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Double Antiplatelet Therapy After Drug-Eluting Stent Implantation

Risk Associated With Discontinuation Within the First Year

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Objectives The goal of this study was to assess the risk associated with double antiplatelet therapy (DAT) discontinuation, and specifically, temporary discontinuation, during the first year after drug-eluting stent (DES) implantation.

Background Doubts remain about the risk of temporary DAT discontinuation within 1 year after DES implantation.

Methods A total of 1,622 consecutive patients undergoing DES implantation at 29 hospitals were followed up at 3, 6, 9, and 12 months to record the 1-year antiplatelet therapy discontinuation (ATD) rate, the number of days without DAT, and the rate of 1-year major cardiac events. Cox regression was used to analyze the association between ATD considered as a time-dependent covariate and 1-year cardiac events.

Results One hundred seventy-two (10.6%) patients interrupted at least 1 antiplatelet drug during the first year after DES implantation, although only 1 during the first month. Most (n = 111, 64.5%) interrupted DAT temporarily (median: 7 days; range: 5 to 8.5): 79 clopidogrel (31 temporarily), 38 aspirin (27 temporarily), and 55 both drugs (53 temporarily). Discontinuation was followed by acute coronary syndrome in 7 (4.1%; 95% confidence interval [CI]: 1.7 to 8.2), a similar rate of major cardiac events to that in patients without ATD (n = 80; 5.5%; 95% CI: 4.4 to 6.8; p = 0.23). ATD was not independently associated with 1-year major cardiac events (hazard ratio: 1.32 [95% CI: 0.56 to 3.12]).

Conclusions ATD within the first year and beyond the first month after DES is not exceptional, is usually temporary, and does not appear to have a large impact on risk. (J Am Coll Cardiol 2012;xx:xxx) © 2012 by the American College of Cardiology Foundation

Premature and permanent thienopyridine discontinuation after drug-eluting stent (DES) implantation conveys a risk for stent thrombosis (1–4), probably on the basis of increased platelet reactivity. Therefore, double antiplatelet therapy (DAT) is recommended for at least 6 to 12 months (5). Although the risk is highest during the first month after

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)

ATD = antiplatelet therapy discontinuation

CI = confidence interval

DAT = double antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

DES implantation and still high within the first 6 months (4,6), a safe time period for antiplatelet therapy discontinuation (ATD) has not yet been defined (7,8). Furthermore, information is scanty about the risk of temporary ATD during the first year that may occur in different scenarios, such as life-threatening hemorrhage, surgical intervention, errors in medical prescription, or lack of adherence. However, the current evidence has been interpreted as implying that any interruption can be dangerous (6,9).

The ACDC (Adherence to Treatment of Coronary Patients After a Catheterization With DES Implantation) is a prospective cohort study addressing the background, incidence, potential predictors, and safety of ATD during the first year after DES implantation (10). It showed that over 14% of patients who received DES interrupted at least 1 antiplatelet drug during the first year after DES implantation, in most cases clopidogrel, usually temporarily, and that discontinuation was most often based on patient decision or medical decisions not associated with major bleeding events or major surgical procedures.

In the present paper, we assess the risk associated with ATD in the ACDC cohort, and specifically, temporary discontinuation, during the first year of DES implantation in terms of cardiac mortality or acute coronary syndrome (ACS).

Methods

Study design and participants. Methods of the ACDC study have been described elsewhere (10). All patients receiving at least 1 DES between January 28, 2008, and April 28, 2008, were recruited by clinical investigators in 29 participating hospitals from Spain. Local investigators were specifically trained and actively participated in the draft of the study protocol.

Study variables included data related to coronary angiography, cardiovascular risk factors, cardiovascular history, complications during admission, and medications at discharge. In addition, psychosocial variables and several hospital characteristics were recorded.

A quality control was performed to ensure consecutive inclusion and quality of data collection in 28 of 29 centers. This quality control led to include retrospectively 75 patients who had been missed by local investigators and to review all the data entered in 5 centers where more than 5 errors/patients were detected.

