Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study

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Summary

Background Dual antiplatelet therapy (DAPT) cessation increases the risk of adverse events after percutaneous coronary intervention (PCI). Whether risk changes over time, depends on the underlying reason for DAPT cessation, or both is unknown. We assessed associations between different modes of DAPT cessation and cardiovascular risk after PCI.

Methods The PARIS (patterns of non-adherence to anti-platelet regimens in stented patients) registry is a prospective observational study of patients undergoing PCI with stent implantation in 15 clinical sites in the USA and Europe between July 1, 2009, and Dec 2, 2010. Adult patients (aged 18 years or older) undergoing successful stent implantation in one or more native coronary artery and discharged on DAPT were eligible for enrolment. Patients were followed up at months 1, 6, 12, and 24 after implantation. Prespecified categories for DAPT cessation included physician-recommended discontinuation, brief interruption (for surgery), or disruption (non-compliance or because of bleeding). All adverse events and episodes of DAPT cessation were independently adjudicated. Using Cox models with time-varying covariates, we examined the effect of DAPT cessation on major adverse events (MACE [composite of cardiac death, definite or probable stent thrombosis, myocardial infarction, or target-lesion revascularisation]). Incidence rates for DAPT cessation and adverse events were calculated as Kaplan-Meier estimates of time to the first event. This study is registered with ClinicalTrials.gov, number NCT00998127.

Findings We enrolled 5031 patients undergoing PCI, including 5018 in the final study population. Over 2 years, the overall incidence of any DAPT cessation was 57·3%. Rate of any discontinuation was 40·8%, of interruption was 10·5%, and of disruption was 14·4%. The corresponding overall 2 year MACE rate was 11·5%, most of which (74%) occurred while patients were taking DAPT. Compared with those on DAPT, the adjusted hazard ratio (HR) for MACE due to interruption was 1·41 (95% CI 0·94–2·12; p=0·10) and to disruption was 1·50 (1·14–1.97; p=0·004). Within 7 days, 8–30 days, and more than 30 days after disruption, adjusted HRs were 7·04 (3·31–14·95), 2·17 (0·97–4·88), and 1·3 (0·97–1·76), respectively. By contrast with patients who remained on DAPT, those who discontinued had lower MACE risk (0·63 [0·46–0·86]). Results were similar after excluding patients receiving bare metal stents and using an alternative MACE definition that did not include target lesion revascularisation.

Interpretation In a real-world setting, for patients undergoing PCI and discharged on DAPT, cardiac events after DAPT cessation depend on the clinical circumstance and reason for cessation and attenuates over time. While most events after PCI occur in patients on DAPT, early risk for events due to disruption is substantial irrespective of stent type.

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Introduction

Percutaneous coronary intervention (PCI) with stent implantation is one of the most widely used cardiovascular interventions for the treatment of coronary artery disease. Unsurprisingly, the effect of adverse events such as major bleeding and myocardial infarction on short-term and long-term risk after PCI have been extensively studied and well documented.[1] However, despite the universal recommendations for dual antiplatelet therapy (DAPT) after PCI,[2] much less is known about the contemporary incidence, timing, and temporal relations between DAPT cessation and subsequent cardiac risk. Additionally, whether or not the effects of DAPT cessation are uniform or vary by the underlying mode in which antiplatelet treatment is withdrawn (eg, bleeding *vs* surgical necessity) is unknown. In part, this uncertainty is due to the absence of standardised and uniform criteria to define DAPT cessation, complicating cross-study comparisons and limiting clinical application.

DAPT cessation is usually classified using binary, on-versus-off approaches that typically ignore the clinical reasons and underlying context in which antiplatelet treatment is discontinued.[3–5] This distinction might be clinically relevant because the effect of DAPT cessation on

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cardiac risk might be attributable to both withdrawal of antiplatelet treatment itself and patient-related risks and circumstances leading to discontinuation.[6] Additionally, findings of excess risk after DAPT cessation previously reported with first-generation drug-eluting stents (DES) might no longer be applicable in contemporary PCI due to widespread use of safer and more effective second-generation DES.[7–9] Finally, whether or not risk after DAPT cessation seen in earlier studies persists or attenuates over long-term follow-up remains unanswered.

To address these clinically important issues, we designed the PARIS (patterns of non-adherence to antiplatelet regimens in stented patients) study, a prospective, international, multicentre, observational registry enrolling an all-comer PCI population designed to assess associations between different modes of DAPT cessation and cardiovascular risk after PCI.

Methods

Study design and population

The PARIS registry is a prospective observational study of patients undergoing PCI with stent implantation in 15 clinical sites in the USA and Europe between July 1, 2009, and Dec 2, 2010. Adult patients (aged 18 years or older) undergoing successful stent implantation in at least one or more native coronary artery and discharged on DAPT were eligible for enrolment. Patients participating in an investigational device or drug study or with evidence of stent thrombosis at the index procedure were excluded. All patients provided written, informed consent.

Objectives

The primary objectives of the PARIS study were to examine the different modes of DAPT cessation in patients with coronary artery disease undergoing PCI with stenting and to assess the associations between these modes and subsequent clinical events. Secondary objectives included the identification of factors related to DAPT cessation and to assess the relation between bleeding and ischaemic events.

