{Sum of days´ supply for all fills in period}}{\text{Total number of days in period}} \right) \text{x } 100$$

Outcome Assessment

As an investigator-initiated branch of **ARIAM-Andalucía** registry (Analysis of Delay in Acute Myocardial Infarction in Andalucía), for the **CREA** (CRuce Entre Antiplaquetarios, NCT02500290) registry over 150 predefined variables regarding patient demographics, baseline comorbidities, clinical presentation, laboratory, electrocardiographic, cardiac imaging and angiographic features, procedural characteristics, medication use, and clinical outcomes, were prospectively captured during the index admission through a standardized electronic case report form (eCRF). After hospital discharge, study data was captured during the outpatient follow-up visits scheduled at the time of hospital discharge according to local protocols. Specifically, for the current analysis data were prospectively tracked by semi-structured telephone interviews with patients or relatives planned at 1, 6 and 12 months after discharge. These included a questionnaire specifically designed for capturing relevant information regarding modes,

reasons and timing of non-adherence to prescribed medications, as well as any clinical event, outpatient visit or hospital readmission that occurred during the course of the study.

Previous being put forward for formal adjudication, self-reported information from patients underwent an extensive validation process. Data validation was performed manually by comprehensive review of any information source from electronic medical records (EMRs), primarily hospital and outpatient clinic files, and, if necessary, from general practitioner, or pharmacy records. All clinical events ultimately underwent formal blinded adjudication, in relation to DAPT exposure status at that time, according to the "on-treatment" principle (i.e., accounting for the temporal precedence of the exposure and the outcome) by consensus of two experienced investigators, that were blinded to calendar year and $P2Y_{12}$ inhibitor exposure, using original anonymized adjudication packs. Random IDs generation ensured the blinded adjudication sequence. Discrepancies were resolved through a consensus discussion with a third consultant cardiologist not involved in the study. The study´s coordinating center at Hospital Universitario Virgen Macarena (Seville, Spain) served as the central coordination site for event adjudication. If deemed necessary vital status and specific causes of death were obtained from the National Civil Registry and Death Certificates Records, respectively. After formal adjudication of clinical endpoints paying careful attention to correct exposure classification, study data were definitely incorporated into a web-based database platform with password protected files for further analysis.

2.3 Time-updated ICPW-adjusted Cox Regression Models

The extended Cox regression model

In prospective cohort studies, when the exposure varies as a function of time during the follow-up period, independent of failure time (namely, time-to-event), such exposure is called "time-dependent," "time-varying," or "time-updated".[2] Therefore, given the time-varying nature of medication adherence in clinical practice, for the current analysis we fitted multivariate time-updated Cox regression models to estimate the causal effect of DAPT cessation (as a time-varying covariate) on the outcome (MACE).

As is often the case in real world settings, medication adherence is frequently related to the outcome of interest independently of the exposure itself. However, this would lead to problems with data interpretation if non-adherence is also related to specific side effects of the medication under evaluation, thus leading to differential non-adherence rates between treatment groups. This phenomenon becomes

more pronounced in the presence of **time-dependent confounding** (i.e., confounders that predict both the subsequent exposure and the outcome, but are also affected by past exposure). On the other hand, standard survival analysis techniques assume independence between time to event and censoring time, and then say that censoring is non-informative (i.e., the probability of being censored is the same for all subjects at risk irrespective of exposure and outcome). Conversely, when the probability of being censored is unevenly distributed across all subjects at risk, we say that censoring is informative. Therefore, **informative censoring** may occur when time to event and time to censoring are dependent, either directly or through covariates (confounders). In the latter case, when dependence is induced through covariates that may influence both the occurrence of the event and censoring, this particular type of informative censoring is called **dependent censoring**. In order to account for issues generated when non-compliance occurs in a no-random fashion (differential medication non-adherence) several methods have been proposed in the literature.[3]

The inverse probability of censoring weighting (IPCW) method

When dependent censoring or time-dependent confounding are present, the extended Cox regression model, whether properly adjusting or not for fixed and time-varying confounders, may produce biased effect estimates.[4,5] In this context, the inverse probability of censoring weighting (IPCW) approach was initially proposed to deal with dependent censoring introduced by non-adherence with study drug in randomized clinical trials.[6] This method provides an unbiased estimator of censoring distribution conditional on covariates when censoring is not random, but rather depends on covariates and time. It is noteworthy, however, that such methodological issues have long been neglected and systematically ignored in previous studies on the topic. By contrast, in this study we extend the standard time-updated Cox model to similarly handle time-varying exposures and time-dependent confounding introduced by treatment switching, including a robust IPCW estimator (resembling a marginal structural Cox model).[5] This approach allows estimation of the causal associations between DAPT exposure and outcome responses in the presence of **time-dependent confounding**, and subsequent selection bias due to **dependent censoring**.[7]

In brief, the IPCW approach is a time-varying exposure analysis, such that, in the case at hand, patients are artificially censored at the time of switching the $P2Y_{12}$ inhibitor initially prescribed at hospital discharge. Then, to adjust for potential selection bias induced by this "artificial censoring", from the time-

point of switching the remaining observations are weighted inversely proportional to the estimated probability of remaining uncensored (i.e., the probability of remaining adherent to the initial $P2Y_{12}$ inhibitor) up to the end of follow-up, conditional on baseline and time-varying covariates. Therefore, this method corrects for censored subjects by giving extra weight to those who remain at risk (uncensored) with similar characteristics to the ones that are censored. The key component in the IPCW approach are the estimated weights that later will be introduced into the survival models to control for such type of informative bias. Furthermore, to account for additional variability introduced by estimating the censoring weights, the models also included a cluster-robust variance estimator. It should be noted that such censoring weights should be estimated under the assumptions of "no unmeasured confounders" and correct model specification.

Estimation of stabilized censoring weights

To obtain the censoring weights according to IPCW method, the likelihood of remaining uncensored (i.e., do not change the assigned $P2Y_{12}$ inhibitor at hospital discharge) was estimated by means of two separate Cox regression models. The first model used only baseline covariates (namely, time-invariant predictors), while the second one was fitted both for baseline and time-varying covariates to estimate the probability of changing the exposure status over time. Importantly, in the case at hand censoring probabilities need to be generated for each $P2Y_{12}$ inhibitor separately, since drug switching was expected to be not random, but rather likely to be attributable to factors that could vary over time depending upon previous exposure, the comorbidity burden, or the occurrence of the outcome of interest (i.e., time-varying confounder).

Specifically, for IPCW it is recommended to use "stabilized weights" to reduce the variance of the effect estimate.[7] To this end, stabilized censoring weights for each person-time interval were derived by the ratio of the estimated censoring probability that each patient remained uncensored conditional on time and past treatment (i.e., the estimated probabilities from the model without covariates), divided by the probability that the patient had not switched the initial $P2Y_{12}$ inhibitor given time, past treatment, and both baseline and time-varying covariates. The list of baseline and time-dependent covariates used in the calculation of the stabilized weights to obtain robust IPCW estimators for clopidogrel and ticagrelor exposures are depicted below:

- **Predictors of change in clopidogrel exposure status due to switching:**

- Baseline covariates: calendar year, age (continuous variable), sex, history of stroke, chronic kidney disease, or anemia, previous bleeding, previous myocardial infarction, ACS type, CRUSADE score (continuous variable), GRACE score (continuous variable), management strategy for index ACS, and presence of multivessel disease.
- Time-varying covariates: change in outcome status during follow-up, either because of a recurrent ischemic event (MI, ST, or unplanned TLR), or a major bleeding (BARC type 3 or 5).

• **Predictors of change in ticagrelor exposure status due to switching:**

- Baseline covariates: calendar year, age (continuous), sex, history of stroke, chronic obstructive pulmonary disease, chronic kidney disease, or anemia, previous bleeding, previous myocardial infarction, ACS type, CRUSADE score (continuous), GRACE score (continuous), management strategy for the index ACS, and the presence of multivessel disease.
- Time-varying covariates: occurrence of dyspnea, the need for surgery, initiation or oral anticoagulation, occurrence of a recurrent ischemic event, or a major bleeding during follow-up.

Multivariate Cox regression modelling

The stabilized weights were incorporated into the time-updated Cox models in order to estimate the measures of association between the exposure (entered as a time-varying categorical variable: DAPT cessation/no cessation) and outcome over time. As previously mentioned, the participating hospitals were entered as a random cluster-effect variable to account for variability in clinical performance across centers, and that introduced by the calculation of the stabilized weights. The survival models were fitted for each clinical outcome accounting for significant predictors in the univariate analysis that showed association with the outcome, and those identified as potentially relevant based on clinical experience, or the previous literature.

Prior to be included into the models, the best fitting functional form of continuous predictors was explored using the multivariable fractional polynomials approach proposed by Sauerbrei et al.,[8] which combines the selection of important variables with the determination of functional form for continuous predictors. The modelling process comprised a stepwise approach with a threshold set at $P < .10$ for entering and $P > .05$ for removing variables from the model. The final regression model was selected by minimizing the Akaike information criterion (AIC) and Bayesian information criterion (BIC), and accounting for multicollinearity (variance inflation factor, VIF; tolerance) to achieve the most parsimonious model while retaining the highest level of explanatory ability. Accordingly, to prevent overfitting as much as

possible, models were adjusted to cope with the general rule of thumb that there should be at least 10 events for each predictor variable (EPV) entered the regression models ("one-in-ten" rule). Therefore, whenever possible the CRUSADE and GRACE scores measured at admission were included as continuous covariates into the survival models to avoid potential overfitting. Model assumption was evaluated using Schoenfeld residuals. Discrimination and calibration of the resulting models was assessed by the c-statistic and calibration slope, respectively. For each outcome, multivariate models with DAPT cessation entered as a time-varying covariate were fitted for baseline (time-independent) and time-varying covariates as follows:

- **Primary Endpoint**

MACE: The main-effect models for MACE were fitted for any DAPT cessation, and for each predefined pattern of non-adherence separately according to the mode, timing and choice of $P2Y_{12}$ inhibitor at the time of DAPT cessation, whenever no strong multicollinearity for the main-effect, and no evidence of a lack of goodness-of-fit was found in each model.