Follow-up. All patients who signed informed consent were interviewed by phone by trained researchers at 3, 6, 9, and 12 months using a standardized questionnaire to determine: 1) vital status; 2) current medications (patients were asked to collect all their current medications and to read out every brand name); 3) medications temporally or permanently interrupted since the previous phone call; 4) reason and duration of discontinuation; and 5) hospital readmissions. For patients who died, a close relative was interviewed. In case of readmission, clinical records were reviewed at the corresponding center and centrally checked by the main investigator team to establish the reason for readmission and medications during hospitalization and at discharge.

From the phone interviews and the review of clinical records, the following data were assessed for each patient: the approximate date of ATD, the antiplatelet drug that had been interrupted (clopidogrel, aspirin, or both), and in the case of resuming the antiplatelet drug, the date of resumption. Thus, the approximate number of days of discontinuation could be determined in each patient.

The main outcomes of interest were ACS and cardiac death. Both were identified from clinical records by the main investigator team, who was blind to the DAT status at the time of endpoint adjudication. ACS required an increase of cardiac necrosis biomarkers above the upper limit for each local laboratory plus either suggestive symptoms or electrocardiogram changes. Cardiac death was considered in cases of ACS, congestive heart failure, or unexpected death not clearly secondary to a noncardiac cause. The events were adjudicated by the main coordinator team with use of the original source documents.

Statistical analysis. Descriptive data are presented as mean ± SD or proportions for individual characteristics.

To explore the association between ATD and 1-year cardiac mortality or ACS, we used survival analysis, patients being censored at the time of the first of the 2 events. Other causes of censoring were death from noncardiovascular causes, bypass surgery, and loss to follow-up. We employed extended Cox regression modeling, introducing the covariate ATD as time dependent. We introduced the variable ATD using a step function that equals 0 all the time the individual is taking clopidogrel and aspirin, and equals 1 when the individual is not taking clopidogrel and aspirin. We also explored the specific effect of interrupting aspirin or clopidogrel, or both, assigning a different value to each category. Additionally, we explored the specific risk of temporary ATD (i.e., the interruption of antiplatelet therapy and subsequent resumption without the occurrence of any new revascularization or cardiovascular event) by censoring, at the time of ATD, patients who interrupted any drug without resumption.

We first estimated the crude effect of ATD, including it in the model as a single variable (i.e., crude estimate). To estimate the adjusted effect of ATD on cardiac death or ACS, we considered those variables that may potentially be common causes of exposure (i.e., ATD) and outcome (11) as candidate confounders. We considered factors related with the global patient risk, factors related with the severity and natural history of the coronary disease, and factors related with the hospital where the patient underwent the procedure (i.e., teaching hospital and mean number of patients receiving stents in 1 year). All these factors were