Definitions

Prespecified modes of DAPT cessation included discontinuation, interruption, and disruption. Discontinuation was defined as recommended, physician-directed withdrawal of antiplatelet treatment for patients thought to no longer need DAPT. Interruption was defined as temporary cessation of antiplatelet treatment due to surgical necessity with reinstitution of DAPT within 14 days. Disruption included cessation of antiplatelet treatment due to bleeding or non-compliance. DAPT cessation was further classified by duration of cessation as either brief (1–5 days), temporary (6–30 days), or permanent (>30 days). Additional binary classifications included elective versus urgent and recommended versus non-recommended. This primary classification of DAPT cessation (discontinuation, interruption, or disruption) was not mutually exclusive because patients could have more than one mode during the course of the study. Additionally, DAPT cessation lasting for more than 30 days (classified as permanent) did not preclude patients from subsequently resuming DAPT after this time interval.

Stent thrombosis was defined according to the Academic Research Consortium (ARC) criteria.[10] Target lesion revascularisation 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. Death was classified as due to cardiac, vascular, or non-cardiovascular causes as specified by ARC criteria.[10] Spontaneous myocardial infarction was defined as the presence of clinical or electrocardiographic changes consistent with myocardial ischaemia in the setting of increased cardiac biomarkers above the upper limit of normal in accordance with the universal definition.[11] Bleeding was classified with the Thrombolysis in Myocardial Infarction (TIMI), acute catheterisation and urgent intervention triage strategy (ACUITY), and Bleeding Academic Research Consortium (BARC) criteria.[12,13]

Major adverse cardiovascular events (MACE) were defined as the composite of cardiac death, definite or probable stent thrombosis, spontaneous myocardial infarction, or clinically indicated target lesion revascularisation. Because target lesion revascularisation could occur due to thrombotic or non-thrombotic events, analyses were repeated with a more restrictive exploratory MACE definition that did not include target lesion revascularisation.

Follow-up

Follow-up was done via telephone by trained research co-ordinators at each participating site at 30 days, 6 months, 12 months, and 24 months. Source documents were obtained for those patients reporting any adverse events (ischaemic or bleeding) or any DAPT cessation. In cases of DAPT cessation, all patients were also asked to provide information about which drug (aspirin or a thienopyridine) was stopped, the dates of stopping and restarting, and the reasons that drug treatment was stopped (physician-direction, need for surgery, bleeding, other). All information was then forwarded to the external Clinical Events Committee (CEC) for formal adjudication of all adverse events and episodes of DAPT cessation.

Statistical analysis

We used Cox regression models to relate the baseline covariates and time-updated DAPT cessation variable to the set of outcome variables: time to first occurrence of a MACE and its individual components. Each DAPT cessation event was adjudicated to be either due to recommended discontinuation, interruption, or

disruption. When patients had more than one DAPT cessation event, the DAPT cessation variable changed only if the new event was potentially more serious (ie, disruption had priority over interruption which in turn had priority over recommended discontinuation). The patient's follow-up time was broken into the periods spent in each of the DAPT cessation categories according to this hierarchy. In the case of the disruption category, the follow-up time was further segmented into periods after the index disruption event, namely 0–7 days, 8–30 days, and more than 30 days. DAPT cessation entered the model as a time-updated categorical variable.

All models were adjusted for the following baseline covariates: age, sex, acute coronary syndrome, location (USA *vs* Europe), stent type (bare metal stent *vs* first-generation DES *vs* second-generation DES), and number of stents implanted. We present results as hazard ratios (HRs) and 95% CIs.

The sample size was based on the estimated association between stent thrombosis (the rarest of the events) and DAPT cessation, with disruption being the assumed mode of highest risk. A sample size of 4600 patients would be needed to detect an HR of 3·3 for disruption (5%) versus no disruption (95%), assuming a stent thrombosis rate of 1·8% for patients whose DAPT drugs were not disrupted with an α of 0·05 and 90% power. The stent thrombosis rate of 1·8% was based on results from multicentre and single-centre registries showing rates of 1·9–2·3% at 2 years.[4,14] We assumed a slightly lower rate in our power calculations as the PARIS registry started at a time when safer second-generation DES were being used much more frequently than first-generation platforms. To account for a 10% attrition rate, this number was increased to 5011.

We calculated the estimated percentage of all MACE events attributed to interruptions and disruptions as follows: for each relevant HR, the expected number of MACE events was the observed number divided by HR.[15] The estimated excess was therefore the observed minus expected number. Adding up the four excesses for after interruption and 0–7 days, 8–30 days, and more than 30 days after start of disruption gives the overall excess of MACE events. The percentage attributable risk is this excess expressed as a percentage of all MACE events. We used Stata (version 12.1) and SAS (version 9.3) for statistical analyses.

This study is registered with ClinicalTrials.gov, number NCT00998127.

Role of the funding source

The study sponsor had no role in the design, collection, analysis, or interpretation of the data, in the writing of the report, or in the decision to submit the article for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled 5031 patients undergoing PCI, including 5018 in the final study population (figure 1). Of the different modes of DAPT cessation, the cumulative incidence at 2 years was highest for discontinuation and lowest for interruption (figure 2). Similar patterns were seen at 30 days and 1 year.