	Time-updated IPCW Cox regression models			
Primary Endpoint (MACE)	**Any DAPT cessation**	**Mode of cessation**	**Timing of cessation**	**$P2Y_{12}$-i choice**
observed events/ covariates included events per variable	218/15 15:1	218/12 18:1	218/13 16:1	218/14 16:1
Baseline covariates (fixed)				
Age (per 10-year increase)	✓	✓	✓	✓
Diabetes	✓	✓	✓	✓
Peripheral artery disease	✓	collinearity	collinearity	✓
Heart failure	✓	collinearity	collinearity	collinearity
Prior myocardial infarction	✓	✓	✓	✓
Cancer	✓	✓	✓	✓
CRUSADE score (per 10-point increase)	✓	✓	✓	✓
GRACE score (per 10-point increase)	✓	✓	✓	✓
LVEF at discharge (per 10%-increase)	✓	✓	✓	✓
Multivessel disease	✓	✓	✓	✓
Complete revascularization	✓	collinearity	✓	✓
Stent type (DES/BMS)	collinearity	collinearity	✓	collinearity
Time-varying covariates				
$P2Y_{12}$ inhibitor (ticagrelor/clopidogrel)	✓	✓	✓	✓
Mode of cessation (discontinuation/disruption)	collinearity	✓	collinearity	✓
Timing of cessation (<90 / >90 days)	✓	✓	✓	✓
Major bleeding (after discharge)	✓	✓	✓	✓

BMS, bare metal stent; DES, drug eluting stent; LVEF, left ventricular ejection fraction

- **Secondary Endpoints**

MACE-2: For the more restrictive definition of the secondary composite endpoint, the main-effect models were fitted for any DAPT cessation, and for each predefined mode of cessation separately:

	Time-updated IPCW Cox regression models	
Secondary Endpoint (MACE-2)	**Any DAPT cessation**	**Mode of cessation**
observed events/ covariates included events per variable	150/10 15:1	150/9 17:1
Baseline covariates (fixed)		
Age (per 10-year increase)	✓	✓
Diabetes	collinearity	collinearity
Peripheral artery disease	✓	collinearity
Heart failure	collinearity	collinearity
Previous myocardial infarction	✓	✓
Cancer	✓	✓
CRUSADE score (per 10-point increase)	✓	✓
GRACE score (per 10-point increase)	collinearity	collinearity
LVEF at discharge (per 10%-increase)	collinearity	✓
Multivessel disease	✓	✓
Complete revascularization	collinearity	collinearity
Stent type (DES vs BMS)	✓	collinearity
Time-varying covariates		
$P2Y_{12}$ inhibitor (ticagrelor/clopidogrel)	✓	✓
Mode of cessation (discontinuation/disruption)	collinearity	✓
Timing of cessation (<90 days / >90 days)	collinearity	collinearity
Major bleeding (after discharge)	✓	✓

BMS, bare metal stent; DES, drug eluting stent; IPCW, inverse probability of censoring weighting; LVEF, left ventricular ejection fraction

Individual components of MACE: Given the relatively small number of events for some individual components of the primary composite endpoint, to prevent overfitting as much as possible, models were adjusted to cope with the general "one-in-ten" rule of thumb that there should be at least 10 events for each predictor variable (EPV) entered the regression models. This rule was relaxed in the case of non-fatal stroke, after excluding intracranial hemorrhages and secondary hemorrhagic transformation of ischemic stroke. Therefore, the distribution of EPV for the models evaluating each component of MACE was as follows: all-cause death (105 events, 10 covariates; EPV 10:1), non-fatal MI (84 events, 8 covariates; EPV 10:1), non-fatal stroke (27 events, 3 covariates; EPV 9:1); and urgent TLR (49 events, 5 covariates; EPV 10:1); definite stent thrombosis (40 events, 4 covariates 4; EPV 10:1).

- **Predictors of DAPT cessation**

Predictors of premature cessation of DAPT were assessed using multivariate time-updated Cox regression models, with linearity of continuous predictors and log-hazard tested using the multivariate fractional polynomial (FP) approach. As a result, nonlinear transformation was required for CRUSADE score only, which entered the models as the best-fitting second-degree FP transformation. However, this covariate was excluded from the final model because of collinearity.

Diagnostics of the time-varying Cox regression models

	c-statistic (95%CI)	Calibration slope (95%CI)	Information criterion (AIC/BIC)	Multicollinearity (VIF /Tolerance)*
Primary endpoint (MACE)				
Any DAPT cessation	0.80 (0.75-0.85)	1.00 (0.95-1.05)	3166 / 3178	1.17 / 0.88
Modes of cessation †	0.74 (0.71-0.78)	0.92 (0.90-0.95)	3165 / 3177	1.25 / 0.83
Timing of cessation ‡	0.75 (0.72-0.78)	1.01 (0.99-1.02)	3150 / 3162	1.32 / 0.80
$P2Y_{12}$ inhibitor §	0.75 (0.71-0.79)	0.96 (0.94-0.99)	2873 / 2884	1.29 / 0.82
Secondary endpoints				
Any DAPT cessation				
MACE-2 #	0.72 (0.67-0.76)	0.95 (0.90-1.00)	2200 / 2211	1.16 / 0.94
All-cause death	0.86 (0.83-0.89)	1.02 (0.97-1.07)	1480 / 1491	1.06 / 0.93
Myocardial infarction	0.75 (0.70-0.81)	0.99 (0.98-1.00)	1176 / 1187	1.27 /0.92
Stroke	0.81 (0.72-0.92)	1.02 (0.67-1.30)	377 / 382	1.35 /0.80
uTLR	0.70 (0.63-0.77)	0.99 (0.88-1.10)	712 / 718	1.41 / 0.78
Definite stent thrombosis	0.61 (0.58-0.70)	0.97 (0.72-1.08)	596 / 608	1.17 / 0.87
Modes of cessation †				
MACE-2 #	0.71 (0.68-0.74)	0.94 (0.89-0.99)	2195 / 2206	1.06 / 0.95
All-cause death	0.85 (0.82-0.88)	1.02 (0.99-1.04)	1488 / 1499	1.06 / 0.94
Myocardial infarction	0.74 (0.69-0.80)	1.04 (0.88-1.20)	1186 / 1198	1.25 / 0.83
Stroke	0.82 (0.74-0.99)	0.82 (0.58-1.08)	360 / 372	1.45 / 0.77
uTLR	0.72 (0.65-0.79)	1.04 (0.99-1.09)	698 / 710	1.18 / 0.87
Definite stent thrombosis	0.74 (0.69-0.80)	1.04 (0.88-1.20)	1186 / 1198	1.25 / 0.83
Predictors of DAPT cessation				
Any cessation	0.77 (0.74-0.81)	1.00 (0.88-1.05)	2477 / 2458	2.58 / 0.75

* mean values
† physician-guided discontinuation/ disruption
‡ early (< 90 days)/ late (> 90 days) cessation
§ ticagrelor/ clopidogrel
# composite of cardiac death, non-fatal myocardial infarction, uTLR, or definite stent thrombosis

AIC, Akaike criterion information; BIC, Bayesian criterion information; CI, confidence interval; DAPT, dual antiplatelet therapy, MACE, major adverse cardiac event; uTLR, urgent target lesion revascularization; VIF, variation inflation factor.

2.4 Subgroup Analysis

We further tested the impact of premature DAPT cessation on MACE risk across the predefined non-adherence categories according to the mode and timing of cessation, stratified by type of $P2Y_{12}$ inhibitor. For subgroup analysis, multiplicative interaction terms were included one at a time into the multivariable models, and adjusted HR with 95%CI were derived for each category across subgroups with no cessation of DAPT as the reference category. The interaction effect between each subgroup and DAPT cessation was estimated in the time-updated Cox regression models using a formal (Wald) test for interaction not adjusted for multiplicity.

We observed that for MACE risk, there was a significant time-varying interaction between the mode of cessation and the choice of $P2Y_{12}$ inhibitor, such that the thrombotic risk after DAPT disruption was significantly higher with ticagrelor than with clopidogrel, particularly within the first 90 days after the index ACS. However, given the differential rate of non-adherence by the choice of $P2Y_{12}$-inhibitor, coupled with the significant impact of DAPT duration on the outcome, we hypothesized that the disproportionate excess of thrombotic risk after disruption of DAPT with ticagrelor compared with clopidogrel, would be largely explained by the shorter observed courses of DAPT after ticagrelor disruption, rather than a potential rebound effect resulting from the reversibility of receptor binding and fastest offset after its interruption compared with clopidogrel.

2.5 Sensitivity analysis

A set of sensitivity analysis were performed to access the robustness of primary analysis.

The Royston-Parmar flexible parametric survival model

The time-updated Cox regression models with time of DAPT cessation discretized into early and late non-adherence, revealed a significant increased risk of MACE after early disruption of ticagrelor compared with clopidogrel. In the light of these findings, together with the significant negative effect of exposure time on the outcome, we further examine whether the effect of DAPT cessation on MACE risk varied by type of $P2Y_{12}$ inhibitor as a continuous function of DAPT duration in time. To this end, we used the Royston-Parmar flexible parametric survival model with DAPT cessation entered as a time-varying covariate (using restricted cubic splines functions with 4 degrees of freedom and 3 internal knots placed at 30, 90 and 180 days), and DAPT duration (as a corollary of exposure time) modelled as a continuous covariate using the

best fitting second-degree fractional polynomial transformation to preserve the continuous nature of data, while accounting for non-linearity on the log hazard function. Within this analytical framework, interaction terms between the mode and time of cessation were included into the models one at a time. Therefore, for each pattern of non-adherence the effect of the corresponding treatment-by-time interaction on MACE risk was graphically represented using duration-response relationship curves, with the response indicating the occurrence of a discrete event in time.

In the case at hand, the duration-response curves describe on y-axis the magnitude of effect (i.e., the relative point estimate or hazard ratio) on MACE risk of DAPT cessation with ticagrelor versus clopidogrel, as a continuous function of DAPT duration (as a subrogate of cessation time) plotted on x-axis. Therefore, in spline analysis the findings for both patterns of non-adherence to DAPT with ticagrelor versus clopidogrel echoed those shown for any DAPT cessation over time. In addition, this analysis revealed no signal of a time-varying interaction between the mode of cessation and $P2Y_{12}$ inhibitor therapy on MACE risk at any DAPT duration strata.