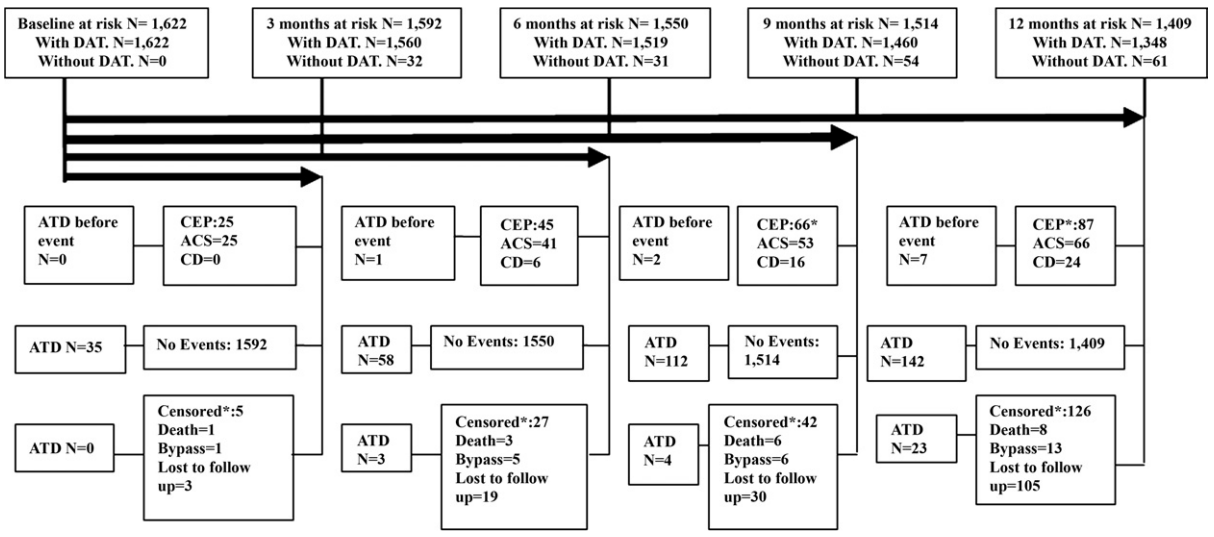

Figure 1 **Outcome Event Incidence Along Follow-Up and Its Relationship With ATD**

Most cases of outcome events were not preceded by antiplatelet therapy discontinuation (ATD). *Censored for other reason different from outcome events. The **boxes on the top** indicate the number of patients at risk at the beginning of each period. Note that a patient may have interrupted antiplatelet therapy at one period and may have resumed the therapy during the following period. ACS = acute coronary syndrome(s); ATD = antiplatelet therapy discontinuation; CD = cardiac death; CEP = composite endpoint; DAT = double antiplatelet therapy.

finally retained if their inclusion modified the coefficient of the effect of the exposure >10%. Proportional hazards assumption was tested for each variable by plots (log (time) versus log [−log (survival)] stratified by the variable).

Several patients died of cardiac causes during the follow-up. In this case, although researchers interviewed their relatives, the possibility of information bias concerning the discontinuation of AT before dying was plausible. Thus, we performed a simulation analysis as sensitivity analysis. The objective was to quantify the impact of a potential information bias. In cases of death from cardiac causes, we simulated different rates of ATD preceding death: 0%, 10%, 25%, 50%, and 100%. Patients who died of cardiac causes were randomly selected for ATD, assuming a Bernoulli distribution. The interval between ATD and death was simulated to be 7 and 15 days. The interval of 7 days was chosen as this was the actual median number of days without DAT in those patients with temporary discontinuation. The previous Cox model was employed to include the variable ATD, again as a time-dependent covariate, but assuming the new ATD distribution. We made 15 iterations to estimate the risk of ATD.

Results

Twenty of 1,985 patients included in the ACDC study died during admission. Thus, there were 1,965 candidates to follow-up. At least 1 time-point follow-up (3, 6, 9, or 12 months) could be assessed in 1,622 (82.5%). In 1,536 patients, follow-up could be achieved for the 4 time points. In the rest, only 2 or 3 follow-up time points were available.

Figure 1 shows the cumulative incidence of the endpoint cardiac mortality or ACS along the 4 time-point study period and its relationship with previous ATD. Eighty-seven of 1,622 patients (5.4%; 95% confidence interval [CI]: 4.3 to 6.6) had a major cardiac event during the first year after DES, but only in 7 of these 87 (8%; 95% CI: 3.3 to 15.9) was a history of ATD recorded. These 7 patients had ACS, and there was important variability concerning the drug interrupted, the moment and duration of interruption, and the time from ATD to event (Table 1). The rate of ATD in patients with events was similar to that among the 1,535 patients without events or who had been censored before the end of follow-up (n = 165, 10.7%; 95% CI: 9.2 to 12.4; p = 0.23). Overall, 172 (10.6%) patients had interrupted at least 1 antiplatelet drug, most of them (n = 111, 64.5%) temporarily: 79 clopidogrel (31 temporarily), 38 aspirin (27 temporarily), and 55 both drugs (53 temporarily). The median number of days without DAT in those who resumed was 7 (interquartile range: 5 to 8.5). The rate of ATD varied slightly across the 4 study intervals: 2.16%, 1.7%, 3.6%, and 3.6%, respectively. Only 1 patient interrupted DAT during the first month after DES implantation. It was to prevent hemorrhagic risk during an admission for endocarditis, and the patient died of sepsis several days later.