Most recommend discontinuations (1394 [87%] of 1611) were for a thienopyridine only—aspirin was almost always continued, whereas for most interruptions (290 [70%] of 412) and half of disruptions (345 [50%] of 691) both a thienopyridine and aspirin were stopped.

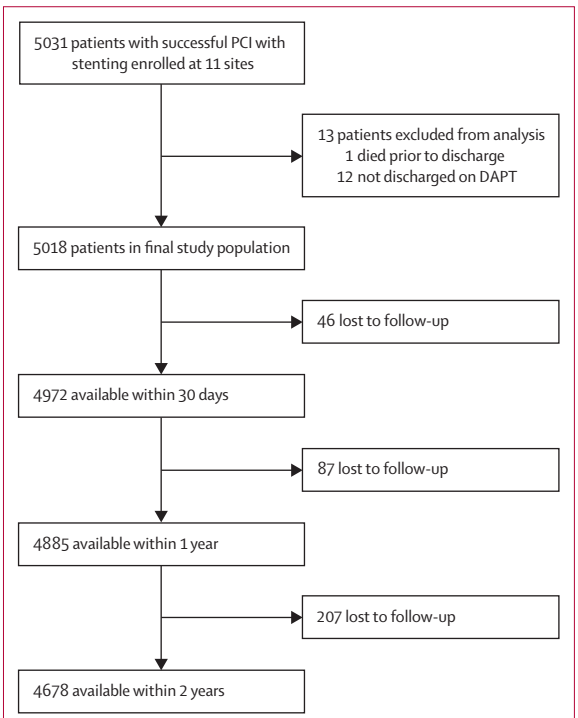

Figure 1: **Trial profile**
DAPT=dual antiplatelet therapy. PCI=percutaneous coronary intervention.

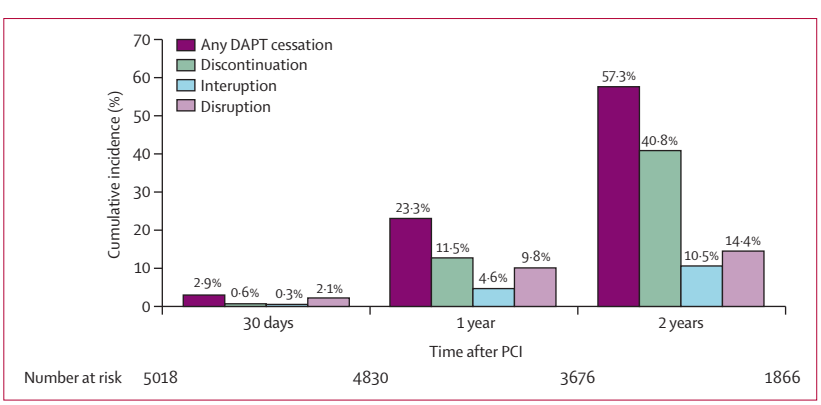

Figure 2: **Cumulative incidence of DAPT cessation**
DAPT=dual antiplatelet therapy. PCI=percutaneous coronary intervention. Incidence calculated as cumulative incidence from a Kaplan-Meier estimate of the time to the first occurrence of DAPT cessation.

The mean duration of sustained DAPT in patients without cessation was 686 days (SD 202), discontinuation was 382 days (169), interruption was 357 days (202), and disruption was 230 days (201). The mean duration of DAPT interruption was 6·2 days (5·7). Tables 1 and 2 compare baseline and procedural characteristics at the time of enrolment after PCI for patients who continued DAPT for 2 years versus the three types of DAPT cessation. DAPT cessations occurred less often in younger patients, patients receiving a DES, and patients with previous myocardial infarction or previous coronary artery bypass graft. Disruptions were more common in patients receiving PCI for an acute coronary syndrome event.

Table 3 shows the cumulative incidence of adverse clinical events. The overall cumulative incidence of MACE was higher than that of TIMI bleeding (table 3). Table 4 shows the 2 year incidence of each type of cardiac event categorised according to the patient's DAPT status prior to the clinical event—most MACE events occurred in patients while taking DAPT.

Figure 3 shows the estimated risk association with the different types of DAPT cessation. For MACE events recommended discontinuation was associated with a reduced risk; disruptions were associated with an increased risk of MACE (figure 3). For disruptions the risk of MACE events was highest for the first 7 days after the start of disruption, and then attenuated over time (figure 3). We recorded broadly similar patterns of risk attenuation after disruption for each event (figure 3).

We calculated the attributable risk of DAPT cessation for interruptions and disruptions only because recommended discontinuation did not increase risk. For MACE, 93 events occurred after interruption or disruption of DAPT compared with an expected 63·1 events if a patient's risk of MACE had been the same as on DAPT. This is an excess of 29·9 events from an overall total of 558 events. Thus, of the overall incidence of MACE

