Patterns and Impact of Dual Antiplatelet Cessation on Cardiovascular Risk After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndromes

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The aim of this study was to examine the patterns and clinical impact of differing modes of dual-antiplatelet therapy (DAPT) cessation after percutaneous coronary intervention (PCI) in patients presenting with and without acute coronary syndromes (ACS). The PARIS (patterns of nonadherence to antiplatelet regimens in stented patients) registry was a multicenter study of 5,018 patients who underwent PCI. DAPT cessation was categorized as physician-recommended discontinuation, interruption, or disruption. Overall rates of 2-year DAPT discontinuation did not differ between non-ACS and ACS patients (38.8% vs 37.2%, p = 0.252). ACS patients were less likely to interrupt DAPT (8.5% vs 10.7% p < 0.001), but were more likely to disrupt DAPT (16.4% vs 11.9%, p < 0001). Adverse events after DAPT cessation were highest after disruption, intermediate with discontinuation, and lowest with interruption across both groups. Disruption of DAPT predicted MACE in both ACS patients (hazard ratio [HR] 2.89 [1.88 to 4.45; p < 0.001]) and non-ACS patients (HR 2.08 [1.29 to 3.35; p = 0.002]). Interruption of DAPT predicated MACE in ACS patients (HR 2.72 [1.35 to 5.48]) but not in non-ACS patients (HR 0.44 [0.14 to 1.40]; $p_{interaction} \leq 0.01$). In conclusion, the incidence of DAPT cessation mode differs by presentation with or without ACS. Physician guided DAPT discontinuation was the most common mode of DAPT cessation and appears to be safe across both groups. There were higher rates of adverse events associated with the interruption of DAPT in ACS patients. **(Am J Cardiol 2019;123:709−716)**

Treatment with dual antiplatelet therapy (DAPT) after drug eluting stent (DES) implantation remains a cornerstone of treatment for patients who undergo percutaneous coronary intervention (PCI).[1] Landmark clinical trials have outlined the current recommendations for DAPT duration in patients presenting with acute coronary syndromes (ACS).[2−4] The risk for ischemic events after cessation of DAPT after PCI may depend not only on duration, but also on the timing and clinical reasoning behind the cessation event. DAPT cessation has traditionally been classified using a binary, on-versus-off approach that ignores the clinical reasoning and underlying context in which the antiplatelet treatment was discontinued. The PARIS (patterns of nonadherence to antiplatelet regiments in stented patients) investigators classified DAPT cessation according to the clinical circumstance of DAPT withdrawal.[5] The PARIS registry has shown that in an all-comers population who underwent PCI, the cardiovascular risk of adverse thrombotic events depends not only on the timing of cessation in relation to stent implantation, but also on the underlying cessation mode.[5] Patients presenting with ACS may be at a higher risk for DAPT cessation and subsequent adverse events from that cessation.[6,7] The adverse outcomes associated with different modes of DAPT cessation

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have not been investigated in ACS versus non-ACS cohorts. Therefore, this post hoc analysis of the large PARIS registry sought to investigate the incidence, patterns, and clinical impact of different modes of DAPT cessation across patients presenting with versus without ACS.

Methods

The present study is a post hoc analysis of the PARIS registry. This was a prospective observational study of patients who underwent PCI with stent implantation in 15 US and European centers between July 1, 2009 and December 2, 2010.[5] Adult patients (aged 18 years or older) who underwent successful stent implantation in ≥1 coronary artery and discharged on DAPT were eligible for enrollment. Patients participating in an investigational device or drug study or with evidence of stent thrombosis at the index procedure were excluded. The study was approved by the institutional review board of each clinical site and all patients provided written, informed consent.

Patients were followed up via telephone by trained research coordinators at each clinical site at 1, 6, 12, and 24-month intervals after PCI to assess DAPT compliance and monitor adverse events. All adverse events were adjudicated independently by an externally blinded clinical events committee.

DAPT cessation was defined according to 3 prespecified modes: (1) discontinuation, (2) interruption, and (3) disruption: (1) discontinuation was defined as recommended, physician directed withdrawal of antiplatelet treatment for patients who were believed to no longer need DAPT. (2) Interruption was defined as temporary cessation of antiplatelet treatment due to surgical/procedural necessity with reinstitution of DAPT within 14 days. (3) Disruption was defined as cessation of antiplatelet treatment due to noncompliance or bleeding.