Statistical Assessment of Additive Interaction Effect

Moderation effect of DAPT cessation on MACE risk by the interaction between the mode of cessation and $P2Y_{12}$ inhibitor status on the additive scale, was assessed by the relative excess risk due to interaction (RERI) and the attributable proportion (AP) due to interaction measures,[9] using the hazard ratios derived from the time-updated Cox models, including the interaction terms, according to the formulas below:

$$RERI = HR_{11} - HR_{10} - HR_{01} + 1\ (HR_{00}) \qquad \textit{[equation 1]}$$

$$AP = \frac{RERI}{HR_{11}} = \frac{HR_{11} - HR_{10} - HR_{01} + 1}{HR_{11}} \qquad \textit{[equation 2]}$$

where HR_{11}, HR_{10} and HR_{01} are the derived hazard ratios for the $P2Y_{12}$ inhibitor-by-cessation mode interaction, and the main-effect for cessation mode, and type of $P2Y_{12}$ inhibitor stopped, respectively. Continuation of antiplatelet regimen 1-year post-ACS is set as the reference category ($HR_{00} = 1$)

The RERI can be interpreted as the part of the hazard ratio that is due to an additive interaction between two factors, in this particular case, the joint effects of the mode and the choice of $P2Y_{12}$-inhibitor at the

time of DAPT cessation. Likewise, the AP is essentially a derivative measure of RERI, representing the percentage of the effect (i.e., the proportion of MACE) in the exposed group (i.e., the DAPT cessation cohort) that can be attributed to the interaction between the mode of cessation and the $P2Y_{12}$-inhibitor class. Both RERI and AP metrics indicate positive interaction when the estimate is greater than zero and negative interaction when the estimate is less than zero. An estimate of zero for the RERI and AP indicates no interaction. The RERI can range from negative infinity to positive infinity. Negative, zero and positive RERI and AP values indicate sub-additivity, exactly additivity and super-additivity, respectively. The Hosmer–Lemeshow delta method was employed to compute the 95%CIs for each RERI and AP estimate. In an additive scale framework, if the upper limit of the 95%CI around RERI or AP is less than 0, then the combined effect is considered to be sub-additive (i.e. negative interaction or antagonism in the additive scale). If the 95%CI around RERI or AP included 0, then the joint effect is considered to be additive (i.e. additivity of independent effects). If the lower limit of the 95%CI around RERI or AP exceeds 0, then the joint effect is considered to be super-additive (i.e. positive interaction or synergism).

SUPPLEMENTARY TABLES

Table 1 of the supplementary data. Baseline characteristics of patients according to dual antiplatelet therapy cessation pattern

	No cessation (n = 2006)	Physician-guided (n = 126)	Disruption (n = 48)	*P* value *
Age, years	63 (54-73)	69 (58-78)	71 (59-78)	.968
≥ 75 years	435 (21.7)	45 (35.7)	14 (29.2)	.415
Sex, Female	532 (26.5)	40 (31.7)	9 (18.8)	.080
Body mass index, kg/m^2	27.7 (4.3)	27.4 (4.5)	27.6 (5.2)	.909
Medical history				
Current smoker	834 (41.6)	46 (36.5)	17 (35.4)	.894
Hypertension	1131 (56.5)	76 (53.2)	36 (75.0)	.071
Diabetes mellitus	623 (31.0)	40 (31.7)	16 (33.3)	.841
Hyperlipidemia	894 (44.6)	67 (53.2)	23 (48.0)	.535
Peripheral arterial disease	108 (5.4)	5 (4.0)	7 (14.6)	**.014**
Chronic obstructive pulmonary disease	114 (5.7)	13 (10.3)	4 (8.3)	.694
Chronic kidney disease	124 (6.2)	12 (9.5)	9 (18.7)	.095
Dialysis	32 (1.6)	1 (0.8)	3 (6.3)	**.032**
History of atrial fibrillation	54 (2.7)	8 (6.3)	1 (2.1)	.256
Myocardial infarction	289 (14.4)	18 (14.3)	12 (25.0)	.094
Percutaneous coronary intervention	295 (14.7)	17 (13.5)	10 (21.0)	.232
Coronary artery bypass grafting	43 (2.0)	3 (2.4)	1 (2.1)	.907
Stroke	142 (7.1)	13 (10.3)	4 (8.3)	.694
History of heart failure	99 (4.9)	8 (6.3)	1 (2.1)	.256
Previous bleeding	47 (2.3)	13 (10.3)	3 (6.3)	.407
Anemia	62 (3.0)	9 (7.1)	5 (10.4)	.478
Cancer †	36 (1.8)	1 (0.8)	2 (4.2)	.127
Clinical presentation				
Non-ST-segment elevation ACS	757 (37.7)	45 (35.7)	25 (52.0)	**.049**
Non-ST-segment elevation MI	672 (33.5)	39 (31.0)	20 (41.6)	**.035**
Unstable angina	85 (4.2)	6 (4.8)	5 (10.4)	
ST-segment elevation MI	1249 (62.3)	81 (64.3)	23 (48.0)	**.049**
Killip class ≥ 2	228 (11.5)	16 (12.7)	11 (23.0)	.096
CRUSADE score	24 (14-38)	31 (21-40)	34 (19-51)	.283
GRACE score	136 (113-161)	137 (116-170)	152 (123-176)	.257
Creatinine clearance, ml/min/1.73 m^2	85 (60-110)	75 (53-97)	72 (41-100)	.322
Left ventricular ejection fraction, %	52.0 (10.8)	52.0 (11.7)	54.0 (12.0)	.389

Data summarized as mean (SD), median (IQR) and n (%). Bold font indicates statistical significance at $P < .05$
* *P* values for comparison between physician-guided discontinuation and disruption
† Diagnosis of cancer more than 3 years before the index ACS
ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction.

Table 2 of the supplementary data. Procedural characteristics, medication use and adherence by mode of cessation

	No cessation (n = 2006)	Physician-guided (n = 126)	Disruption (n = 48)	*P* value*
Procedural characteristics				
Radial artery approach	1331 (66.4)	79 (62.7)	30 (62.5)	.547
Culprit vessel				
Left main	74 (3.7)	1 (0.8)	1 (2.1)	.990
Left anterior descending	819 (40.8)	41 (32.5)	18 (37.5)	.537
Right coronary artery	671 (33.4)	47 (37.3)	17 (35.4)	.823
Left circumflex	335 (16.7)	20 (16.0)	7 (14.6)	.841
Graft	30 (1.5)	3 (2.4)	1 (2.1)	.907
MINOCA	50 (2.5)	10 (7.9)	2 (4.2)	.380
Multivessel disease †	925 (46.0)	51 (40.5)	26 (54.0)	.104
PCI complexity ‡	467 (46.6)	20 (39.2)	9 (34.6)	.698
Number of stents implanted (per patient)	1.6 (1.2)	1.3 (1.1)	1.3 (1.3)	.971
Complete revascularization #	542 (58.6)	23 (45.2)	14 (53.8)	.119
Glycoprotein IIb/IIIa inhibitors	225 (11.2)	14 (11.0)	4 (8.3)	.591
Management strategy ‖				
PCI, any	1809 (90.2)	99 (78.5)	41 (85.4)	.311
Drug-eluting stent	1576 (87.0)	71 (71.7)	31 (75.6)	.337
CABG surgery	47 (2.3)	4 (3.2)	3 (6.3)	.356
Conservative (Medical treatment only)	154 (7.6)	25 (19.8)	5 (10.4)	.418
Medication use/DAPT adherence				
β-Blocker	1745 (87.0)	102 (81.0)	38 (79.2)	.791
Statin	1942 (97.0)	118 (93.7)	46 (95.8)	.580
RAAS blocker	1806 (92.7)	104 (82.5)	38 (79.2)	.608
Proton-pump inhibitor	1548 (77.2)	84 (66.7)	36 (75.0)	.288
$P2Y_{12}$ inhibitor				.218
Ticagrelor	1018 (50.7)	40 (31.7)	20 (41.6)	
Clopidogrel	988 (49.3)	86 (68.3)	28 (58.4)	
Duration of DAPT, days	365 (365-375)	220 (104-332)	156 (74-	**.024**
Medication possession ratio (1-year), %	0.86 (0.13)	0.68 (0.29)	0.46 (0.30)	**.018**

Data summarized as mean (SD), median (IQR), and n (%). Bold font indicates statistical significance at $P < .05$

* Physician-guided discontinuation *vs* DAPT disruption

† Multivessel disease defined as at least two major vessels (≥ 2 mm diameter) from a different territory with lesions deemed angiographically significant (≥ 50% stenosis of the left main stem, ≥ 70% stenosis in other major coronary vessel, or 30% to 70% stenosis with fractional flow reserve ≤ 0.8)

‡ PCI with at least one of the following characteristics: 3 vessels treated, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation with 2 stents implanted, total stent length >60 mm, treatment of chronic total occlusion, unprotected left main PCI, or bypass graft PCI

For patients with multivessel disease

‖ Percentages do not sum to 100% because some patients (n = 7) underwent CABG following PCI for the index ACS

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; MINOCA; myocardial infarction with non-obstructive coronary arteries; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone system

Table 3 of the supplementary data. Relative rates and timing of early and late non-adherence to DAPT stratified by mode and underlying reasons for cessation

Modes and reasons for DAPT cessation	n (%)	Timing of cessation* (Duration of DAPT, days)	*P* value †
Any cessation	174 (8.3)	204 (96-321)	
Early discontinuation (< 90 days)	42 (24.0)	53 (30-72)	**.043**
Physician-guided discontinuation	27 (64.3)	54 (32-64)	
Perceived risk ‡			
High bleeding risk + Low ischemic risk	2 (7.5)	41 (38-41)	
Low ischemic risk	5 (18.5)	62 (53-84)	
High bleeding risk	9 (33.3)	60 (55-86)	
Surgery or invasive procedures	7 (26.0)	40 (16-73)	
Oral anticoagulation	1 (3.7)	30	
Unspecified (personal preferences)	3 (11.0)	33 (16-33)	
DAPT disruption	15 (35.7)	50 (28-74)	
Patient non-compliance	4 (26.6)	**29 (11-80)**	
Bleeding event	11 (73.4)	53 (30-74)	
Late discontinuation (90-365 days)	132 (76.0)	260 (182-340)	.117
Physician-guided discontinuation	99 (75.0)	285 (185-340)	
Perceived risk ‡			
High bleeding risk + Low ischemic risk	12 (12.1)	317 (187-345)	
Low ischemic risk	32 (32.4)	321 (218-345)	
High bleeding risk	23 (23.3)	255 (182-339)	
Surgery or invasive procedures	12 (12.1)	242 (131-309)	
Oral anticoagulation	11 (11.1)	240 (150-300)	
Unspecified (personal preferences)	9 (9.0)	338 (155-345)	
DAPT disruption	33 (25.0)	239 (156-278)	
Patient non-compliance	5 (15.2)	187 (168-282)	
Bleeding event	27 (81.8)	243 (151-280)	
Side effects (dyspnea)	1 (3.0)	95	

Data expressed as n (%), and median (IQR).
Bold font denotes statistically significant results at $P < .05$

* Timing of DAPT cessation defined as the time interval from the index admission date until the end of persistent drug exposure, expressed as median and (IQR) days

† *P* values from non-parametric tests comparing the trend in DAPT duration across the predefined non-adherence categories according to the mode and underlying reasons for early and late DAPT cessation respectively. Differences in the time of cessation across non-adherence categories strata were statistically significant for early non-compliant disruption only (bold font)

‡ Perceived change in ischemic and bleeding risk profile over time according to the treating physician´s opinion

Abbreviations: DAPT, dual antiplatelet therapy; IQR, interquartile range

Table 4 of the supplementary data. Cumulative incidence and timing of DAPT cessation according to the predefined patterns of non-adherence stratified by type of $P2Y_{12}$ inhibitor