	No DAPT cessation (N=2304)	Recommended discontinuation (N=1611)		Interruption (N=412)		Disruption (N=691)	
		Value	p value*	Value	p value*	Value	p value*
Age in years	62·9 (11·4)	64·7 (10·9)	<0·0001	65·3 (10·7)	0·0001	64·8 (12·3)	<0·0003
Women	559 (24%)	404 (25%)	0·56	103 (25%)	0·75	213 (31%)	0·001
Education							
Less than secondary	288 (13%)	178 (11%)	0·17	29 (7%)	0·001	98 (14%)	0·25
Secondary	1015 (44%)	970 (60%)	<0·0001	171 (42%)	0·34	327 (47%)	0·13
Tertiary	693 (30%)	303 (19%)	0·0001	151 (37%)	0·008	200 (29%)	0·57
Advanced degree	264 (12%)	115 (7%)	<0·0001	53 (13%)	0·41	53 (8%)	0·005
Body-mass index (kg/m^2)	29·5 (5·7)	28·7 (5·3)	<0·0001	30·0 (5·5)	0·09	29·3 (6·2)	0·44
Hypertension	1860 (81%)	1258 (78%)	0·043	355 (86%)	0·009	536 (78%)	0·069
Previous myocardial infarction	637 (28%)	329 (20%)	<0·0001	109 (27%)	0·62	139 (20%)	0·0001
Previous CABG	374 (16%)	169 (11%)	<0·0001	67 (16%)	0·99	75 (11%)	0·001
Stroke	79 (3%)	52 (3%)	0·73	17 (4%)	0·48	25 (4%)	0·81
Peripheral vascular disease	188 (8%)	120 (7%)	0·42	33 (8%)	0·92	51 (7%)	0·51
Current smoker	445 (35%)	315 (41%)	0·004	62 (27%)	0·041	159 (40%)	0·044
Diabetes	829 (36%)	456 (28%)	0·0001	150 (36%)	0·87	219 (32%)	0·038
Silent ischaemia	267 (12%)	159 (10%)	0·087	36 (9%)	0·087	60 (9%)	0·031
Stable angina	1093 (48%)	808 (50%)	0·10	236 (57%)	<0·0001	293 (43%)	0·018
Acute coronary syndrome	938 (41%)	640 (40%)	0·54	140 (34%)	0·01	338 (49%)	<0·0001
Thienopyridine on discharge							
Clopidogrel	2120 (92%)	1486 (92%)	0·80	386 (94%)	0·24	643 (93%)	0·37
Prasugrel	163 (7%)	81 (5%)	0·009	26 (6%)	0·58	44 (6%)	0·52
Triple therapy	66 (3%)	154 (10%)	<0·0001	26 (6%)	<0·0001	68 (10%)	<0·0001
Thienopyridine insurance coverage	2164 (95%)	1540 (96%)	0·053	393 (96%)	0·40	640 (93%)	0·085
DAPT recommendation at discharge							
1 month maximum	92 (4%)	156 (10%)	<0·0001	27 (7%)	0·02	71 (10%)	<0·0001
1 year maximum	1600 (69%)	1227 (76%)	<0·0001	280 (69%)	0·67	445 (65%)	0·01
Greater than 1 year	611 (27%)	227 (14%)	<0·0001	102 (25%)	0·52	174 (25%)	0·51

Data are mean (SD) or n (%). Because patients could have had more than one mode of DAPT cessation over the study period, patients are grouped by worst DAPT status achieved according to hierarchy of disruption, interruption, recommended discontinuation, and on DAPT. CABG=coronary artery bypass graft. DAPT=dual antiplatelet therapy. *p values are for each DAPT status versus the no DAPT cessation category, and are not adjusted for multiple comparisons.

Table 1: **Baseline characteristics**

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	No DAPT cessation (N=2304)	Recommended discontinuation (n=1611)		Interruption (n=412)		Disruption (n=691)	
		n (%)	p value*	n (%)	p value*	n (%)	p value*
PCI vessel							
Left main	77 (3%)	44 (3%)	0·28	11 (3%)	0·48	26 (4%)	0·60
Left anterior descending	1066 (46%)	766 (48%)	0·43	183 (44%)	0·49	309 (45%)	0·47
Proximal left anterior descending	498 (22%)	407 (25%)	0·008	85 (21%)	0·65	127 (18%)	0·066
Left circumflex	747 (32%)	468 (29%)	0·025	130 (32%)	0·73	205 (30%)	0·17
Right coronary artery	806 (35%)	549 (34%)	0·56	150 (36%)	0·58	255 (37%)	0·36
Number of vessels treated							
One	1941 (84%)	1406 (87%)	0·008	355 (86%)	0·32	590 (85%)	0·47
Two	334 (15%)	194 (12%)	0·027	52 (13%)	0·32	98 (14%)	0·84
Three	29 (1%)	11 (1%)	0·078	5 (1%)	0·94	3 (<0·5%)	0·064
Bifurcation lesion	255 (11%)	211 (13%)	0·054	36 (9%)	0·16	93 (14%)	0·085
Chronic total occlusion	86 (4%)	66 (4%)	0·56	16 (4%)	0·88	24 (4%)	0·75
Thrombotic lesion	156 (7%)	178 (11%)	<0·0001	25 (6%)	0·60	56 (8%)	0·23
Stent type							
Bare metal stent	255 (11%)	325 (20%)	<0·0001	68 (17%)	0·002	163 (24%)	<0·0001
First-generation drug-eluting stent	347 (15%)	194 (12%)	0·007	58 (14%)	0·61	75 (11%)	0·005
Second-generation drug-eluting stent	1702 (74%)	1092 (68%)	<0·0001	286 (69%)	0·060	453 (66%)	<0·0001
Total stent length							
≤20 mm	875 (38%)	591 (37%)	0·41	174 (42%)	0·10	279 (40%)	0·26
>20 mm	1429 (62%)	1020 (63%)	0·41	238 (58%)	0·10	412 (60%)	0·26
Number of stents implanted							
One	1250 (54%)	892 (55%)	0·49	247 (60%)	0·032	393 (57%)	0·22
Two	664 (29%)	460 (29%)	0·86	94 (23%)	0·012	197 (29%)	0·88
Three or more	390 (17%)	259 (16%)	0·48	71 (17%)	0·88	101 (15%)	0·15