Each DAPT cessation event was independently adjudicated to be due to either physician recommended discontinuation, interruption (<14 days), or disruption (further stratified according to bleeding or noncompliance) in accordance with the above definitions. The patient's follow-up time was broken into the periods spent in each of the DAPT cessation categories according to this hierarchy. Importantly, this classification of DAPT cessation was not mutually exclusive as patients could have more than 1 mode during the course of the study period.

ACS was defined as acute MI according to the third universal definition[8] or unstable angina according to the Braunwald Classification.[9] Q wave-MI was defined as the development of new, pathological Q waves of at least 0.4 seconds in 2 consecutive leads. Non-Q wave MI, postprocedure, was defined as elevation of CK-MB or troponin >3 times the upper limit of normal within 48 hours from the index procedure. Spontaneous MI was defined as the presence after 48 hours from the index procedure of clinical and/or ECG changes consistent with myocardial ischemia with any increase above the upper limit of normal in biomarkers of myocardial injury.

MACE was defined as the composite of cardiac death, definite or probable stent thrombosis, spontaneous MI, and target lesion revascularization. Bleeding was classified with the thrombolysis in myocardial infarction, acute catheterization and urgent intervention triage strategy, and bleeding academic research consortium criteria.[10] Target lesion revascularization was defined as any repeat intervention of the target lesion or surgical bypass of the target vessel and further classified as clinically indicated or not clinically indicated. Stent thrombosis was defined according to the academic research consortium criteria.[11] Death was classified as due to cardiac, vascular, or noncardiovascular causes as specified by academic research consortium criteria.[11]

Patients were categorized according to presentation with versus without ACS at index-PCI. Continuous variables are presented as mean (±SD) and categorical variables by count and percentages. Differences between ACS and non-ACS patients were assessed using Student's *t* test for continuous variables and the chi-square test for categorical variables. Two-year rates of DAPT discontinuation, interruption, and disruption were estimated using the Kaplan-Meier method to plot time to first cessation event. Rates of each mode of DAPT cessation were compared in patients with and without ACS using the log-rank test. Associations between DAPT cessation mode and MACE were examined using a multivariate Cox regression model. All models were adjusted for the following baseline covariates: age, gender, diabetes, hypertension, previous MI, dyslipidemia, peripheral vascular disease, current smoking, thienopyridine insurance coverage, location (USA vs Europe), stent type (bare metal stent vs first generation DES vs second-generation DES), and number of stents implanted.

In case 2 DAPT cessation events occurred before MACE, the mode of cessation attributed to that event changed only if the new event was potentially more serious (i.e., disruption had priority over interruption which had priority over discontinuation). Of note, due to the application of time-varying covariates, the relation of DAPT cessation events to MACE in time cannot be depicted in Kaplan-Meier curves as the individual patient might shift cessation category before the occurrence of MACE as described above.

Results are presented as hazard ratios (HRs) with 95% confidence intervals and p values. Statistical programming and analyses were performed with SAS (version 9.3) and Stata (version 2.1).

Results

The study cohort comprised 5,018 patients who underwent PCI of which 41% (n = 2,056) presented with ACS, predominantly as unstable angina (44.2%, n = 909), followed by NSTEMI (39.3%, n = 808) and STEMI (11.1%, n = 228). The mean patient age was 63.9 years and 25.4% were women. Table 1 shows the baseline characteristics for patients presenting with versus without ACS at index PCI. Patients with ACS were younger, less likely to have comorbidities such as dyslipidemia, hypertension, or diabetes, and less likely to have a family history of CAD. Patients with ACS also had lower educational levels, had lower rates of coverage for thienopyridine expenses by insurance/government and were twice as likely to be current smokers. At baseline, patients with ACS had less previous CAD, peripheral artery disease, PCI or CABG, and cerebral transient ischemic attacks. Additionally, ACS patients twice as often

