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Causes, Timing and Impact of Dual Antiplatelet Therapy Interruption For Surgery (From the PARIS Registry)

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ABSTRACT

Temporary interruption of dual antiplatelet therapy (DAPT) is not infrequently required in patients undergoing percutaneous coronary intervention (PCI). We sought to describe the procedures and outcomes associated with DAPT interruption in patients treated with DAPT following successful PCI from the PARIS registry (n=5018). DAPT interruption was pre-specified as physician recommended cessation for <14 days. The main endpoints of interest for this analysis were cardiac death, myocardial infarction or stent thrombosis occurring subsequent to DAPT interruption. Of the study cohort, 490 (9.8%) patients experienced 594 DAPT interruptions over 2-years following PCI. Only 1antiplatelet agent was interrupted in 57.2% cases and interruption was frequently recommended by non-cardiologists (51.3%). Where type of surgery was reported, majority of DAPT interruptions occurred for minor surgery (68.4% vs. 31.6%) and a similar cessation pattern of single versus dual antiplatelet cessation was observed regardless of minor or major surgery. Subsequent to DAPT interruption, 12 patients (2.4%) patients experienced 1 thrombotic event each, of which 5 (1.0%) occurred during the interruption period. All events occurred in patients who stopped both agents (8/12) or clopidogrel-only (4/12) with no events occurring due to aspirin cessation alone. In conclusion, in the PARIS registry, 1 in 10 patients were recommended DAPT interruption for surgery within 2-years of PCI. Interruption was more common for a single agent rather than both antiplatelet agents regardless of severity of surgery, and was frequently recommended by non-cardiologists. Only 1% of patients with DAPT interruption experienced a subsequent thrombotic event during the interruption period, which mainly occurred in patients stopping both antiplatelet agents.

Key words: surgical interruption, dual antiplatelet therapy, percutaneous coronary intervention, major adverse cardiac outcomes

INTRODUCTION

Currently, the American College of Cardiology Foundation/ American Heart Association/ Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) percutaneous coronary intervention (PCI) guidelines recommend discontinuation of dual antiplatelet therapy (DAPT), with ongoing aspirin if possible for surgery and recommencement of a $P2Y_{12}$ receptor inhibitor as soon as possible in the post-operative period (Class IIa, C). However, the level of evidence in support of this recommendation is scarce, relying mainly on expert consensus[1]. A recent ACC/AHA focused guideline update provides a class IB-NR recommendation for DAPT discontinuation prior to elective surgery, at 6 months after drug eluting stent (DES) implantation, based on results from the prospective, multicenter observational PARIS (Patterns of Non-adherence to Anti-platelet Regiments In Stented Patients) registry[2]. This guideline also advises that surgery may be considered between 3-6 months after DES PCI, however, surgery should be delayed to beyond 3 months where possible (Class IIb, C-EO)[2]. Therefore, the present analysis describes in detail the procedures and outcomes associated with DAPT interruption in patients undergoing successful PCI from the PARIS registry [3].

METHODS

The PARIS registry was a multinational registry of 5018 patients enrolled in 15 clinical sites in the US and Europe between July 1 2009 and Dec 2 2010 and discharged on DAPT following successful PCI [3]. Pre-specified categories of DAPT cessation were physician recommended discontinuation, brief interruption (<14 days) or non-recommended disruption. The present study is a descriptive analysis of patients enrolled in the PARIS registry who interrupted DAPT within 2 years after coronary stent implantation. Major surgery was defined as a surgical procedure requiring general anesthesia or hospital admission and was categorized as cardiothoracic, abdomino-pelvic, orthopedic or endocrine related surgery. Minor surgery was defined as an out-patient procedure that was

performed as a day case and included endoscopy, dental work, biopsy, spinal injections, eye surgery and joint injections.