Table 2 shows the baseline characteristics of the study population according to the ATD status. Patients who interrupted DAT had a lower rate of prior coronary angioplasty and a higher rate of comorbidities such as chronic obstructive pulmonary disease, chronic renal impairment, and previous major hemorrhage. There were no relevant

Table 1 Features of ATD in 7 Patients With Subsequent Events

	Type of Drug Interrupted	Days to ATD	Treatment Resumed Before Event	Type of Event	Days From ATD to Event	Days From ATD Resumption to Event	Total Days Without DAT
Patient #1	Both	191	No	ACS	14	NA	14
Patient #2	Both	90	No	ACS	3	NA	3
Patient #3	Clopidogrel	84	Yes	ACS	246	239	7
Patient #4	Clopidogrel	60	No	ACS	328	NA	328
Patient #5	Aspirin	266	Yes	ACS	14	4	10
Patient #6	Both	180	No	ACS	193	NA	193
Patient #7	Aspirin	94	No	ACS	222	NA	222

ACS = acute coronary syndrome; ATD = antiplatelet therapy discontinuation; DAT = double antiplatelet therapy; DES = drug-eluting stent(s); NA = not applicable.

differences between both groups concerning psychosocial characteristics. Finally, patients who interrupted DAT were attended less often in more active centers (i.e., with higher rates of patients receiving stents in 1 year).

Risk of ATD during the first year after DES implantation. The unadjusted global risk (hazard ratio [HR]) of cardiac death or ACS associated with ATD was 1.93 (95% CI: 0.87 to 4.28; p = 0.1): 1.95 (95% CI: 0.47 to 7.99; p = 0.35) for isolated aspirin discontinuation, 1.34 (95% CI: 0.32 to 5.5; p = 0.68) for isolated clopidogrel discontinuation, and 2.71 (95% CI: 0.84 to 8.72) for DAT discontinuation. When adjusting for potential confounders, the association remained nonsignificant (Table 3). The same was true when assessing the risk of the isolated temporary ATD by censoring the patients who did not resume DAT at the time of ATD: HR: 0.86 (95% CI: 0.21 to 3.6; p = 0.83).

SIMULATION STUDY. Figure 2 shows the HR and 95% CI of cardiac death or ACS when simulating, in those patients who died of cardiac reasons, a rate of ATD 7 days before dying of 0%, 10%, 25%, 50%, 75%, and 100%. The risk of major cardiac events associated with ATD would have been statistically significant if at least 18.8% of patients who died had interrupted DAT 7 days before dying (HR: 2.04; 95% CI: 1.01 to 4.1). In other words, in our sample, we would have had to misclassify at least 18.8% who died of cardiac causes concerning ATD (i.e., false negatives) to conclude that there was not a statistically significant risk of cardiac events associated with ATD when actually there was. Similar results were obtained simulating the interruption of DAT 15 days before dying (data not shown).

Discussion

The ACDC study shows that although ATD during the first year after DES implantation is not exceptional, in most instances, it was a temporal interruption, the antiplatelet medication being resumed in the following days (median: 7 days). Most importantly, it was not necessarily followed by major cardiovascular events, at least in patients who interrupted DAT later than 1 month after stenting, which was the most common situation in our population.