Table 1
Baseline characteristics

Variable	Acute coronary syndrome		p value
	YES (n = 2,056)	NO (n = 2,962)	
Men	1519 (73.9%)	2220 (74.9%)	0.39
Age (years)	62.67 ± 12.19	64.92 ± 10.62	<.0001
Dyslipidemia requiring medication*	1337 (65.0%)	2464 (83.2%)	<.0001
Hypertension requiring medication	1507 (73.3%)	2502 (84.5%)	<.0001
Family history of coronary artery disease	605 (29.4%)	1001 (33.8%)	0.001
Current smoker	571 (27.8%)	410 (13.8%)	<.0001
Diabetes mellitus	575(28.0%)	1079(36.4%)	<.0001
Education level−less than secondary	312 (15.2%)	281 (9.5%)	<.0001
Thienopyridine not covered by insurance	157 (7.6%)	85 (2.9%)	<.0001
Previous myocardial infarction	413 (20.1%)	801 (27.0%)	<.0001
Previous coronary stent	595 (28.9%)	1251(42.2%)	<.0001
Previous coronary artery bypass graft	252 (12.3%)	433 (14.6%)	0.02
Stroke	73 (3.6%)	100 (3.4%)	0.74
Transient ischemia attack	46 (2.2%)	91 (3.1%)	0.07
Previous coronary artery disease (prior PCI, CABG, MI)	830 (40.4%)	1659 (56.0%)	<.0001
Peripheral vascular disease	136 (6.6%)	256 (8.6%)	0.008
Braunwald unstable angina	909 (44.2%)	N/A	
Non Q-wave MI	808 (39.3%)	N/A	
Q-wave MI	228 (11.1%)	N/A	
Admission medications			
Aspirin	1122 (54.6%)	2453 (82.8%)	<.0001
Thienopyridine	539 (26.2%)	1462 (49.4%)	<.0001
Anticoagulant	100 (4.9%)	152 (5.1%)	0.67
Proton pump inhibitor	381 (18.5%)	609 (20.6%)	0.08
Loading dose	1908 (92.8%)	2437 (82.3%)	<.0001
Unfractionated heparin on admission	1082 (52.6%)	267 (9.0%)	<.0001
Bivalirudin	939 (45.7%)	1394 (47.1%)	0.33
Glycoprotein IIb/IIIa inhibitor	376 (18.3%)	308 (10.4%)	<.0001

Numbers represent n (%).
* Dyslipidemia requiring medication: Requiring any statin therapy for raised low-density lipoprotein-cholesterol or total cholesterol.

had a BMS implanted (Table 1). Procedurally, the majority of patients—75.7% in the non-ACS and 69.5% in ACS patients—had second generation DES implanted. Other treatment differences in baseline medication and procedural characteristics are inherent to treatment algorithms in ACS versus non-ACS and are outlined in (Table 2).

Figure 1 describes the incidence of the 3 different modes of DAPT cessation stratified by ACS category. The rates of 2-year DAPT discontinuation were similar between ACS and non-ACS patients (37.2% vs 38.8%, p = 0.25). ACS patients were less likely to have DAPT interrupted (8.5% vs 10.7%, p < 0.001) but they were more likely to have a disruption of DAPT (16.4% vs 11.9%, p < 0001). When stratified further, this higher rate of disruption in the ACS cohort was driven primarily by patient noncompliance with DAPT (11.6% vs 7.6%, p < 0.001) as opposed to stopping DAPT due to bleeding complications (5.6% vs 4.6%, p = 0.10) (Supplementary Appendix 1). The cumulative incidence of DAPT cessation over 2 years is further described in Kaplan-Meier cumulative incidence curves in Figure 1 according to mode of cessation.

Table 3 and Figure 2A show the two year clinical outcomes stratified by ACS vs. non-ACS strata. Presentation with ACS at baseline PCI conferred significantly higher risk for 2-year clinical outcomes. ACS patients had significantly higher MACE, driven primarily by definite or probable stent thrombosis and spontaneous MI, as well as a trend towards higher rates of cardiac mortality and major bleeding assessed as bleeding academic research consortium ≥3.