The primary endpoint of the main study was 2-year major adverse cardiac events (MACE), defined as a composite of cardiac death, spontaneous myocardial infarction (MI), definite/probable stent thrombosis or target lesion revascularization[3]. For the present analysis, clinical outcomes of interest were individual thrombotic endpoints, cardiac death, spontaneous MI and definite/probable stent thrombosis, occurring subsequent to DAPT interruption. Spontaneous MI was defined as presence of clinical or electrocardiographic changes consistent with ischemia in the setting of increased biomarkers according to the third universal definition. Stent thrombosis was defined as per the Academic research consortium criteria. All events were adjudicated by an independent clinical events committee following standardized definitions [3].

Baseline characteristics are presented in groups of patients with versus without any DAPT interruption during 2 years of follow-up. Categorical data are presented as frequencies and compared using the chi-squared test. Continuous data are presented as means ± standard deviation (SD) and compared using the Student's t-test. Patterns of interruption and incidence of events rates subsequent to interruption were described only in the group with any DAPT interruption. Statistical significance was accepted at the 95% confidence level ($p < 0.05$). Statistical analyses were performed using SAS version 9.2 (Cary, North Carolina, USA).

RESULTS

The study cohort comprised 9.8% (n =490) patients experiencing DAPT interruption and 90.2% (n =4528) patients without any interruption over 2 years. **Tables 1** and **2** show the baseline characteristics. There were no differences by age or sex between the groups. Patients with interruption had greater prevalence of hypertension, dyslipidemia and prior PCI, but similar prevalence of diabetes and lower prevalence of smoking or ACS presentation. Most of the patients experiencing interruption

were enrolled in the US rather than Europe. With respect to procedural characteristics, majority of the patients in both groups underwent PCI to a single vessel, commonly to the left anterior descending artery and nearly three-quarters of patients were treated with second generation DES. Patients with interruption were more likely to receive shorter stent lengths with smaller stent diameter, than their counterparts without interruption.

Over 2 years there were 594 records of DAPT interruptions involving 490 (9.8%) patients, of which 206 (4.1%) patients had interruptions in the first year with a peak around 365 days from index PCI (**Figure 1**). Interruptions occurred for both major and minor surgery throughout the follow-up period. Overall, minor surgery was more common than major surgery (68.4% vs. 31.6%). **Figure 2** illustrates the specific reasons for surgery in this cohort. Out of 339 (57.1%) cases where the authority recommending DAPT interruption was known, interruption was equally recommended by cardiologists (48.7%) and non-cardiologists (51.3%) (**Figure 3**).

Among all DAPT interruptions, dual antiplatelet cessation occurred in 42.8% (n=254) and single antiplatelet agent cessation in 57.2% (n=340) cases, of which clopidogrel-only cessations were more frequent (n=192, 32.3%) than aspirin-only cessations (n=148, 24.9%). Where the specific type of surgery was known (373 interruptions in 312 patients), single antiplatelet and clopidogrel-only cessation was more common regardless of minor or major surgery: 56.9% single agent cessations in minor surgery cases (clopidogrel-only 37.3%, aspirin-only 19.6%) and 56.8% single agent cessations in major surgery cases (clopidogrel-only 29.7%, aspirin-only 27.1%).

Subsequent to DAPT interruption, 12 (2.4%) unique patients experienced 1 thrombotic event each, including 4 cardiac deaths and 8 spontaneous MIs. No patients with DAPT interruption experienced definite/probable stent thrombosis. Only 5 events, all MIs, occurred within 2 weeks of DAPT interruption; 2 events with major surgery, 2 with minor surgery and in 1 case the type of surgery was unknown. These 5 events accounted for 1.0% of all patients and 0.8% of all interruptions. Of these

5 events, 4 occurred beyond 1 year from PCI; 2 cases had both antiplatelet agents stopped and 3 cases had clopiodgrel-only cessation. The remaining 7 events (4 cardiac deaths and 3 MI) occurred between day 76 and 725 of DAPT interruption and in all these cases DAPT had been re-initiated, therefore being unlikely to be related to interruption itself.