Interruption of antiplatelet drugs has been shown to be deleterious in several contexts (12), particularly DES thrombosis after clopidogrel discontinuation (1,4,13). However, the impact of discontinuation is less clear after the study by Kimura et al. (14), which casts doubts about the actual role of thienopyridines associated with aspirin for preventing stent thrombosis. Likewise, in another registry (4), clopidogrel discontinuation was not associated with stent thrombosis when it occurred later than 6 months after DES implantation. Although our study was not aimed at assessing stent thrombosis, the tight relationship between stent thrombosis and cardiac death and ACS (4,15,16) leads to similar conclusions regarding the risk assessment of ATD.

The absence of risk of major cardiovascular events associated with ATD found in the present study may be explained by several reasons. First, the rate of ATD during the first month after stenting, the period with the highest risk for ATD (2,3), was negligible. Second, most patients discontinued only clopidogrel or aspirin, and discontinuation was temporary in most, its median duration being 7 days. This is in agreement with recent studies in which a risk of stent thrombosis associated with isolated clopidogrel discontinuation was not shown (14) or was limited to the early period of the treatment (4,17), and where the highest rate of stent thrombosis was usually detected beyond 1 week after discontinuation (4,14). And, third, although in our study the rate of patients undergoing DES implantation in the context of ACS reached 58%, this rate is lower than in other series that have recorded devastating consequences of clopidogrel discontinuation (3), which is probably the context in which DAT is more advantageous. In fact, a recent study about clopidogrel discontinuation after ACS showed a higher risk of death or nonfatal myocardial infarction in those patients who definitely interrupted clopidogrel therapy (18).

Bias may play a role in the results. Specifically, the presence of information bias concerning antiplatelet use could, if extreme, invalidate the results. This risk is especially high in those patients who died, and thus the interviewee had to be a relative. Therefore, we simulated that the information obtained from the relative was wrong in the sense of "favoring" a potential underlying relationship between ATD and major cardiac events. Considering the most unfavorable scenario of misclassification of ATD in those patients who died from cardiac causes, at least 18.8% wrong ATD categorizations would have been needed to falsely conclude an absence of significant risk associated with ATD. Although we believe that such a high