Associations between mode of DAPT cessation and MACE are shown in Figure 2A. The risk of MACE associated with disruption and discontinuation was similar in magnitude and direction across ACS strata. The risk of MACE associated with DAPT disruption was similar in ACS patients (HR 1.72 [1.20 to 2.48; p = 0.003]) and non-ACS patients (HR 1.55 [1.05 to 2.30; p = 0.03]). Hazard ratios were consistent across ACS strata with negative interaction testing by cessation mode.

In a secondary exploratory analysis, a narrower MACE definition was investigated which included cardiac death, spontaneous MI, and definite/probable ST (Figure 2B). With this narrower MACE definition the interruption of DAPT was associated with increased rates of restricted-MACE in ACS patients (HR 2.72 [1.35 to 5.48]) but not in non-ACS patients (HR 0.44 [0.14 to 1.40]; $p_{interaction} \leq 0.01$). There was no significant difference in adverse events between ACS and non-ACS cohorts regarding discontinuation or disruption in this restricted analysis.

Discussion

In this analysis of 5,018 ACS versus non-ACS patients who underwent PCI from the PARIS registry we report the following key findings: (1) the overall rates of DAPT

Table 2
Procedural characteristics

Variable	Acute coronary syndrome		p value
	YES (n = 2,056)	NO (n = 2,962)	
PCI coronary artery			
Left main	52 (2.5%)	106 (3.6%)	0.04
Left anterior descending	923 (44.9%)	1401 (47.3%)	0.09
Proximal left anterior descending	438 (21.3%)	679 (22.9%)	0.18
Left circumflex	592 (28.8%)	958 (32.3%)	0.007
Right	797 (38.8%)	963 (32.5%)	<.0001
Bifurcation lesion	274 (13.3%)	321 (10.8%)	0.007
Chronic total occlusion	59 (2.9%)	133 (4.5%)	0.003
Thrombotic lesion	379 (18.4%)	36 (1.2%)	<.0001
STENT TYPE			
Bare metal stent	509 (24.8%)	375 (12.7%)	<.0001
Drug eluting stent−1st generation	202 (9.8%)	472 (15.9%)	<.0001
Drug eluting stent−2nd generation	1428 (69.5%)	2241 (75.7%)	<.0001
Number of stents implanted			0.43
1	1162 (56.5%)	1620 (54.7%)	
2	563 (27.4%)	852 (28.8%)	
>2	331 (16.1%)	490 (16.5%)	
Total stented length (mm)			0.14
≤20	811 (39.4%)	1108 (37.4%)	
>20	1245 (60.6%)	1854 (62.6%)	
Glycoprotein IIb/IIIa inhibitor	376 (18.3%)	308 (10.4%)	<.0001
DISCHARGE MEDICATIONS			
Aspirin	2056 (100.0%)	2962 (100.0%)	
Thienopyridine	2056 (100.0%)	2962 (100.0%)	
Anticoagulant	135 (6.6%)	183 (6.2%)	0.58
Proton pump inhibitor	495 (24.1%)	679 (22.9%)	0.34

Numbers represent n (%).

cessation were similar between groups, but patients presenting with ACS were more likely to have nonrecommended disruption of DAPT whereas interruption was less common; (2) the number of adverse events after DAPT cessation was highest after disruption, intermediate with discontinuation, and lowest with interruption in both groups; (3) in patients presenting with ACS, the interruption of DAPT was associated with increased rates of restricted-MACE outcomes, including cardiac death, MI, and ST.

Our approach to classifying DAPT according to specific mode of cessation allows for a nuanced analysis of the incidence and outcomes in these high-risk patients. Novel findings from this analysis demonstrate that the underlying modes of cessation of antiplatelet agents after PCI vary between patients with and without ACS. Overall, patients with ACS were younger, had fewer co-morbidities, less previous CAD, and displayed unfavorable health behavior illustrated by a twofold increased rate of current smoking as well as unfavorable socioeconomic characteristics in terms of lower degrees of education and less medical insurance coverage for P2Y[11] inhibitors. Costs of medication, copayment or both, as well as lower levels of education are well-recognized predictors of poor adherence to medication.[12,13] Younger age and asymptomatic chronic disease with lack of physical cues, such as underlying CAD or diabetes mellitus, are further proved reasons for medication nonadherence.[14] These factors are significantly more prevalent in the ACS subset of this PCI cohort. Within this population, physician-guided discontinuation was the most common mode of DAPT cessation across both groups and did not significantly differ by ACS presentation. Most notably, ACS patients were more likely to disrupt therapy in a nonrecommended manner compared with their non-ACS counterparts.