	DAPT cessation by type of $P2Y_{12}$ inhibitor *							
	All patients (n= 2180)		**Ticagrelor group (n= 1078)**		**Clopidogrel group (n= 1102)**			
Patterns of non-adherence to DAPT	**Incidence**	**Timing**	**Incidence**	**Timing**	**Incidence**	**Timing**	***P* value †** Incidence	Timing
Any cessation	174 (8.3)	204 (96-321)	60 (5.8)	203 (120-325)	114 (10.6)	190 (87-318)	**< .001**	.546
Physician-guided	126 (6.0)	220 (104-332)	40 (66.6)	240 (135-337)	86 (75.5)	205 (89-321)	**< .003**	.186
Disruption	48 (2.4)	156 (74-247)	20 (33.4)	160 (78-231)	28 (24.5)	141 (72-278)		.544
Early cessation (< 90 days)	42 (2.0)	53 (30-72)	11 (1.0)	56 (14-68)	31 (2.8)	53 (35-72)	**.003**	.800
Physician-guided	27 (1.2)	54 (32-64)	5 (45.4)	56 (55-64)	22 (71.0)	52 (32-62)	**.001**	.417
Disruption	15 (0.7)	50 (28-74)	6 (54.6)	22 (14-57)	9 (29.0)	53 (45-72)		**.035**
Late cessation (> 90 days)	132 (6.4)	260 (182-340)	49 (4.7)	240 (179-339)	83 (8.1)	275 (185-340)	**.003**	.628
Physician-guided	99 (4.8)	285 (185-340)	35 (71.4)	293 (180-339)	64 (77.0)	283 (185-340)	.416	.918
Disruption	33 (1.7)	239 (156-278)	14 (28.6)	203 (160-243)	19 (23.0)	248 (128-324)		.362

Data are the number and 1-year incidence of cessation events (from weighted Kaplan-Meier estimator). Non-adherence incidence for ticagrelor and clopidogrel cohorts across cessation modes strata expressed as the relative percentage of cessation events within each non-adherence category (namely, early and late DAPT cessation).

Timing of DAPT cessation expressed as the median and (IQR) time, in days, since the index ACS-related admission until time of permanent DAPT discontinuation (namely, DAPT duration). Bold font indicates statistical significance at P < .05.

* $P2Y_{12}$ inhibitor usage status ascertained at the time of DAPT cessation, or censoring for the non-adherent and adherent cohorts, respectively

† *P* values from tests comparing the incidence and timing of non-adherence to DAPT with ticagrelor *vs* clopidogrel according to the predefined patterns of cessation

ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; IQR, interquartile range

Table 5 of the supplementary data. Duration-response relationship for the association between DAPT cessation and MACE risk as a continuous function of DAPT duration in time, stratified by $P2Y_{12}$ inhibitor

	Duration of dual antiplatelet therapy *											
	< 30 days			30-90 days			90-180 days			180-365 days		
	aHR (95%CI)	*P* value	$P_{interaction}$ †	*aHR* (95%CI)	*P* value	$P_{interaction}$ †	aHR (95%CI)	*P* value	$P_{interaction}$ †	aHR (95%CI)	*P* value	$P_{interaction}$ †
Any cessation	1.18 (1.10-1.26)	**< .001**	**< .001**‡	1.10 (1.02-1.30)	**.019**		1.00 (0.96-1.05)	.713		0.98 (0.93-1.02)	.188	
Ticagrelor	1.25 (1.07-1.43)	**.005**	.456	1.13 (1.06-1.20)	**< .001**	.292	1.00 (0.90-1.12)	.890	.979	1.00 (0.99-1.02)	.185	.433
Clopidogrel	1.08 (1.05-1.11)	**< .001**		1.04 (1.00-1.08)	**.044**		1.00 (0.98-1.03)	.410		1.01 (1.00-1.03)	.051	
Physician-guided	1.30 (1.25-1.38)	**< .001**	**< .001**‡	1.20 (1.00-1.46)	**.047**		1.02 (0.94-1.12)	.495		1.00 (0.98-1.02)	.476	
Ticagrelor	1.36 (1.11-1.67)	**.003**	.391	1.10 (1.06-1.15)	**.001**	.890	1.04 (0.99-1.08)	.076	.505	0.96 (0.80-1.20)	.880	.956
Clopidogrel	1.24 (1.21-1.29)	**< .001**		1.15 (0.75-1.35)	.570		0.95 (0.60-1.36)	.665		0.98 (0.70-1.36)	.908	
Disruption	1.35 (1.20-1.51)	**< .001**	**< .001**‡	1.27 (1.23-1.31)	**< .001**		1.13 (0.98-1.27)	.081		1.07 (0.97-1.16)	.085	
Ticagrelor	1.45 (1.22-1.71)	**< .001**	.204	1.23 (1.10-1.37)	**< .001**	.731	1.14 (1.06-1.24)	**.001**	.915	1.08 (0.92-1.27)	.349	.811
Clopidogrel	1.39 (1.25-1.53)	**< .001**		1.19 (1.00-1.42)	**.043**		1.13 (0.98-1.32)	.090		1.06 (0.89-1.26)	.487	

Bold font denotes statistical significance at $P < .05$

Table shows the results from the Royston-Parmar flexible parametric survival models (FPM) including an interaction term between DAPT cessation and exposure duration. Models were derived for each mode of cessation separately (entered as a categorical time-varying covariate) according to the last $P2Y_{12}$-inhibitor used prior to the event. To this end, the time-varying association between DAPT cessation and MACE risk was modelled using restricted cubic spline functions with 4 degrees of freedom (internal knots placed at 30, 90 and 180 days), with DAPT duration entered as continuous scale variable based on the best fitting second-degree fractional polynomial transformation. When modeling the response (i.e., MACE risk) after DAPT cessation as a function of exposure time (i.e., DAPT duration), we found a stepwise increase in the observed risk of MACE after drug cessation with decreasing durations of DAPT regardless of cessation mode and the $P2Y_{12}$-i choice. This risk was only evident within the first 90 days of treatment, and then attenuated with prolonged courses of treatment

* Data are time-varying adjusted hazard ratios (for every 10-day reduction in DAPT duration from standard 12-month course) for 1-year MACE with corresponding 95%CIs for each mode of cessation across different DAPT duration intervals, stratified by type of $P2Y_{12}$-i

† *P* value from formal tests for interaction between the mode of cessation and $P2Y_{12}$-i therapy as a function of DAPT duration (entered as continuous covariate) in time

‡ *P* value for trend in the adjusted risk of MACE associated with each cessation mode across the full spectrum of DAPT duration

aHR, adjusted hazard ratio; CI confidence interval; DAPT, dual antiplatelet therapy; FPM, flexible parametric model; MACE, major adverse cardiac events; $P2Y_{12}$-i, $P2Y_{12}$ inhibitor

Table 6 of the supplementary data. Analysis of additive interaction between DAPT cessation and the $P2Y_{12}$ inhibitor class on MACE risk

DAPT cessation patterns by $P2Y_{12}$ inhibitor type	Additive interaction measures			
	RERI * (95%CI)	***P* value**	**AP * (95%CI)**	***P* value**
Disruption ticagrelor *vs* clopidogrel	0.12 (-0.99–1.24)	.826	0.02 (-0.64–0.69)	.939
Physician-guided discontinuation ticagrelor *vs* clopidogrel	0.04 (-0.50–0.29)	.184	0.01 (-0.84–0.60)	.149
Early cessation ticagrelor *vs* clopidogrel	0.64 (0.18–1.20)	**.023**	0.48 (0.10–0.94)	**.035**
Late cessation ticagrelor *vs* clopidogrel	0.12 (-0.90–0.58)	.673	0.09 (-0.72–0.93)	.593

Bold font denotes statistically significant results at $P < .05$.

*Moderation analysis adjusted for CRUSADE and GRACE scores (both as continuous covariates), history of cancer, multivessel disease, complete revascularization for the index ACS, and LVEF at discharge.

On the basis of additive interaction measures between DAPT cessation and $P2Y_{12}$-i therapy, the relative excess risk of thrombotic events after disruption of ticagrelor *vs* clopidogrel was 12% (RERI 0.12, 95%CI -0.99–1.24), and after physician-guided discontinuation was 4% (RERI 0.04, 95%CI -0.50–1.24). Among the subjects treated with ticagrelor compared with those who received clopidogrel, approximately 2% of the subsequent risk of MACE after DAPT cessation was attributed to disruption (AP 0.02, 95%CI -0.64–0.69), and 1% to physician-guided discontinuation (AP 0.01). However, neither of these interaction measures between the mode of cessation and $P2Y_{12}$ inhibitor therapy were significant on the additive scale. Conversely, measures of additive interaction between the time course of DAPT cessation and $P2Y_{12}$ inhibitor class was statistically significant after early discontinuation of treatment (within 90 days after discharge). Accordingly, 64% (RERI 0.64) of the relative excess risk of MACE, and nearly half of the total number of thrombotic events (AP 0.48) after early DAPT cessation were attributable to the discontinuation of ticagrelor as compared to clopidogrel.

aHR, adjusted hazard ratio; AP, attributable proportion of interaction; CI, confidence interval; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; RERI, relative excess risk due to interaction.

Table 7 of the supplementary data. Adjusted risk of major adverse cardiac events associated with the different patterns of non-adherence to DAPT according to the PARIS registry *

	Patients	Events	aHR (95%CI) †	*P* value
	n	n (%)		
MACE	2180	218 (10.0)		
No Cessation	2006	188 (9.3)	Reference	
Physician-guided discontinuation	107	12 (11.2)	1.28 (0.91-1.80)	.141
Interruption	19	4 (21.5)	1.27 (0.89-1.83)	.232
Disruption	48	14 (29.8)	**1.35 (1.10-1.65)**	**.003**
MACE-2	2180	150 (7.0)		
No Cessation	2006	136 (6.8)	Reference	
Physician-guided discontinuation	107	4 (3.8)	1.09 (0.81-1.46)	.537
Interruption†	19	3 (15.5)	1.28 (0.87-1.90)	.203
Disruption	48	7 (16.2)	**1.33 (1.05-1.63)**	**.016**

Data are number of patients, and number of observed events (1-year incidence, %) of MACE from weighted Kaplan-Meier estimator. Boldface font indicates statistically significance at $P < .05$.

* According to the PARIS (Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients) registry, DAPT cessation was classified into physician-guided discontinuation, disruption for bleeding, or non-compliance, and interruption due to invasive procedures or the need for surgery

† Adjusted HRs with (95%CIs) from fully adjusted time-updated Cox regression models with doubly robust IPCW estimators and participating hospitals entered as a random-effects variable (cluster robust variance estimators)

MACE, composite of all-cause death, non-fatal MI, non-fatal stroke, uTLR, or definite ST

MACE-2, composite of cardiovascular death, non-fatal MI, uTLR, or definite ST

aHR, adjusted hazard ratio; CI, confidence interval; IPCW, inverse probability of censoring weighting; MACE, major adverse cardiac events; MI, myocardial infarction; uTLR, urgent target lesion revascularization; ST, stent thrombosis.