Table 2 Baseline Characteristics of the Study Population According to ATD

	No ATD (n = 1,450)		ATD (n = 172)		Global (n = 1,622)		
	Valid, n		Valid, n		Valid, n		p Value
Demographic and cardiovascular risk factors							
Age, yrs	1,435	64 ± 11	172	65 ± 12	1,607	64.1 ± 11	0.19
Women	1,450	317 (21.9%)	172	33 (19.2%)	1,622	350 (21.6%)	0.49
Active smoker	1,450	320 (22.1%)	172	39 (22.7%)	1,622	359 (22.1%)	0.85
Hypercholesterolemia	1,450	881 (60.8%)	172	104 (60.5%)	1,622	985 (60.7%)	0.93
Hypertension	1,450	972 (67%)	172	113 (65.7%)	1,622	1,085 (66.9%)	0.73
Diabetes mellitus	1,450	529 (36.5%)	172	59 (34.3%)	1,622	588 (36.3%)	0.61
Cardiovascular history							
Peripheral artery disease	1,450	169 (11.7%)	172	27 (15.7%)	1,622	196 (12.1%)	0.14
Stroke	1,450	71 (4.9%)	172	10 (5.8%)	1,622	81 (5%)	0.58
Heart failure	1,450	85 (5.9%)	172	12 (7%)	1,622	97 (6%)	0.50
Pacemaker	1,450	16 (1.1%)	172	2 (1.2%)	1,622	18 (1.1%)	1.00
Valvular prosthesis	1,450	4 (0.3%)	172	2 (1.2%)	1,622	6 (0.4%)	0.13
Atrial fibrillation	1,450	58 (4%)	172	11 (6.4%)	1,622	69 (4.3%)	0.16
Previous AMI	1,450	423 (29.2%)	172	43 (25%)	1,622	466 (28.7%)	0.28
Previous CABG	1,450	120 (8.3%)	172	11 (6.4%)	1,622	131 (8.1%)	0.46
Previous PTCA	1,450	405 (27.9%)	172	35 (20.3%)	1,622	440 (27.1%)	0.04
Other conditions							
Chronic obstructive pulmonary disease	1,450	136 (9.4%)	172	25 (14.5%)	1,622	161 (9.9%)	0.04
Chronic renal impairment	1,450	90 (6.2%)	172	21 (12.2%)	1,622	111 (6.8%)	0.01
Previous major hemorrhage	1,450	26 (1.8%)	172	9 (5.2%)	1,622	35 (2.2%)	0.01
Previous major surgery	1,450	417 (28.8%)	172	56 (32.6%)	1,622	473 (29.2%)	0.33
Chronic hepatic disease	1,450	14 (1%)	172	4 (2.3%)	1,622	18 (1.1%)	0.11
Oncologic disease	1,450	26 (1.8%)	172	3 (1.7%)	1,622	29 (1.8%)	1.00
Surgery scheduled for the following year	1,450	39 (2.7%)	172	5 (2.9%)	1,622	44 (2.7%)	0.80
Long-term AT before admission	1,450	754 (52%)	172	88 (51.2%)	1,622	842 (51.9%)	0.87
Long-term AC before admission	1,450	57 (3.9%)	172	8 (4.7%)	1,622	65 (4%)	0.68
Psychosocial characteristics							
Immigrant	1,450	43 (3%)	172	7 (4.1%)	1,622	50 (3.1%)	0.48
Professional situation							0.6
Employed	1,431	490 (34.2%)	168	51 (30.4%)	1,599	541 (33.8%)	
Retired	1,431	782 (54.6%)	168	100 (59.5%)	1,599	882 (55.2%)	
Unemployed	1,431	40 (2.8%)	168	3 (1.8%)	1,599	43 (2.7%)	
Other situation	1,431	119 (8.3%)	168	14 (8.3%)	1,599	133 (8.3%)	
Education level							
Low education level	1,429	399 (27.9%)	167	50 (29.9%)	1,596	449 (28.1%)	0.76
Medium education level	1,429	632 (44.2%)	167	69 (41.3%)	1,596	701 (43.9%)	
High education level	1,429	398 (27.9%)	167	48 (28.7%)	1,596	446 (27.9%)	
PHQ9							
Low/medium disorder	1,431	1,250 (87.4%)	167	147 (88%)	1,598	1,397 (87.4%)	0.90
Moderate to severe disorder	1,431	181 (12.6%)	167	20 (12%)	1,598	201 (12.6%)	

Continued on next page

rate of misclassification is unlikely, even in this worst scenario, the risk of serious events associated with ATD would have ranged from an HR of 1.01 to an HR of 4.1, which is a far less devastating effect than reported in other studies (2,4). The bias of wrong ATD classification in those patients who did not die seems less likely. Conversely, it could also be possible that the high rate of adverse events associated with clopidogrel discontinuation observed in other studies (3) was partially due to a bias in the sense of detecting more ATD in those patients with events.

Studies usually evaluate the status of thienopyridine use at certain time intervals (3,4,13), and occasionally, they have analyzed it immediately before an event (4,14,15). In the present study, we assessed the consequences of the most common situation, that is, the temporal discontinuation of clopidogrel and/or aspirin for a few days with subsequent resumption. This has received less attention, or its evaluation has been less clear, probably because of its complexity. In addition to the problems in adherence assessment, there are difficulties of definition that hinder comparison or interpretation in different studies. For instance, in some studies (13), complete interruption is defined as any discontinuation lasting for longer than a given period, not providing further data on its actual duration. In fact, most studies lack information about the temporary or permanent character of discontinuation (18).