The overall impact of DAPT cessation on adverse outcomes after PCI was similar by presentation with versus without ACS in our primary MACE outcome. Risk for adverse events was highest with disruption, intermediate with interruption and lowest with discontinuation irrespective of ACS group and consistent with the primary findings in the overall PARIS cohort.[5] Within this study, the disruption of DAPT had clear consequences across groups, as demonstrated by significantly higher rates of spontaneous MI and higher rates of stent thrombosis. Importantly, the differences in disruption rates between ACS and non-ACS patients were not driven by patients discontinuing medications secondary to bleeding, but by nonadherence. In contrast, patients with physician recommended discontinuation had a very low risk of adverse ischemic events regardless of ACS category.

In an exploratory analysis using a restricted MACE definition, (Figure 2B) patients presenting with ACS who interrupted DAPT had increased rates of restricted-MACE outcomes compared with their non-ACS counterparts. Although our results suggest that both ACS and non-ACS patients may benefit from increased healthcare input to improve medication adherence and access to medications, our restricted-MACE analyses indicate that DAPT

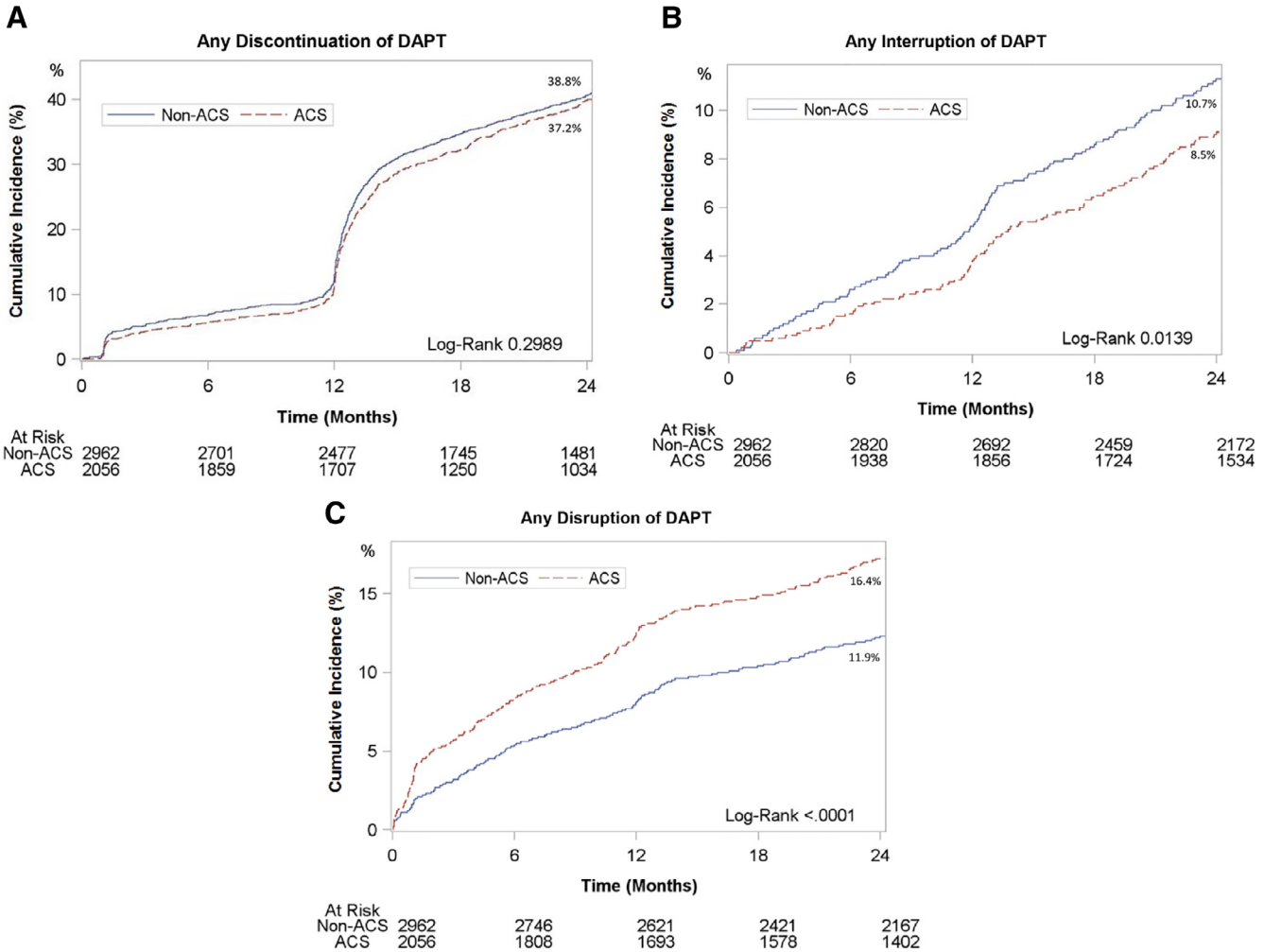

Figure 1. (*A, B, C*): Kaplan-Meier cumulative incidence curves for discontinuation, interruption, and disruption, stratified by ACS presentation through 2 years follow-up.

interruption should be particularly avoided in ACS patients. These patients should be queried regularly about DAPT adherence, as higher adverse events were associated with this group. Increasing social supports, predischarge education focusing on DAPT adherence and methods to decrease post-ACS anxiety and depression are useful methods which have been previously shown to positively impact medication adherence and post-MI outcomes.[15]