DAPT=dual antiplatelet therapy. PCI=percutaneous coronary intervention. *p values are for each DAPT status versus the no DAPT cessation category, and are not adjusted for multiple comparisons.

Table 2: **Procedural details by DAPT status**

events in this population, 5·4% can be statistically attributed to interruption or disruption of DAPT. The risk attributable to interruption or disruption was 15·0% for spontaneous myocardial infarction, 7·7% for definite or probable stent thrombosis, 4·1% for target lesion revascularisation, and 7·4% for cardiac death. These estimates of percent attributable risk are based on statistical associations of excess risk and do not necessarily indicate a causal relation.

In supplementary analyses, use of a more restrictive MACE definition that did not include target lesion revascularisation yielded associations for discontinuation and disruption that were qualitatively similar in direction and magnitude with our overall findings (appendix). By contrast with this finding, the higher risk with interruption seen with the original MACE definition was attenuated after we excluded target lesion revascularisation, suggesting that increased risk due to interruption was mainly driven by revascularisation. We recorded results consistent with our primary findings after excluding patients receiving bare metal stents alone (n=811; appendix). Results remained consistent with our overall findings when analysed in subgroups defined by the original recommended duration of DAPT and risk was numerically higher when discontinuation or disruption occurred with both versus one antiplatelet medication (appendix). However, risk with interruption was consistent when one or both drugs were stopped. Our landmark analyses showed that risk with all modes of DAPT cessation was highest in the first 6 months after stent implantation with less risk after 6 months or 12 months.

Discussion

Our findings show that the most common mode of DAPT cessation within 2 years of stent implantation was physician-guided discontinuation with an incidence of 40·8%, whereas the corresponding rate of brief interruption was 10·5% and of disruption was 14·4%. Disruptions due to bleeding or non-compliance were associated with a substantially increased risk of MACE, although this association largely attenuated after 30 days. Compared with those remaining on DAPT, patients who had temporary DAPT interruption lasting up to 14 days did not have an increased rate of thrombotic events, and physician-guided discontinuation was associated with a

See Online for appendix

	Number of events	Incidence (%)
MACE		
30 days	48	1·0%
1 year	363	7·4%
2 years	558	11·5%
Spontaneous myocardial infarction		
30 days	22	0·4%
1 year	108	2·2%
2 years	180	3·8%
Definite or probable stent thrombosis		
30 days	27	0·5%
1 year	55	1·1%
2 years	71	1·5%
Clinically indicated target lesion revascularisation		
30 days	24	0·5%
1 year	249	5·1%
2 years	356	7·4%
Cardiac death		
30 days	15	0·3%
1 year	85	1·7%
2 years	148	3·1%
Bleeding (TIMI major)		
30 days	15	0·3%
1 year	68	1·4%
2 years	101	2·1%

*Incidence calculated as cumulative incidence from a Kaplan-Meier estimate of the time to the first occurrence of the adverse event. TIMI=thrombolysis in myocardial infarction. MACE=major adverse cardiovascular event.

Table 3: **Cumulative incidence of adverse events***

substantially lower MACE risk. Because most adverse events occurred while patients were taking DAPT, the overall contribution of DAPT cessation on cardiac risk was small, thereby challenging existing paradigms for extension of antiplatelet treatment in otherwise stable patients after PCI. Results remained consistent using an alternative definition of MACE that excluded target lesion revascularisation, in patients receiving DES alone, and in subgroups defined by the original duration of DAPT at time of PCI. These findings provide novel and clinically relevant insight on the complex interactions between DAPT cessation and cardiovascular risk in the contemporary PCI era.

Although many studies have reported the incidence or effect of DAPT cessation on subsequent cardiovascular risk, most included selected cohorts and were limited by absence of standardised definitions for DAPT cessation that did not incorporate the underlying context in which treatment was discontinued.[3–5,16–18] By contrast with these studies, we enrolled a large multinational sample in an all-comer design that is more akin to real-world PCI practice patterns. More importantly, all modes and occurrences of DAPT cessation were strictly defined, prespecified, and independently adjudicated by an external committee. This design, coupled with an analytic approach that accounted for the time-varying nature of DAPT cessation, allowed us to clearly show that risk after stopping antiplatelet treatment is highly dependent on both the time interval and context in which treatment is discontinued.