Table 2 Continued

	No ATD (n = 1,450)		ATD (n = 172)		Global (n = 1,622)		
	Valid, n		Valid, n		Valid, n		p Value
Admission features							
Acute coronary syndrome (admission diagnosis)	1,450	840 (57.9%)	172	107 (62.2%)	1,622	947 (58.4%)	0.29
Worst Killip class III–IV during admission	1,450	37 (2.6%)	172	9 (5.2%)	1,622	46 (2.8%)	0.05
Heart failure during admission	1,450	85 (5.9%)	172	12 (7%)	1,622	97 (6%)	0.50
Major hemorrhage during admission	1,450	7 (0.5%)	172	0 (0%)	1,622	7 (0.4%)	1.00
Ejection fraction below 45% at discharge (n = 1,203)	1,072	167 (15.6%)	131	25 (19.1%)	1,203	192 (16%)	0.31
AC therapy prescribed at discharge	1,446	32 (2.2%)	171	6 (3.5%)	1,617	38 (2.4%)	0.28
Off-label indications of DES	1,439	937 (65.1%)	169	81 (47.9%)	1,608	1,018 (63.3%)	<0.001
Type of DES							
Sirolimus	1,450	221 (15.24%)	172	23 (13.37%)	1,622	244 (15.04%)	0.574
Everolimus	1,450	500 (34.48%)	172	50 (29.07%)	1,622	550 (33.91%)	0.173
Paclitaxel	1,450	560 (38.62%)	172	66 (38.37%)	1,622	626 (38.59%)	1.000
Zotarolimus	1,450	234 (16.14%)	172	27 (15.7%)	1,622	261 (16.09%)	1.000
Patient included in clinical trial	1,445	183 (12.7%)	170	22 (12.9%)	1,615	205 (12.7%)	0.90
Hospital characteristics							
University hospital	1,450	1,249 (86.1%)	172	145 (84.3%)	1,622	1,394 (85.9%)	0.49
Private funding	1,450	181 (12.5%)	172	18 (10.5%)	1,622	199 (12.3%)	0.54
Mean number of patients attended							0.033
<500 patients/yr	1,450	453 (31.2%)	172	60 (34.9%)	1,622	513 (31.6%)	
500–1,000 patients/yr	1,450	523 (36.1%)	172	73 (42.4%)	1,622	596 (36.7%)	
>1,000 patients/yr	1,450	474 (32.7%)	172	39 (22.7%)	1,622	513 (31.6%)	

Values are mean ± SD or n (%). *10 years per unit of risk increase; †>100 beds per unit of risk increase; ‡100 patients per unit of risk increase; §>Cutoff PHQ value = 10.
AC = anticoagulant; AMI = acute myocardial infarction; AT = antiplatelet therapy; CABG = coronary artery bypass grafting; PHQ = Patient Health Questionnaire-915; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.

Temporary ATD may occur in different scenarios, more often in the context of bleeding events or invasive procedures (10). In the present work, we used extended Cox regression modeling with a time-dependent covariate, which permits us to examine the continuous risk of ATD and thus the implications of temporary ATD. Our results suggest that a discontinuation for a few days (median: 7 days) of ATD after the first month of DES implantation may be reasonably safe in terms of major cardiac events. However, the absence of a statistically significant association may have been because of insufficient power, as convincing instances of stent thrombosis shortly after ATD have been reported. Moreover, it is possible that some of the cardiac events observed in the ACDC study, with or without DAT, may have been due to stent thrombosis. In any case, our study suggests that the risk associated with temporary ATD may not be so devastating as implied in previous reports. This information could be helpful in situations with conflicting risks, such as the unexpected need for major noncardiac surgery in patients with DES, but needs further confirmation because stent thrombosis, even if rare, may have dire consequences.