Interestingly, non-ACS patients who interrupted DAPT to undergo surgery had very few adverse thrombotic events (Figure 2A/B). Currently, the ACC/AHA guidelines recommend that nonelective cardiac surgery may be considered

Table 3
Two-year clinical outcomes according to presentation with ACS

Variable	Total (n = 5,018)	Acute coronary syndrome		Log-rank p value
		YES (n = 2,056)	NO (n = 2,962)	
Death	4.71% [4.15%, 5.35%]	5.32% [4.41%, 6.41%]	4.29% [3.61%, 5.10%]	0.08
Cardiac death	3.08% [2.63%, 3.61%]	3.55% [2.82%, 4.47%]	2.75% [2.21%, 3.42%]	0.10
Target vessel revascularization	9.18% [8.40%, 10.04%]	9.69% [8.46%, 11.09%]	8.83% [7.84%, 9.94%]	0.28
Stent thrombosis	1.46% [1.16%, 1.84%]	2.15% [1.60%, 2.89%]	0.99% [0.68%, 1.43%]	0.0006
Target lesion revascularization	7.44% [6.73%, 8.22%]	8.05% [6.92%, 9.35%]	7.02% [6.14%, 8.03%]	0.16
Major adverse cardiovascular events	6.53% [5.87%, 7.26%]	8.12% [6.99%, 9.41%]	5.43% [4.66%, 6.33%]	0.0002
Any spontaneous myocardial infarction	3.78% [3.27%, 4.36%]	5.02% [4.13%, 6.09%]	2.92% [2.37%, 3.61%]	0.0002
Major bleeding (BARC ≥3)	8.32% [7.57%, 9.13%]	9.09% [7.90%, 10.45%]	7.78% [6.85%, 8.83%]	0.08
TIMI major	2.11% [1.74%, 2.56%]	2.25% [1.68%, 3.02%]	2.01% [1.55%, 2.59%]	0.55

Numbers represent unadjusted 2-year Kaplan-Meier rates (%) with 95% confidence intervals.
Major adverse cardiovascular events—cardiac death, spontaneous myocardial infarction, and stent thrombosis.
BARC = bleeding academic research consortium; TIMI = thrombolysis in myocardial infarction.