For example, compared with patients remaining on DAPT, those who had physician-guided discontinuation were at significantly lower risk of MACE, an association that was driven largely by differences in revascularisation and might be indicative of treatment bias. A more relevant finding, however, is that sustained antiplatelet treatment (ie, on DAPT) did not confer additional benefits in relation to thrombotic risk reduction versus recommended discontinuation. We detected a slight, albeit non-significant, reduction in stent thrombosis and cardiac death associated with the latter mode of DAPT cessation. These findings contrast with earlier reports suggesting a potential protective effect with lengthy DAPT durations after PCI.[5,18,19] One potential explanation for these differences is that the benefits of extending DAPT might be more apparent in patients receiving first-generation DES, which are associated with a higher rate of thrombotic events compared with the safer second-generation platforms, which were often used in the present study.[8] Additionally, previous studies tended to categorise DAPT status as either on or off DAPT at discrete timepoints. As shown by our results, such grouping ignores the pronounced heterogeneity in risk among off-DAPT patients and might magnify any putative benefits of remaining on DAPT. Third, our findings do not lend support to a causal inference regarding recommended DAPT discontinuation and subsequent cardiac risk. Rather, a more plausible explanation is that physicians appropriately discontinue DAPT in very low-risk patients thereby accounting for lower MACE events after discontinuation (ie, reverse causality). Patients remaining on DAPT, for example, had a higher prevalence of previous myocardial infarction, coronary artery bypass graft, and diabetes mellitus compared with those with recommended discontinuation at baseline. This idea is also lent support by the findings of Airoldi and colleagues,[14] who showed a numerically higher rate of thrombotic events in patients remaining on DAPT 6 months after PCI versus those safely discontinuing at this timepoint.

DAPT cessation due to bleeding or non-compliance (ie, disruption) occurred in about 10% of patients at year 1 and 14% of patients at year 2. In view of the underlying context in which disruptions occurred, findings of increased risk with this mode of DAPT cessation were not entirely unexpected. A novel finding, however, is that risk after disruption was brief, attenuating within 30 days. Although short, this time interval lends support to a causal basis for these associations as the pro-thrombotic effects of platelet withdrawal usually manifest within 2–3 weeks.[14,20] The slight and non-significant increase in risk associated with disruption beyond

	On-DAPT	Discontinuation	Interruption	Disruption	Total
MACE	413 (74%)	52 (9%)	26 (5%)	67 (12%)	558
Spontaneous myocardial infarction	116 (64%)	18 (10%)	7 (4%)	39 (22%)	180
Definite or probable stent thrombosis	57 (80%)	3 (4%)	1 (1%)	10 (14%)	71
Clinically indicated target lesion revascularisation	274 (77%)	31 (9%)	20 (6%)	31 (9%)	356
Cardiac death	100 (68%)	15 (10%)	7 (5%)	26 (18%)	148

MACE=major adverse cardiovascular event. DAPT=dual antiplatelet therapy.

Table 4: **Number of events for each clinical outcome by worst DAPT cessation status achieved before the MACE event**