Table 8 of the supplementary data. Sensitivity analysis for the risk of major adverse cardiac events associated with the predefined patterns of non-adherence to DAPT in selected cohorts

	No Cessation	Any DAPT Cessation			Physician-guided Discontinuation			DAPT Disruption		
	n (%)	n (%)	aHR (95%CI)*	*P* value	n (%)	aHR (95%CI)*	*P* value	n (%)	aHR (95%CI)*	*P* value
Cohort #1 †										
MACE	185 (9.4)	29 (17.1)	1.41 (1.13-1.76)	**.002**	16 (12.7)	1.34 (0.97-1.87)	.075	13 (28.2)	1.43 (1.16-1.73)	**.001**
MACE-2	133 (6.7)	14 (8.5)	1.29 (1.05-1.59)	**.016**	7 (6.0)	1.17 (0.85-1.61)	.331	7 (16.3)	1.37 (1.07-1.75)	**.012**
Cohort #2 †										
MACE	170 (9.1)	27 (18.7)	1.33 (1.10-1.61)	**.002**	14 (13.8)	1.23 (0.99-1.52)	.058	13 (30.2)	1.39 (1.23-1.57)	**.001**
MACE-2	123 (6.7)	12 (8.6)	1.42 (1.02-1.90)	**.041**	6 (6.0)	1.20 (0.84-2.02)	.227	6 (15.2)	1.44 (1.03-2.04)	**.036**
Cohort #3 †										
MACE	158 (8.9)	26 (19.7)	1.45 (1.24-2.09)	**<.001**	14 (14.9)	1.47 (0.99-2.18)	.054	12 (31.6)	1.58 (1.19-2.10)	**.002**
MACE-2	123 (6.5)	12 (9.4)	1.57 (1.03-2.43)	**.040**	6 (6.6)	1.40 (0.86-2.46)	.185	6 (17.3)	1.64 (1.20-2.47)	**.016**

Boldface font indicates statistically significance at $P < .05$

Data are number and 1-year cumulative incidence (%) of MACE events from weighted Kaplan-Meier estimators

* adjusted HRs with (95%CIs) from fully adjusted time-updated Cox regression models with doubly robust IPCW estimators and participating hospitals entered as a random effects variable (robust variance estimators), among selected cohorts after exclusion of patients more likely to discontinue DAPT during the follow-up to account for reverse causality

† Cohort #1: (n = 2,133) after excluding patients who underwent CABG surgery during the index ACS hospitalization (n= 47)
Cohort #2: (n = 1,997) after exclusion of patient with conservative management (i.e., those receiving medical treatment only) (n = 183)
Cohort #3: (n = 1,899) after exclusion of the two previous cohorts (n= 230), and patients who underwent PCI without stenting (namely, balloon angioplasty only) (n= 51)

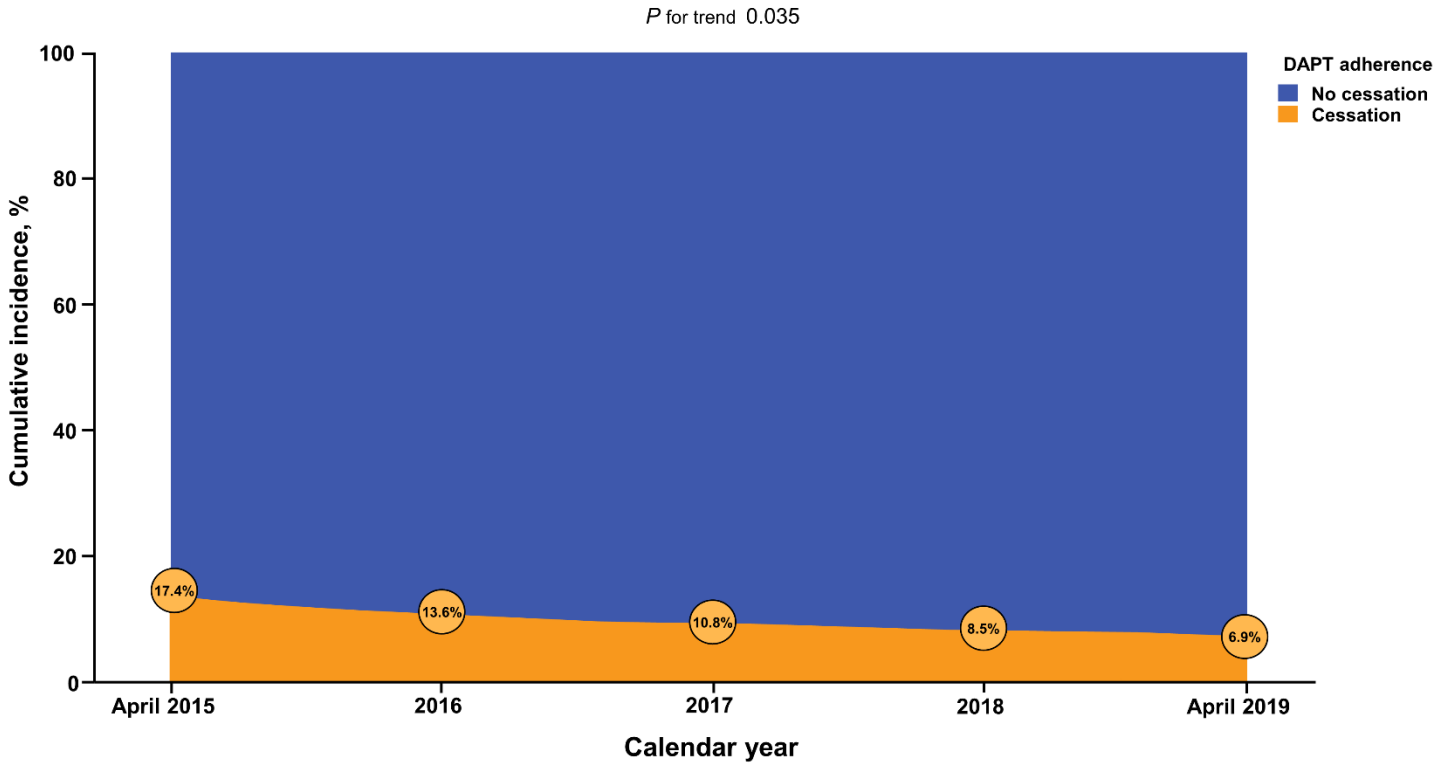
MACE, composite of all-cause death, non-fatal MI , non-fatal stroke, uTLR, or definite ST

MACE-2, composite of cardiovascular death. non-fatal MI, uTLR, or definite ST

ACS, acute coronary syndrome; aHR, adjusted hazard ratio; CI, confidence interval; IPCW, inverse probability of censoring weighting; MACE, major adverse cardiac events; MI, myocardial infarction; uTLR, urgent target lesion revascularization; ST, stent thrombosis.

SUPPLEMENTARY FIGURES

Figure 1 of the supplementary data. Temporal trends in adherence to DAPT during the study period



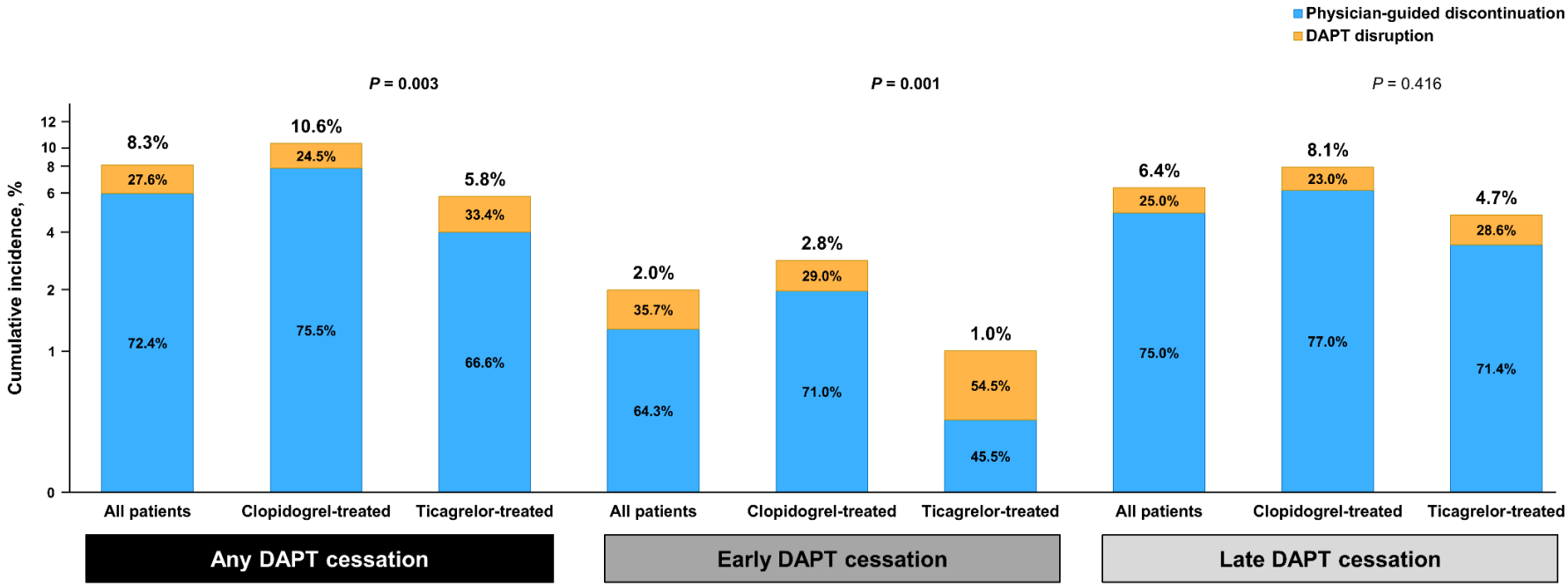
The figure shows the temporal trend in non-adherence to DAPT with ticagrelor and clopidogrel among patients with acute coronary syndrome prospectively included in the CREA-ARIAM registry between March 2015 and April 2019. Numbers inside the circles represent the overall crude incidence rate of premature DAPT cessation per calendar year

P value derived from the Cochran-Armitage test for linear trend in the non-adherence rate to DAPT over time

Adherence to DAPT increased modestly over time, while the overall incidence of non-adherence remained relatively low during the study time

DAPT, dual antiplatelet therapy

Figure 2 of the supplementary data. Cumulative incidence of non-adherence to DAPT according to the mode and timing of cessation by type of $P2Y_{12}$ inhibitor