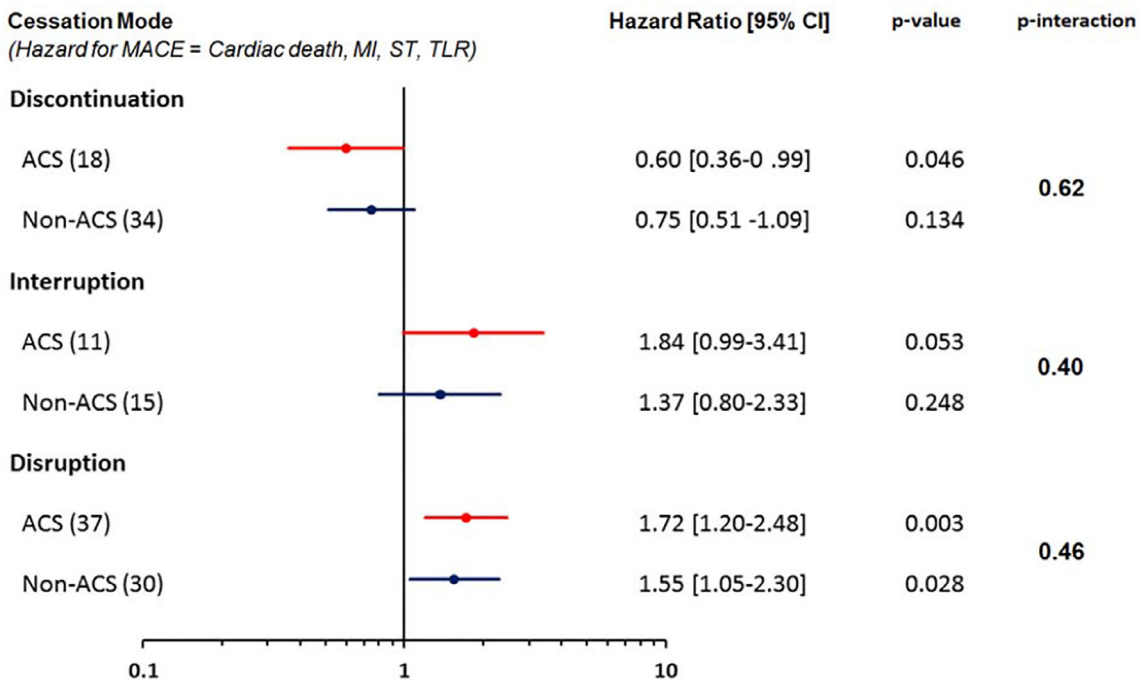

Figure 2A. Association of mode of DAPT cessation according to acute coronary syndrome (ACS) strata with the *MACE definition* of cardiac death, spontaneous myocardial infarction, definite or probable stent thrombosis and clinically indicted target lesion revascularization.