Overall, 8 of 12 (66.7%) events occurred in patients who stopped both agents, while the remaining 4 events occurred in patients who interrupted only clopidogrel. There were no thrombotic events in patients with temporary cessation of aspirin alone (**Figure 4**).

DISCUSSION

The current report from the PARIS registry shows the following 1. physician recommended temporary DAPT interruption for surgery occurred in approximately 1 in 10 patients over 2 years following PCI; 2. single antiplatelet interruptions were more common, whereas both aspirin and $P2Y_{12}$ inhibitor interruption occurred in roughly 4 out of 10 patients; 3. the recommendation for DAPT interruption was made by cardiologists and non-cardiologists alike and in close to 70% of cases interruption was for minor rather than major surgery; 4. DAPT interruptions peaked at 12 months, suggesting that both major and minor procedures were generally postponed to beyond the first year after PCI; 5. the incidence of adverse outcomes associated with DAPT interruption was extremely low and only 1% of patients undergoing interruption for surgery experienced a thrombotic event during the interruption period. Moreover, this occurred exclusively in patients who stopped both antiplatelet agents or in patients that stopped clopidogrel only. No events occurred in patients who temporarily interrupted aspirin alone. No ST events occurred in patients temporarily interrupting DAPT.

Our rate of DAPT interruption within the first year after PCI, in a cohort predominantly treated with 2nd generation DES was 4.1%, in keeping with prior data with rates between 2.5 - 5% [4-6]. Our findings are also consistent with previous data that majority of interruptions occur for minor procedures including ocular or dental procedures, endoscopies and biopsies [5].

With respect to stent selection in patients with planned surgery, PCI frequently results in bare metal stent (BMS) implantation, potentially withholding the advantages of 2nd generation DES from these patients [7]. Indeed, the current ACCF/AHA/SCAI guidelines recommend balloon angioplasty or BMS implantation followed by 4-6 weeks of DAPT in patients requiring elective surgery within 12 months of PCI (class IIa, B) [1]. This can apply to nearly 16% of PCI patients who may have planned surgery within 12 months of stent implantation, as noted from the recent Leaders free trial population [8]. However, newer DES with faster endothelialization profiles and shorter DAPT requirements may allow DES implantation to be first option in these patients [8].

While increased thrombogenicity is inherent to the immediate post-operative period,[9] it is unclear whether antiplatelet interruption early after PCI is uniformly detrimental irrespective of factors such as stent type and PCI indication. During the early PCI experience with BMS, high rates of death and MI were reported in case of surgery within the first 2-5 weeks, and stent thrombosis accounted for most of the fatal events[10, 11]. This time frame corresponds to the 4 week period of vascular healing after BMS implantation[12]. Subsequent studies with 1st generation DES showed that non-cardiac surgery within the first year after stent implantation was an independent predictor of 30-day death, MI and revascularization. The EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) registry with majority 1st generation DES use, reported a 27-fold increase in composite thrombotic outcomes within 7 days of non-cardiac surgery performed in the first year of PCI [6]. Event rates were higher when surgery was performed within 6 months of PCI and stabilized thereafter, [13, 14] as a function of delayed or incomplete vessel healing due to the effect of anti-proliferative drug or polymer [15-17].

Conversely to these data, one study found no significant association between MACE after elective non-cardiac surgery and time from PCI with 1st generation DES [18]. Similarly in our cohort, we found that 4 out of 5 patients experiencing thrombotic events within 14 days of interruption were >1 year post-PCI. Further, for events occurring between 76-725 days post interruption, DAPT had been reinitiated in all patients, and thus interruption cannot be causatively linked to the thrombotic events.

Nevertheless our sample size of patients with interruption was too small to enable definitive conclusions for future recommendations.