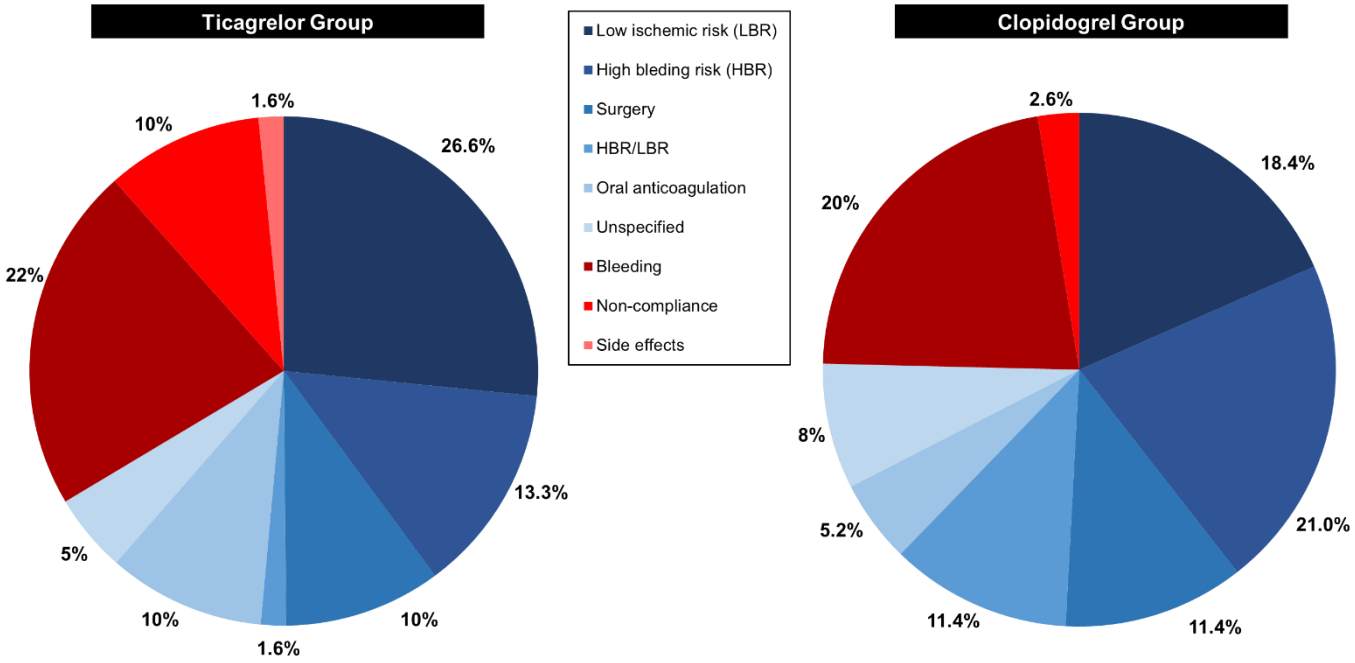
Data are the cumulative incidence of non-adherence to DAPT according to the mode (physician-guided discontinuation/disruption) and timing (early, < 90 days/ late, > 90 days) of cessation within 1 year after ACS, stratified by type of $P2Y_{12}$ inhibitor (ticagrelor/clopidogrel)

The percentage above each column represents the overall incidence of DAPT cessation according to the time of drug discontinuation for the entire study population, and for the clopidogrel- and ticagrelor-treated cohorts separately. The numbers within the columns show the relative proportion of each cessation mode (blue and yellow columns for physician-guided discontinuation and disruption, respectively) among the predefined non-adherence categories according to the timing of cessation

P values comparing the relative rates of non-adherence to DAPT between the clopidogrel- and ticagrelor-treated groups, according to the mode and timing of cessation.

DAPT, dual antiplatelet therapy

Figure 3 of the supplementary data. Relative rates of the underlaying reasons for DAPT cessation by type of $P2Y_{12}$ inhibitor



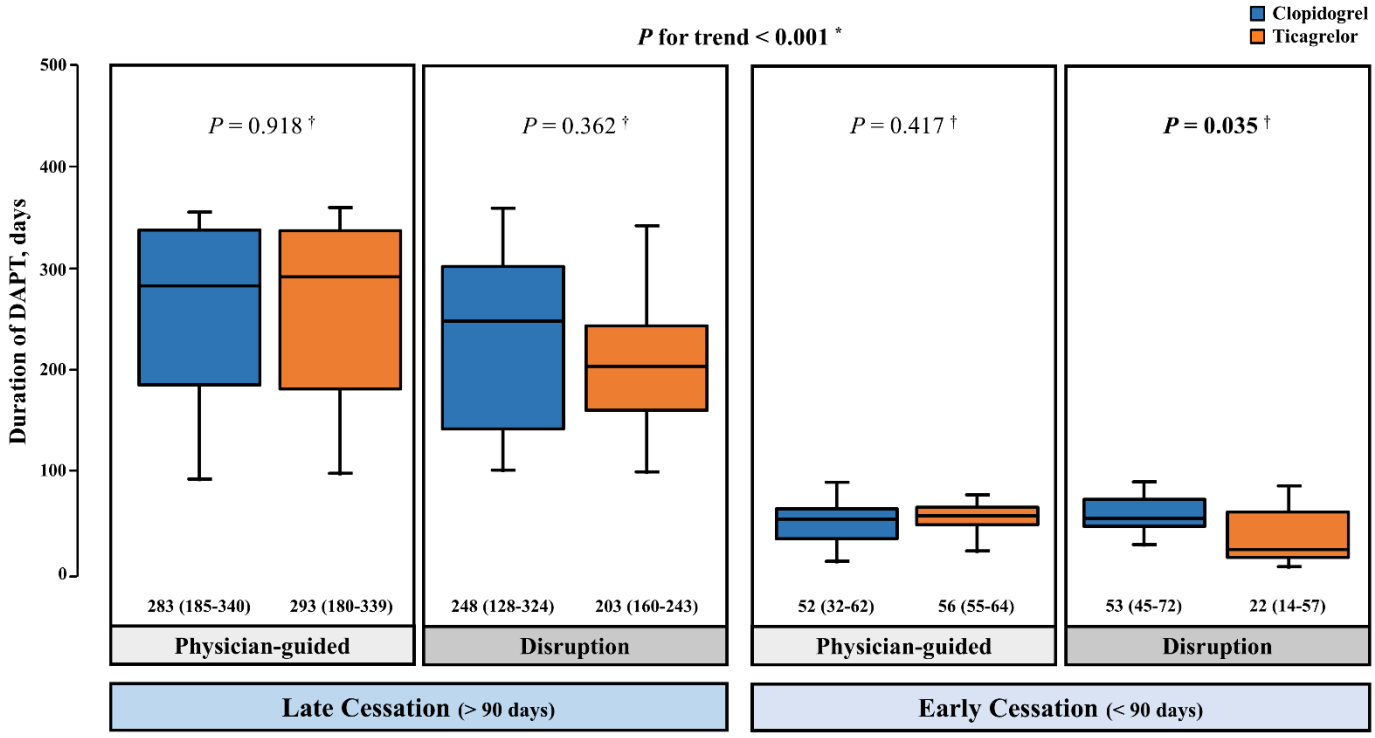
The figure shows the distribution of underlying reasons for DAPT cessation among patients treated with ticagrelor and clopidogrel, categorized according to the predefined patterns of non-adherence to DAPT as shown below:

Physician-guided discontinuation: perceived risk change (LIR, HBR, HBR/LIR); need for surgery or invasive procedures; oral anticoagulation initiation; unspecified reason (personal preference of the attending physician)

Disruption: bleeding complications; patient non-compliance (patient perception of no additional benefit of prolonging treatment, dosing-related issues, drug-related costs, and lack of affordability); drug-related side effects (gastrointestinal, bruising, cardiac pauses, dyspnea ...)

DAPT, dual antiplatelet therapy; HBR, high bleeding risk; LIR, low ischemic risk

Figure 4 of the supplementary data. Timing of DAPT discontinuation by cessation mode stratified by type of $P2Y_{12}$ inhibitor



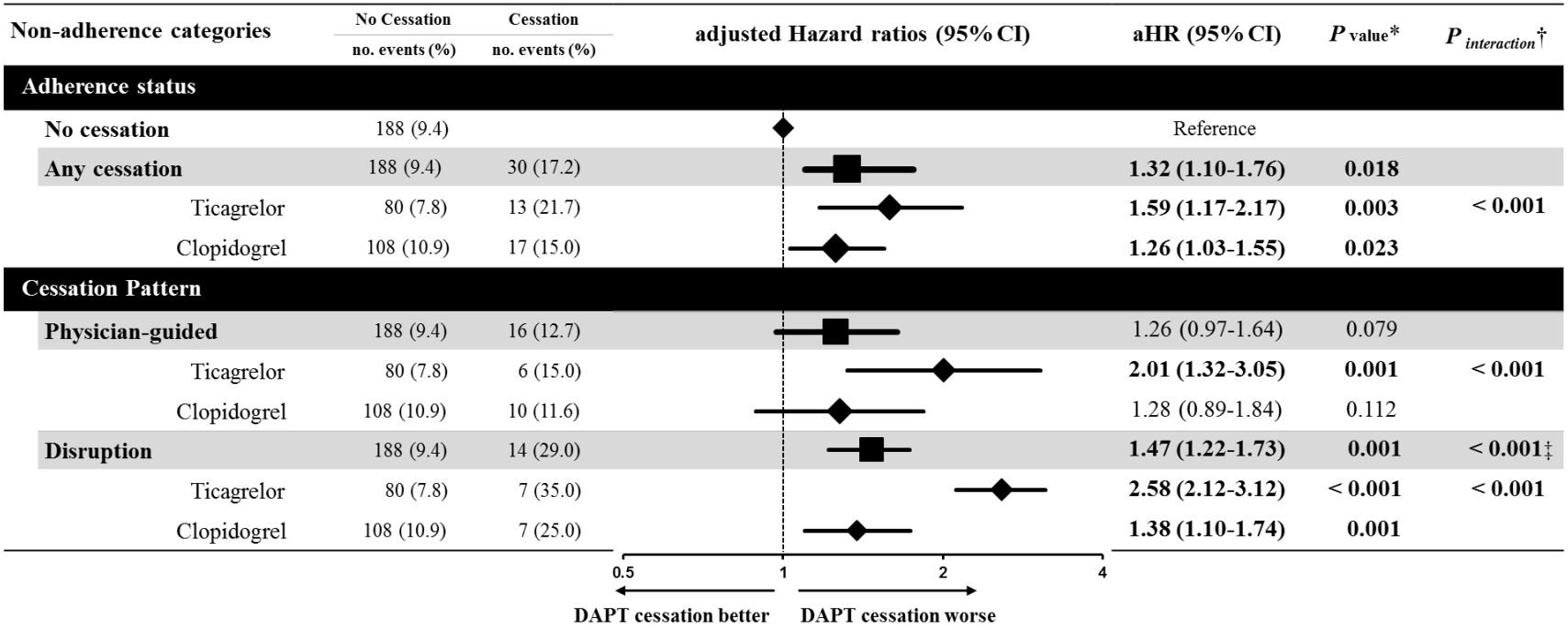
Data depict the median and (IQR) duration of DAPT, expressed in days from the date of hospital discharge until time of permanent drug discontinuation. Box plots are drawn for subgroups according to the predefined non-adherence categories by mode and timing of DAPT cessation, stratified by the choice of $P2Y_{12}$ inhibitor at the time of drug discontinuation.