Study limitations and strengths. A total of 343 of 1,965 (17.4%) patients were finally not followed up, in most cases because they refused to participate. Although there were no

Table 3 Adjusted Risk of Major Cardiac Event Associated With DAT Discontinuation During the First Year After DES Implantation

	HR	95% CI	p Value
Antiplatelet therapy discontinuation	1.32	0.56–3.12	0.526
Aspirin	1.33	0.32–5.49	0.696
Clopidogrel	1.29	0.31–5.34	0.725
Both	1.34	0.32–5.63	0.685
Age (each 10 yrs)	1.37	1.10–1.70	0.005
Chronic obstructive pulmonary disease	1.81	1.04–3.14	0.035
Chronic renal impairment	2.88	1.66–4.99	<0.001
Worst Killip class III–IV during admission	1.65	1.04–2.61	0.032
Off-label indications of DES	1.85	1.10–3.09	0.020

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

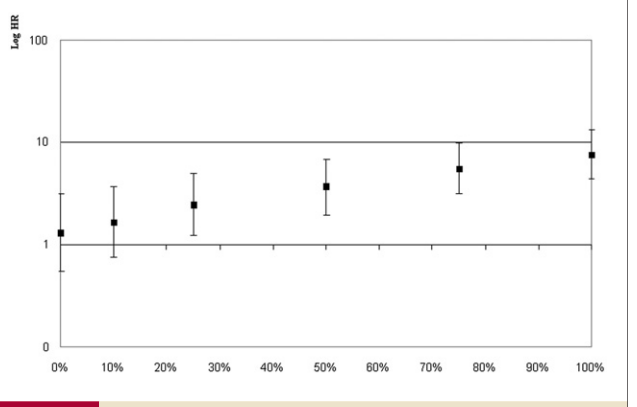

Figure 2 Risk of Outcome Event According to Different Simulated Rates of ATD Before Death

The ordinate expresses the log hazard ratios (HR) and 95% confidence intervals (error bars) of cardiac death or acute coronary syndrome when simulating, in those patients who died of cardiac causes, a rate of antiplatelet therapy discontinuation (ATD) before dying of 0%, 10%, 25%, 50%, 75%, and 100%.

important differences between both cohorts (Online Appendix I), some kind of selection bias is possible. Particularly problematic are the 23 patients from this cohort who died and in whom compliance with antiplatelet medication could not be assessed. Stent thrombosis associated with ATD cannot be ruled out as the ultimate cause of death. As previously reported (10), none of these patients had undergone invasive procedures or hospitalization for hemorrhagic complications before death, which are the most frequent circumstances we found associated with temporary ATD. However, ATD on patient initiative is still possible. As additional information, we could find out that none of these deaths occurred during the first month after stenting and that at least in 13 of them, the cause of death was not cardiac. Similarly, 105 of 1,622 patients (6.47%) were censored before completing 1 year of follow-up because of loss to follow-up, and thus their final status could not be determined. However, most of these follow-up losses occurred during the last follow-up period (i.e., from the 9th to the 12th month) when the risk associated with ATD is likely lower.

A potential recall bias may exist concerning follow-up information. However, most patients received a phone call not later than 3 months after the previous one, and this could minimize such bias. On the other hand, repeated calls may have led patients to be more compliant with medication, so that in fact, the estimated rate of ATD could be lower than it would have been in other contexts. Finally, confounding bias is also possible.

Our study has additional strengths. We systematically evaluated antiplatelet medication resumption after discontinuation with a structured survey, which is an uncommon practice in studies assessing ATD, as is the distinction between both drugs. We did a thorough quality control to ensure consecutive inclusion and quality of data collection, as previously reported (10). Finally, clinical records of readmitted patients were centrally reviewed by the main investigator team.

Conclusions

ATD within the first year and beyond the first month after DES is not exceptional and is usually temporary. Although further knowledge about individual risk is desirable, our results suggest that discontinuation for a few days (median: 7 days) of DAT after the first month of DES implantation may be reasonably safe in terms of major cardiac events.

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Key Words: adherence ■ antiplatelet therapy ■ compliance ■ drug-eluting stents ■ interruption.

APPENDIX

For a supplementary table and a list of the ACDC study investigators, please see the online version of this paper.