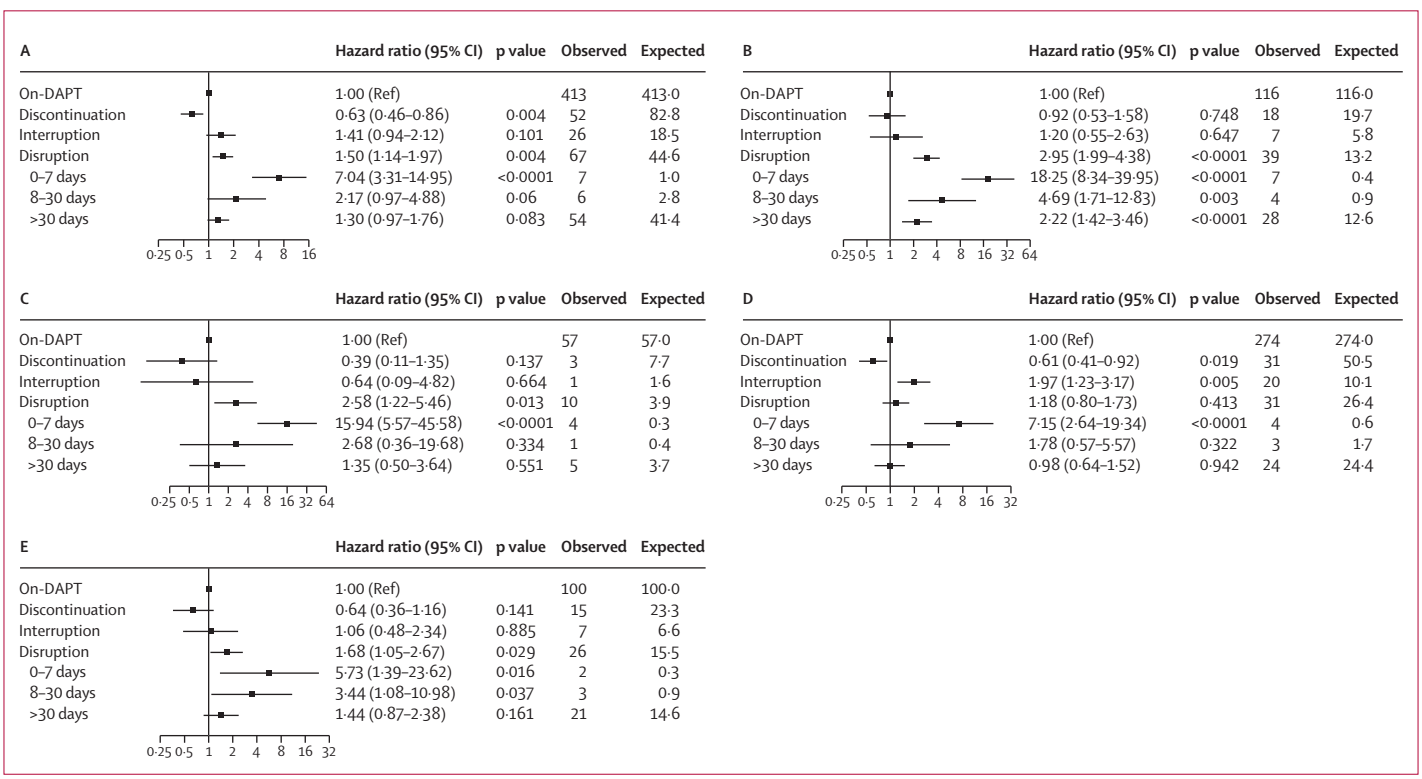

Figure 3: **Risk of ischaemic endpoints**

Results of Cox model analyses for risk of major adverse cardiovascular event (MACE; A), spontaneous myocardial infarction (B), definite or probable stent thrombosis (C), target lesion revascularisation (D), and cardiac death (E). Boxes are hazard ratio point estimates and error bars are 95% CIs. DAPT=dual antiplatelet therapy.

30 days (HR 1·30, 95% CI 0·97–1·76) might show residual confounding from other clinical or demographic risk factors. Other ischaemic adverse events after PCI, including recurrent myocardial infarction, show a similar temporal gradient with risk that largely diminishes after 1 month.[1] By contrast with this finding, previous reports suggest that non-thrombotic complications of PCI, such as major bleeding, result in a persistent increase rather than attenuation of risk over time.[1] Our findings, therefore, provide insight on previously hypothesised links between bleeding, DAPT cessation, and adverse events.[14,20] However, the small number of events occurring in the first 30 days after disruption resulted in imprecise risk estimates and need substantiation in larger studies.

Brief or temporary DAPT interruptions lasting up to 14 days were the least common mode of DAPT cessation with an incidence of 10% at 2 years. Although overall MACE risk was increased after interruption, this association was mainly driven by revascularisation, which comprised the largest number of events (n=20) after interruption. More importantly, we did not detect any association between interruption and subsequent thrombotic events. Similar findings from a multicentre Spanish registry were reported by Ferreira-Gonzalez and colleagues,[21] who also did not detect any associations between temporary DAPT cessation and thrombotic events. Despite the consistent results in both studies, overall rates of interruption and adverse events were low in both cohorts, thereby limiting power to detect small differences.

The clinical relevance of our findings is shown by the fact that the role of antiplatelet therapy after PCI, both in

Panel: **Research in context**

Systematic review

We searched PubMed and Google Scholar using combinations of the terms "dual antiplatelet therapy", "DAPT", "stent thrombosis", "percutaneous coronary intervention (PCI)", "DAPT adherence", "DAPT discontinuation", and "drug eluting stents (DES)" without language or date restriction. We identified several studies showing consistent associations between cessation of dual antiplatelet therapy and cardiovascular risk after PCI.[5,14,17,18,20] We also identified several reports suggesting a protective effect of extended DAPT use,[3,16] even beyond 1 year.[16] These studies were limited, however, by lack of prespecified and standardised criteria to classify DAPT status as most studies were not designed to prospectively assess risk with DAPT cessation. Also, DAPT status was usually classified as either on or off DAPT without consideration of the underlying clinical context in which antiplatelet therapy was withdrawn. Moreover, most reports assessed outcomes in patients receiving earlier (first-generation DES) with much less data reported for associations between DAPT cessation and cardiovascular risk with safer second-generation platforms commonly used in contemporary PCI.

Interpretation

In this large contemporary registry of over 5000 patients with PCI, we detected substantial heterogeneity in both the incidence and risk associated with DAPT cessation according to the underlying context in which antiplatelet therapy was withdrawn. Cardiovascular risk was significantly increased only after DAPT cessation due to non-compliance or bleeding (disruption). Within 30 days after disruption, however, risk was largely attenuated. We detected no significant increase in thrombotic events in patients with brief (<14 days) interruption of DAPT for surgical procedures. Because most adverse cardiovascular events (74%) occurred while patients were taking DAPT, the overall effect of DAPT cessation on cardiac risk was slight. These novel findings draw attention to the importance of standardised and uniform approaches in defining DAPT status and suggest that overall improvements in PCI safety might have mitigated the effect of DAPT cessation on cardiac risk.