Based on recent randomized trial data at least a 6-month period after PCI with 2nd generation DES may be advisable before recommending interruption for surgery[19, 20]. Although prolonged DAPT has been shown to decrease the risk of stent thrombosis, this is at the expense of higher bleeding[21]. Moreover, shorter DAPT durations may not be associated with greater risk of stent thrombosis in patients receiving new-generation DES[22]. Further data are needed to understand the safety of early interruption with the use of these stents.

Contrary to the ACCF/AHA/SCAI guidelines, which recommend aspirin continuation through the peri-operative period[23], we found that over 40% patients stopped both anti-platelet agents regardless of major or minor surgery. This discordance between guidelines and practice reflects the conflicting clinical evidence for the optimal perioperative regimen. Large multicenter cohort studies have shown that complete interruption of anti-platelet therapy earlier than 5 days before surgery[24] and re-initiation later than 48 hours after coronary artery bypass surgery [25] increased the risk of ischemic events. A systematic review and meta-analysis including 8 randomized controlled trials and 15 observational studies showed that pre-operative aspirin increased post-operative bleeding in PCI patients, but this could potentially be avoided by the use of aspirin doses <325 mg/day[26]. In a small RCT, Oscarsson et al. demonstrated that in high-risk patients undergoing non-cardiac surgery, perioperative low dose aspirin continued to the third postoperative day, reduced the risk of MACE without increasing bleeding[27]. Conversely, the POISE-2 RCT refuted the benefits of continued peri-operative aspirin against increased the risk of major bleeding. However less than one-third of POISE-2 trial patients had a history of coronary artery disease and only 5% had prior PCI[28].

Our findings of a 1% rate of thrombotic events in patients interrupting DAPT, suggests that DAPT interruption for surgery is not a tremendous concern following contemporary PCI. Further, since

adverse events were limited to patients stopping either clopidogrel or both antiplatelet drugs prior to surgery, aspirin-only interruption could be considered as a suitable option. Notwithstanding, with the availability of newer stents and the use of potent $P2Y_{12}$ therapies in PCI, future studies are needed to re-examine these associations. Physician recommended interruption should continue to be tailored to individual patient ischemic and bleeding risks.

This present study is limited by its observational nature, relatively small sample size of patients with DAPT interruption, particularly within the first 6 months of PCI, and small number of events. However these data are derived from an all-comer international multicenter PCI population, reflecting the patterns in managing patients treated with second generation DES. Our rates of interruption for surgery are similar to reports from other international cohorts, supporting the findings of this analysis [4-6]. These data are drawn from patients treated with aspirin and clopidogrel and do not apply to the use of potent $P2Y_{12}$ therapies. We did not collect specific information on post-surgery bleeding. In the absence of stent thrombosis, it may be inferred that MI events were non-stent related and might include causes such as Takotsubo cardiomyopathy, which has been observed post surgery [29].

In conclusion, 1 in 10 patients are recommended DAPT interruption for surgery within 2 years of PCI. Interruption is more common for single rather than dual antiplatelet agent cessation, regardless of major or minor surgery and is uniformly recommended by cardiologists and non-cardiologists. Only 1% of patients with physician recommended DAPT interruption experienced a thrombotic event during the interruption period, which mainly occurred in patients who stopped both antiplatelet agents.

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Figure legends

Figure 1: Frequency of interruption over the follow up period.

Figure 2: Types of surgical procedures requiring dual antiplatelet treatment interruption

Figure 3: Recommending sources for dual antiplatelet treatment interruption by physician specialty

Figure 4: Withdrawal patterns of antiplatelet agents in DAPT interruption patients experiencing thrombotic events.