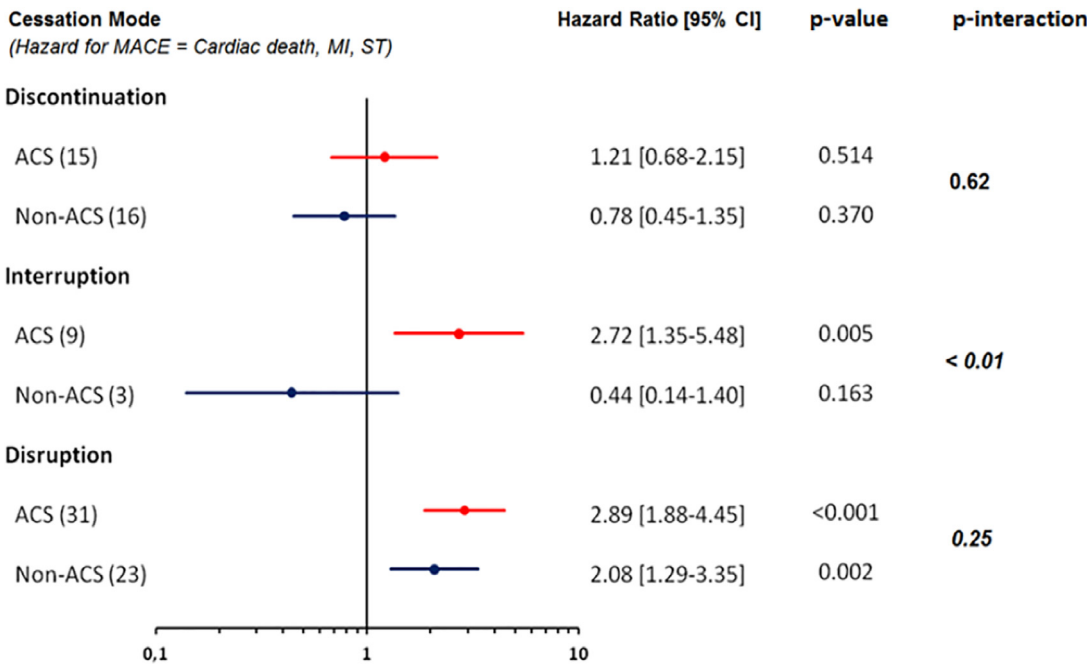

Figure 2B. Association of mode of DAPT cessation according to acute coronary syndrome (ACS) strata with the *restricted MACE definition* of cardiac death, spontaneous myocardial infarction, and definite or probable stent thrombosis.

after 3 months of treatment with DAPT. Although this recommendation relies primarily on expert opinion (Class 2b, LOE−C) our results provide evidence to support the safety of the brief interruption of DAPT for less than 14 days in the perioperative period in non-ACS patients. A similar recommendation for ACS patients cannot be made, given the increased risk of adverse events within the restricted MACE analysis. These results may indicate that noncardiac elective surgery within 6 months of PCI with DES may need to be limited to non-ACS patients only.[16]

The American Society of Regional Anesthesia Guidelines for perioperative management of patients on antiplatelet therapy recommends that all elective surgery after DES implantation should be postponed for 12 months after PCI.[17] Our results in non-ACS patients do not support this recommendation given the very low rate of adverse events within the interruption group. In terms of revascularization before noncardiac surgery, the ACC/AHA guidelines hold a Grade III "no benefit" recommendation (LOE−B) for BMS implantation followed by 30 days of DAPT.[18] As mentioned, our finding of very low rates of cardiac death and MI for patients who interrupted DAPT for surgery in the non-ACS subset indicates that this precaution may be unnecessary.[19]

This study indicates that DAPT >6 months in ACS may be associated with reduced ischemic end points irrespective of patient characteristics, aligning with current guidelines for ACS treatment.[20] These results have to be interpreted in light of 2 pivotal studies that were conducted in primarily non-ACS patients treated with first generation DES, showing that the vast majority (up to 80%) of definite or probable stent thrombosis occur in the first 6 months after DES implantation, and additionally, the median time interval from P2Y[11] therapy discontinuation to ST increases from several days to several months after the first 6 months, weakening the idea of a direct relation between DAPT cessation and the occurrence of ST beyond 6 months after PCI.[14,21]

Our study had several important limitations including an observational design that precludes causal inferences and introduces the possibility of residual confounding. The primary follow-up method through telephone call may potentially have introduced recall bias in our study. To minimize this, the PARIS study required independent adjudication of all episodes of DAPT cessation by use of any available source documentation including clinic visits, hospital admissions, or written prescriptions. Further limitations include the fact that the cumulative use of Ticagrelor or Prasugrel was only 6% of the studied platelet inhibitors, limiting the generalizability of our findings toward more potent antiplatelets.

In conclusion, the incidence of DAPT cessation mode differs by presentation with or without ACS. ACS patients were less likely to interrupt DAPT but were more likely to have disruption of DAPT compared with non-ACS patients. Physician guided DAPT discontinuation was the most common mode of DAPT cessation and appears to be safe across both groups. There were higher rates of adverse events associated with the interruption of DAPT in ACS patients. The impact of DAPT cessation on adverse outcomes was similar between ACS and non-ACS cohorts for both discontinuation and disruption.

Disclosures

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Roxana Mehran: CONSULTING FEES/HONORARIA: Janssen J+J, Maya Medical, Sanofi, Boston Scientific, Merck, AstraZeneca, Abbott Vascular, Covidien, CSL Berhing RESEARCH/RESEARCH GRANTS: BMS/Sanofi-Aventis, Lilly/DSI, The Medicines Company, Regado, STENTYS.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.11.051.

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