terms of mandatory duration and as a contributor to risk, has shifted over the past 10 years. Although concerns for late thrombosis led to the recommendation for extended DAPT with first-generation DES, the widespread introduction of safer second-generation DES might have mitigated the overall effect of DAPT cessation on adverse events after PCI. This novel paradigm is evident in the results of randomised studies suggesting that short DAPT durations of even 3–6 months could be safe with second-generation DES.[22,23] Findings from the PARIS registry provide a complementary and real-world perspective that is concordant with findings from randomised trials reported in the past 2 years. First, when we analysed DAPT cessation in the context of time after PCI, we saw that risk was highest in the first 6 months after stent implantation. Similar results have been reported by others, suggesting the possibility of a temporal inflection point of about 6 months after PCI beyond which risk with DAPT cessation is minimal.[24] Second, we saw that most MACE events (74%) occurred while patients were receiving rather than not receiving DAPT. Even stent thrombosis, the most feared complication of DAPT cessation, occurred mainly while patients were taking DAPT (in 57 [80%] of 71 patients). As a result, attributable risk for MACE due to the different modes of DAPT cessation was slight, varying between 7% and 15% depending on the individual event. The weak effect of DAPT cessation on adverse events might also be indicative of overall trends for improved safety after PCI.[25–27]

Our study had several important limitations, including an observational design that precludes causal inferences and introduces the possibility of residual confounding on our risk estimates. Additionally, we did not collect detailed information about several psychosocial parameters such as mental health, income, or ethnic origin that could affect both adherence to DAPT and cardiovascular risk. In view of the primary method of follow-up via telephone, recall bias could have occurred in our study. To minimise this, however, the PARIS study required adjudication of all episodes of DAPT cessation by use of any available source documentation including clinical visits, hospital admissions, or written prescriptions when available. Additionally, over time we would expect that recall bias would result in a random misclassification of DAPT status in patients with and without events, thereby attenuating our associations to the null. Although we detected associations between early (days 1–7) DAPT disruption and cardiac risk, these findings might lack reliability despite statistical significance because of the small number of events (n=7) in this time interval. Our findings, therefore, warrant substantiation in larger studies with greater power. Because cerebrovascular events were not a study endpoint, we were also unable to examine the associations between DAPT cessation and stroke. Finally, use of novel $P2Y_{12}$ inhibitors such as ticagrelor or prasugrel was uncommon, which might limit the generalisability of our findings to patients treated with these agents after PCI.

Results from the PARIS registry show that the effect of DAPT cessation on cardiac risk after PCI is not uniform but varies substantially by underlying mode, a novel finding with important implications for both clinical practice and future study design. Rather than relying on potentially misleading on-versus-off groupings for DAPT cessation, subsequent studies should incorporate common approaches to classify the reason for DAPT cessation. Standardised definitions for DAPT cessation after PCI, analogous to those commonly used for myocardial infarction and bleeding, will substantially enhance the quality and generalisability of future trials.

Contributors

RM, SP, AC, and MWK designed the study. CA, SP, UB, and SS did the statistical analysis. UB, RM, and GD wrote the first draft of the paper. PGS, GW, BW, TDH, ASK, TS, DJC, PBB, GD, II, RW, DA, MWK, CMG, JBH, MA, DJM, and FS critically reviewed subsequent versions.

Conflicts of interest

RM has received institutional research grant support from The Medicines Company, Bristol-Myers Squibb/Sanofi-Aventis, and Lilly/Daiichi Sankyo, and consulting fees from Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, Janssen Pharmaceuticals, Maya Medical, Merck, Regado Biosciences, and Sanofi-Aventis, and serves on the

advisory board of Covidien, Janssen Pharmaceuticals, and Sanofi-Aventis. PGS has received research grants (to INSERM U698) from Mount Sinai School of Medicine, consulting fees from Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo-Lilly, GlaxoSmithKline, Lilly, Merck-Sharpe-Dohme, Novartis, Otsuka, Pfizer, Roche, The Medicines Company, and Vivus, and institutional research grant support and consulting fees from Sanofi and Servier. ASK has received consulting fees from WebMD. TS has received speaker honoraria from Eli Lilly/Daiichi Sankyo. DJC has recieved income or speaking honoraria from Eli Lilly, AstraZeneca, Medtronic, and Abbott Vascular, and institutional research grant support from Medtronic, Abbott Vascular, Boston Scientific, Eli Lilly, and AstraZeneca. PBB has received institutional research grants from The Medicines Company, AstraZeneca, Eli Lilly/Daiichi Sankyo, and Bristol-Myers Squibb/Sanofi, and consulting fees from Janssen and Medicure. GD serves on the advisory board and has received lecture honoraria from Bristol-Myers Squibb/Sanofi-Aventis. RW and has received research grant support from Boston Scientific, Medtronic, Volcano, Lilly/Daiichi-Sankyo, AstraZeneca, and Abbott Vascular, and consulting fees from Abbott Vascular, Biotronik, Boston Scientific, and Volcano, and serves on the speakers' bureau of Boston Scientific, Medtronic, AstraZeneca, Biotronik, and Abbott. JBH has received consulting fees from BSC, Abbott, Medtronic, and St Jude. CMG has received research grant support from Angel Medical, Atrium Medical, Bayer, Ikaria, Janssen/Johnson & Johnson, Lantheus Medical Imaging, Merck, Portola, Roche Diagnostics, Sanofi-Aventis, Stealth Peptides, St. Jude Medical, Volcano, and Walk Vascular, and consulting fees from AstraZeneca, Baxter Healthcare, Bayer, CRF, Consensus Medical, CSL Behring, Cytori Therapeutics, Eli Lilly/Daiichi Sankyo, Exeter Group, Genentech, GSK, Janssen/Johnson & Johnson, Ortho McNeil, St. Jude, and The Medicines Company. All other authors declare that they have no conflicts of interest.

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