DAPT, dual antiplatelet therapy

Table 1. Baseline characteristics

	Interruption of DAPT Treatment		
	Yes	**No**	**p-value**
Variable	**(N = 490)**	**(N = 4528)**	
Age (years), mean ± SD	65.24 ± 10.71	63.56 ± 11.40	0.99
Women	133 (27.1%)	1146 (25.3%)	0.38
Body mass index (kg/m ^{2}), mean ± SD	30.06 ± 5.66	29.18 ± 5.63	0.99
Dyslipidemia requiring medication	396(80.7%)	3405 (75.2%)	0.006
Hypertension requiring medication	422(85.9%)	3587 (79.2%)	<0.0001
Family History of Coronary Artery Disease	179(36.5%)	1427 (31.5%)	0.024
Current Smoker	74(15.1%)	907 (20.0%)	0.009
Diabetes Mellitus	176(35.8%)	1478 (32.6%)	0.14
Previous Myocardial Infarction	130(26.5%)	1084 (23.9%)	0.20
Previous Percutaneous Coronary Intervention	229 (46.7%)	1741 (38.5%)	<0.0001
Previous Coronary Artery Bypass Surgery	75(15.3%)	610 (13.5%)	0.26
Stroke	19(3.9%)	154 (3.4%)	0.58
Transient Ischemia Attack	14(2.9%)	123 (2.7%)	0.86
Peripheral Vascular Disease	41(8.4%)	351 (7.8%)	0.63
CARDIAC STATUS AT ADMISSION			
• Silent Myocardial Ischemia	46(9.4%)	476 (10.6%)	0.44
• Stable Angina Pectoris	270(55.0%)	2168 (47.9%)	0.002
• Acute Coronary Syndrome	174(35.4%)	1882 (41.6%)	0.01
REGION			<0.0001
• Europe	20(1.5%)	1338 (98.5%)	

Variable	Interruption of DAPT Treatment Yes (N = 490)	No (N = 4528)	p-value
• United States	470(12.8%)	3190 (87.2%)	
DISCHARGE MEDICATIONS			
Thienopyridine type			0.022
• Clopidogrel	458(93.3%)	4177 (92.3%)	
• Prasugrel	32(6.5%)	282 (6.2%)	
Warfarin	31(6.3%)	283 (6.3%)	0.95
Proton Pump Inhibitor	117(23.9%)	1057 (23.3%)	0.79

Table 2. Procedural characteristics

Variable	Interruption of DAPT Treatment		
	Yes (N = 490)	No (N = 4528)	p-value
Narrowed coronary artery			
• Left Main	12(2.4%)	146 (3.2%)	0.35
• Left anterior descending	226(46.0%)	2098 (46.3%)	0.93
• Proximal left anterior descending	102(20.8%)	1015 (22.4%)	0.42
• Left circumflex	158(32.2%)	1392 (30.7%)	0.49
• Right	167(34.0%)	1593 (35.2%)	0.63
Number of narrowed coronary arteries			0.90
• 1	422(85.9%)	3870 (85.5%)	
• 2	63(12.8%)	615 (13.6%)	
• 3	5(1.0%)	43 (0.9%)	
Bifurcation lesion	42(8.6%)	553 (12.2%)	0.018
Chronic total occlusion	20(4.1%)	172 (3.8%)	0.76
Thrombotic lesion	25(5.1%)	390 (8.6%)	0.007
Stent type			0.72
• Bare metal stent	89(18.1%)	726 (16.0%)	
• Drug eluting stent, 1st generation	67(13.6%)	607 (13.4%)	
• Drug eluting stent, 2nd generation	365(74.3%)	3195 (70.6%)	
Number of stents implanted			0.003
• 1	301(61.3%)	2481 (54.8%)	
• 2	106(21.6%)	1309 (28.9%)	
• >2	83(16.9%)	738 (16.3%)	

Variable	Interruption of DAPT Treatment		
	Yes (N = 490)	No (N = 4528)	p-value
Total stented length (mm)			0.012
• ≤20	213(43.4%)	1706 (37.7%)	
• >20	277(56.4%)	2822 (62.3%)	
Maximum stent diameter (mm), mean ± SD	3.06 ± 0.48	3.12 ± 0.50	0.0044