* *P* value for trend in the median duration of DAPT across the predefined non-adherence categories by mode and timing of drug cessation, stratified by $P2Y_{12}$ inhibitor type.

† *P* values from non-parametric tests comparing the median duration of DAPT until unplanned discontinuation of ticagrelor versus clopidogrel, across the different non-adherence categories according to the mode and timing of DAPT cessation. Differences between ticagrelor- and clopidogrel-treated patients were only evident among those who disrupted DAPT within the first 90 days after hospital discharge, with significant shorter courses of treatment in the former (*P* = .035).

DAPT dual antiplatelet therapy; IQR, interquartile range

Figure 5 of the supplementary data. Adjusted risk of MACE associated with the predefined modes of DAPT cessation stratified by type of $P2Y_{12}$ inhibitor



The forest plot depicts the number, incidence (%), and adjusted hazard ratios with (95%CIs) for MACE risk associated with each mode of DAPT cessation, stratified by $P2Y_{12}$ inhibitor usage status. Effect estimates are derived from time-updated IPCW Cox regression models for DAPT non-adherence as a whole, and for each pattern of cessation separately. Specifically, models included the corresponding multiplicative cessation-by-treatment interaction term according to the mode and choice of $P2Y_{12}$ inhibitor at the time of cessation, with no cessation of DAPT as the reference category

Solid squares and the width of continuous horizontal lines in black represent the aHRs and corresponding 95%CIs for MACE after any DAPT cessation, after physician-guided discontinuation, and for disruption *vs* no cessation of DAPT. Solid diamonds, and associated continuous horizontal lines in black represent the aHRs and their 95%CIs for the occurrence of MACE after discontinuation of ticagrelor *vs* clopidogrel, according to the cessation mode. The square and diamond areas are proportional to the number of subjects at risk in each subgroup

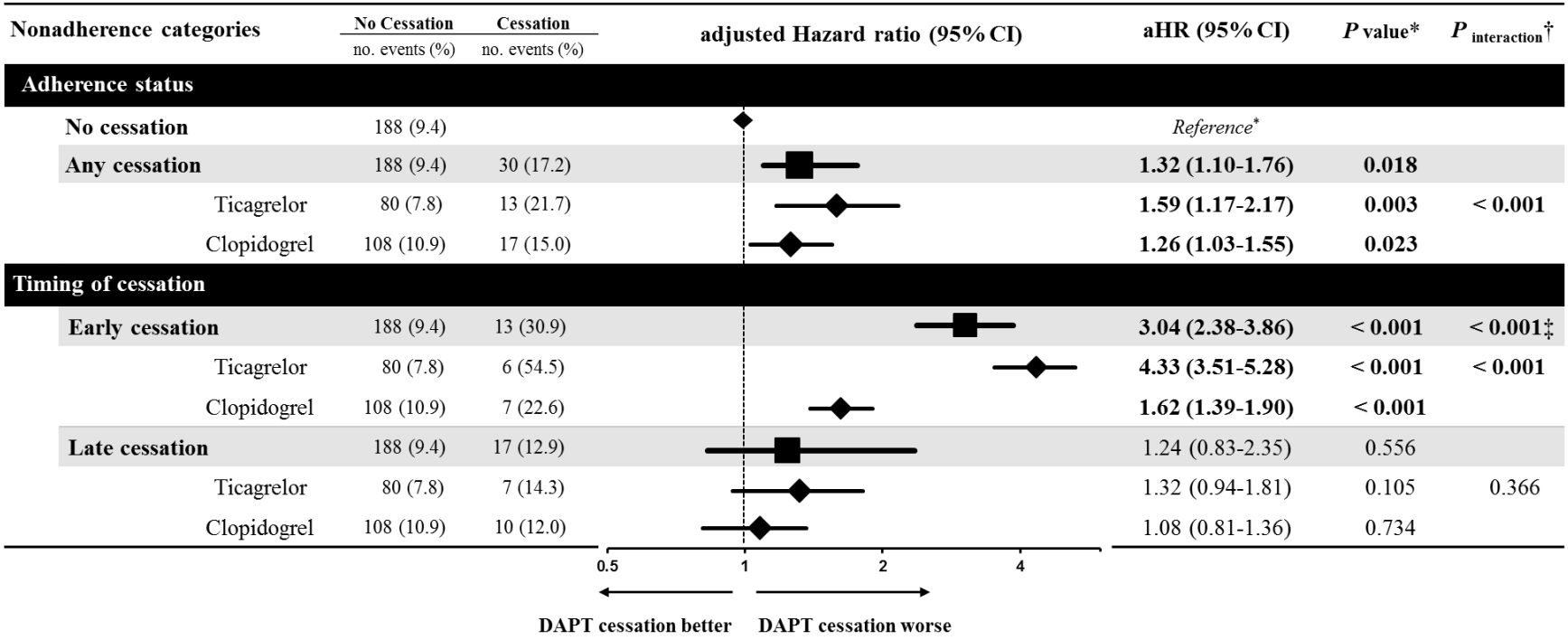
* *P* values for comparison of DAPT cessation *vs* no cessation

† *P* values for formal (Wald) tests of interaction between DAPT cessation and $P2Y_{12}$ inhibitor status (estimates not adjusted for multiple comparisons)

‡ *P* values comparing the overall effect of DAPT cessation on MACE risk after disruption *vs* physician-guided discontinuation

aHR, adjusted hazard ratio; CI, confidence interval; DAPT dual antiplatelet therapy; IPCW, inverse probability of censoring weighted; MACE, major adverse cardiac event

Figure 6 of the supplementary data. Forest plot for MACE risk according to the time of cessation by $P2Y_{12}$ inhibitor type



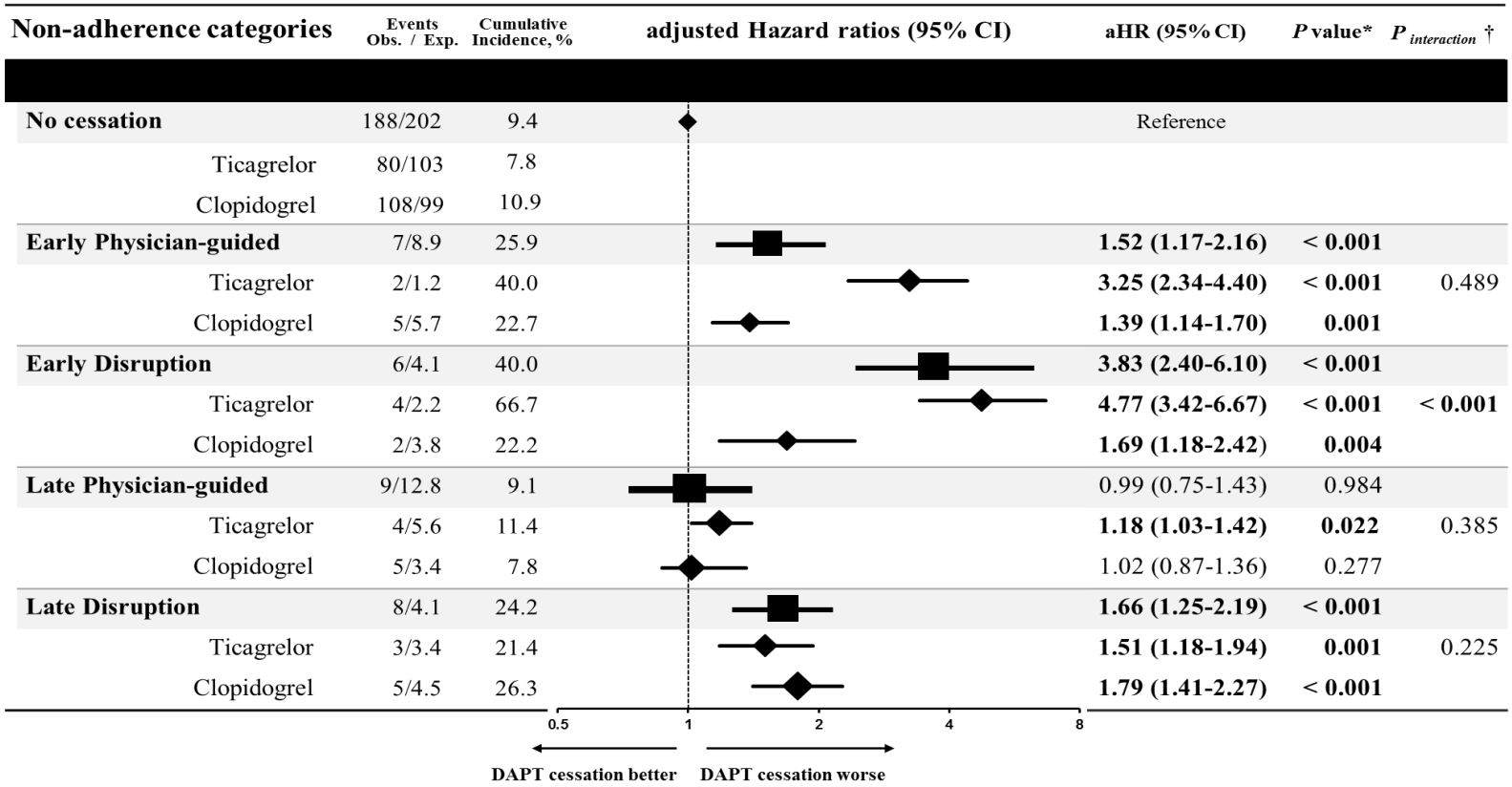
The forest plot depicts the number, incidence (%) and adjusted hazard ratios with 95%CIs for MACE risk associated with the predefined DAPT non-adherence categories according to the time course of cessation (early, < 90 days; late, > 90 days), stratified by $P2Y_{12}$ inhibitor status. Effect estimates are derived from time-updated IPCW Cox regression models for DAPT non-adherence as a whole, and for early, and late cessation of DAPT separately. Models include a multiplicative cessation-by-treatment interaction term according to the timing of cessation and the choice of $P2Y_{12}$ inhibitor, with no cessation of DAPT as the reference category

Solid squares and the width of continuous horizontal lines in black represent the aHRs and corresponding 95%CIs for MACE after any, early, and late cessation of DAPT *vs* no cessation as the reference category. Solid diamonds, and continuous horizontal lines in black represent the aHRs and their 95%CIs for the occurrence of MACE after any discontinuation of ticagrelor *vs* clopidogrel, and according to cessation time. The square and diamond areas are proportional to the number of subjects in each subgroup.

* *P* values for comparison of thrombotic risk following DAPT cessation *vs* no cessation
† *P* values for formal (Wald) tests of interaction between DAPT cessation patterns and $P2Y_{12}$ inhibitor status (estimates not adjusted for multiple comparisons)
‡ *P* values comparing the overall effect on MACE risk of early *vs* late DAPT cessation

aHR, adjusted hazard ratio; CI, confidence interval; DAPT dual antiplatelet therapy; IPCW, inverse probability of censoring weighted; MACE, major adverse cardiac event

Figure 7 of the supplementary data. Forest plot for MACE risk according to the mode and timing of cessation by $P2Y_{12}$ inhibitor type



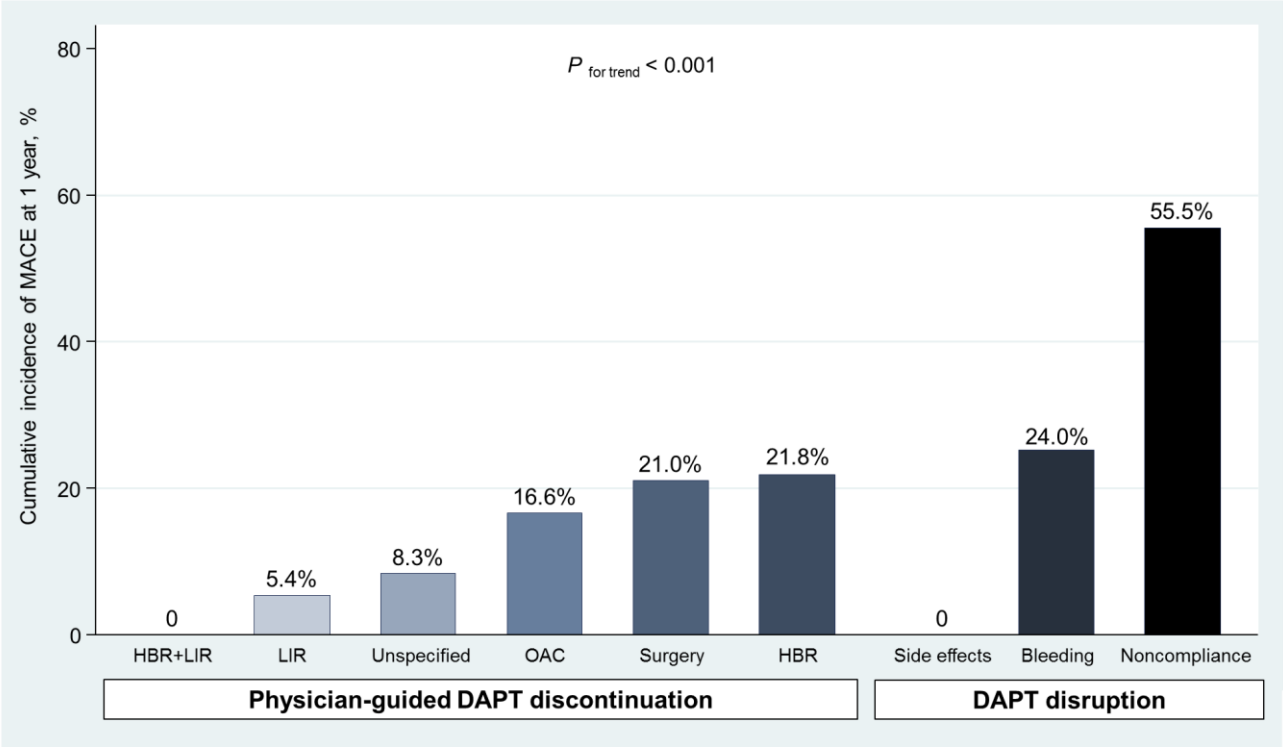
The forest plot depicts the number of observed and expected events, the cumulative incidence (%), and aHR (95%CI) for the primary endpoint. Effect estimates (with DAPT continuation as the reference category) are derived from IPCW Cox regression models for each DAPT non-adherence category (as a time-updated categorical covariate) according to the mode and timing of cessation, stratified by the choice of $P2Y_{12}$ inhibitor. The placement of the center of diamonds and squares on the x-axis and the width of horizontal lines represent the point estimate (aHR) and the corresponding 95%CI, respectively. The square and diamond areas are proportional to the number of subjects in each subgroup

* *P* values comparing effects of premature DAPT cessation across the predefined non-adherence categories according to mode, timing and type of $P2Y_{12}$ inhibitor

† *P* values for formal (Wald) tests of interaction between the non-adherence categories by mode and timing of cessation stratified by $P2Y_{12}$ inhibitor status (not adjusted for multiple comparisons)

aHR, adjusted hazard ratio; CI, confidence interval; DAPT dual antiplatelet therapy; IPCW, inverse probability of censoring weighted; MACE, major adverse cardiac events

Figure 8 of the supplementary data. MACE incidence by mode and underlying reason for DAPT cessation

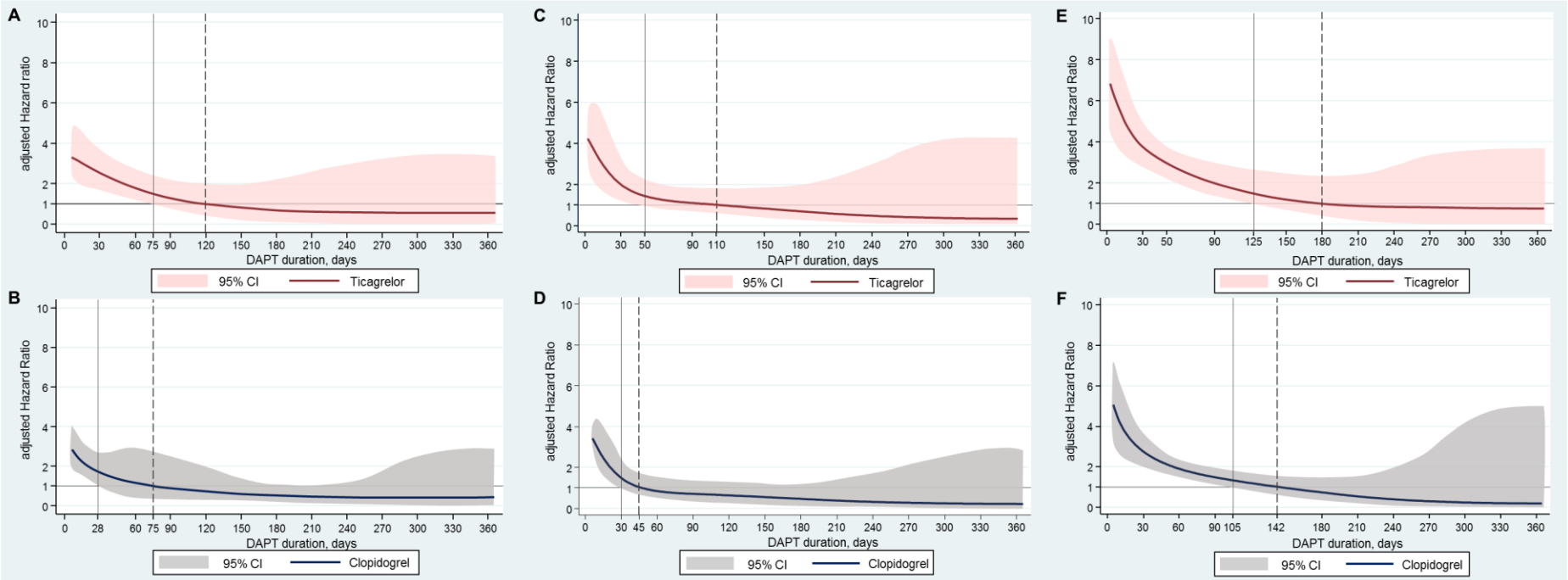


Data depict the cumulative incidence of MACE (from censoring weighted Kaplan-Meier estimators) according to the mode and underlying reason for premature cessation of DAPT within the first year after the index acute coronary syndrome.

P value from the weighted log-rank test for trend in MACE incidence across non-adherence categories defined by the underlying reasons for DAPT cessation. There was a significant increase in the incidence of MACE according to the reason for cessation, with the highest observed rate of thrombotic events after disruption of DAPT due to non-compliance

DAPT dual antiplatelet therapy; HBR, high bleeding risk; LIR, low ischemic risk; MACE, major adverse cardiac events; OAC, oral anticoagulation

Figure 9 of the supplementary data. Duration-response curves for MACE risk as a function of DAPT duration according to the mode of cessation and the choice of $P2Y_{12}$ inhibitor



The figure depicts the duration-response curves for the association between DAPT cessation and MACE risk as a continuous function of DAPT duration with ticagrelor (upper panels) and clopidogrel (lower panels) after any DAPT cessation, panel (A) and panel (B); after physician-recommended discontinuation, panel (C) and panel (D); and following disruption, panel (E) and panel (F). For each mode of cessation, duration-response curves are plotted separately according to the choice of $P2Y_{12}$ inhibitor at the time of its discontinuation. The non-linear duration-response relationship was modelled as a continuous function of DAPT duration in time (entered as the best fitting second-degree fractional polynomial transformation) within a flexible parametric survival analytical framework, using restricted cubic splines functions (with three internal knots placed at 30, 90, and 180 days) to model each cessation mode separately as a time-updated covariate

Results of duration-response analysis based on flexible parametric survival models are expressed as time-varying aHRs (solid lines in dark blue and red for clopidogrel and ticagrelor, respectively), and their corresponding 95%CIs (grey and light red shaded areas for clopidogrel and ticagrelor, respectively) as a continuous function of duration of exposure to DAPT. In each panel, the dashed and solid vertical lines over the x-axis indicate the null-effect intercepts for the point (aHR) and interval (95%CI) smoothed estimates of MACE risk after DAPT cessation, respectively. These landmark points represent the values of continuous exposure duration to uninterrupted DAPT at which the smoothed curves for the aHR and corresponding 95%CI for MACE risk after DAPT cessation cross the horizontal solid line over the y-axis at value = 1 (namely, the `null-effect´ point)

aHR, adjusted hazard ratio; CI, confidence interval; DAPT, dual antiplatelet therapy; MACE, major adverse cardiac events

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