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Time-Dependent Associations Between Actionable Bleeding, Coronary Thrombotic Events, and Mortality Following Percutaneous Coronary Intervention

Results From the PARIS Registry

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ABSTRACT

OBJECTIVES The aim of this study was to examine the independent associations between actionable bleeding (AB) and coronary thrombotic events (CTE) on mortality risk after percutaneous coronary intervention (PCI).

BACKGROUND The independent impact of AB and CTE on mortality risk after PCI remains poorly characterized.

METHODS A post hoc analysis was conducted of the PARIS (Patterns of Non-Adherence to Dual Antiplatelet Therapy in Stented Patients) registry, a real-world cohort of 5,018 patients undergoing PCI with stent implantation. CTE included definite or probable stent thrombosis or myocardial infarction. AB was defined as Bleeding Academic Research Consortium type 2 or 3. Associations between CTE and AB, both of which were modeled as time-dependent covariates, and 2-year mortality risk were examined using extended Cox regression.

RESULTS Over 2 years, the cumulative incidence of CTE, AB, and all-cause mortality was 5.9% (n = 289), 8.1% (n = 391), and 4.7% (n = 227), respectively. Adjusted hazard ratios for mortality associated with CTE and AB were 3.3 (95% confidence interval: 2.2 to 4.9) and 3.5 (95% confidence interval: 2.3 to 5.4), respectively. Temporal gradients in risk after either event were highest in the first 30 days and declined rapidly thereafter. Thrombotic events occurring while patients were on versus off dual-antiplatelet therapy were associated with a higher mortality risk, whereas risk related to AB was not influenced by dual-antiplatelet therapy status at the time of bleeding.

CONCLUSIONS Intracoronary thrombosis and AB are associated with mortality risks of comparable magnitude over a 2-year period after PCI, findings that might inform risk/benefit calculations for extension versus discontinuation of dual-antiplatelet therapy. (J Am Coll Cardiol Intv 2016;9:1349–57) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AB = actionable bleeding

BARC = Bleeding Academic Research Consortium

CI = confidence interval

CTE = coronary thrombotic event(s)

DAPT = dual-antiplatelet therapy

HR = hazard ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

ST = stent thrombosis

Thrombotic complications following percutaneous coronary intervention (PCI), such as stent thrombosis (ST) and myocardial infarction (MI), are associated with a markedly increased risk for subsequent adverse events, including mortality (1-3). Mitigating such risk requires dual-antiplatelet therapy (DAPT), the length of which may vary by a patient's clinical presentation, risk factors, or stent platform. The unavoidable corollary to such therapy is bleeding, however, which also is associated with increased risk for both short- and long-term mortality (2,4). As a result, identifying the optimal duration of DAPT that minimizes bleeding risk without compromising antithrombotic efficacy has become a highly relevant area of clinical investigation. Although multiple randomized trials have examined the impact of different durations of DAPT after PCI, results thus far have been somewhat inconsistent, further complicating decision making in this regard (5-7).

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However, because intracoronary thrombosis and bleeding represent the gains and costs from extension of DAPT, weighing the relative impact of each event on post-PCI mortality may provide a more nuanced appraisal of the risks and benefits of such a strategy. Although several studies have examined such associations, some evaluated bleeding and thrombosis separately, with limited data reported after mutual adjustment for both types of events (8-10). This is a clinically relevant distinction, as frequently observed contributors to bleeding, such as older age, renal dysfunction, and ST-segment deviation (11), are also linked with increased risks for thrombosis (12,13), suggesting that many patients may be at high and comparable risk for both events. Accordingly, we sought to examine the association between both bleeding and thrombotic complications, on subsequent mortality risk in a large and contemporary cohort of patients undergoing PCI.

METHODS

STUDY DESIGN AND POPULATION. The details of the PARIS (Patterns of Non-Adherence to Dual Antiplatelet Therapy in Stented Patients) registry have been previously reported in detail (14). In brief, the PARIS registry was a prospective observational study of patients undergoing PCI with stent implantation at 15 clinical sites in the United States and Europe between July 1, 2009, and December 2, 2010. Adult patients (18 years of age or older) undergoing stent implantation in at least 1 native coronary artery and discharged on DAPT were eligible for enrollment. All patients provided written informed consent.

DEFINITIONS. ST was defined according to the Academic Research Consortium criteria (15). MI was defined in accordance with the universal definition (16). For the present analysis, coronary thrombotic events (CTE) were defined as definite or probable ST or MI. Bleeding was classified using the Bleeding Academic Research Consortium (BARC) criteria (17). We classified actionable bleeding (AB) as BARC type 2 or 3. BARC type 2 is defined as clinically overt hemorrhage requiring medical attention, whereas BARC type 3 includes bleeds with a hemoglobin decrease of at least 3 g/dl, requiring transfusion or surgical intervention. Death was classified as cardiac or noncardiac per the Academic Research Consortium definitions (15). Our primary intent was to examine mortality risk related to nonfatal CTE and bleeding, as both of these events were either reduced or increased by a prolonged DAPT strategy (6). As a result, we did not model associations for events that

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may be considered fatal, such as BARC type 5 bleeds or those occurring on the same day as death.

FOLLOW-UP. Follow-up was done via telephone by trained research coordinators 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 (ischemic or bleeding) and 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 drug treatment was stopped (physician direction, need for surgery, bleeding, other). All information was then forwarded to the external Clinical Events Committee for formal adjudication.

STATISTICAL ANALYSIS. Baseline clinical, demographic, and procedural characteristics are presented as mean ± SD or count (percentage) for continuous and categorical variables among patients with and without AB and with and without CTE, respectively. Analyses were repeated after excluding patients who experienced both AB and CTE over the study period (n = 66).

The cumulative incidence of CTE, AB, and death at 2 years was calculated using the Kaplan-Meier method as the time to first occurrence of each adverse event. We then examined associations between CTE, AB, and death. In these analyses, all-cause death at 2 years served as the dependent outcome, whereas CTE and AB represented the key independent variables of interest. As CTE and AB occur over time, we generated time-dependent covariates for these exposures, thereby allowing subjects to contribute exposure time before and after the occurrence of either adverse event. To account for the timing of CTE in relation to PCI and the different components of CTE (ST or MI), the time-dependent covariate for CTE was hierarchical, in which the most severe state was defined as nonperiprocedural ST followed by nonperiprocedural MI and then periprocedural ST or MI. Analogously, AB was entered as a hierarchical time-dependent covariate in which the highest risk state was nonperiprocedural BARC type 3 followed by nonperiprocedural BARC type 2 and then periprocedural bleeding. Hazard ratios (HR) were generated using extended Cox regression, a flexible modeling approach that allows departures from proportional hazards with covariates that either interact with or vary by time (18,19). Models were adjusted using the following covariates that were either significantly different between exposure groups or plausibly related to mortality: age, sex, acute coronary syndrome, stent type, region (United States vs. Europe), diabetes mellitus, final TIMI (Thrombolysis In Myocardial Infarction) flow grade <3, current smoking, peripheral vascular disease, triple therapy at discharge, proton pump inhibitor use, body mass index, maximal stent diameter, prior PCI, prior MI, prior coronary artery bypass grafting, prior stroke, chronic kidney disease, and hemoglobin. The effect sizes of CTE and AB were directly compared using the Wald test, controlling for other covariates.

Mortality associations were also examined in different clinical subgroups with formal interaction testing between the main effects of subgroup (yes or no) and CTE or AB. Additional analyses were performed to examine the influence of DAPT status at the time of CTE or AB and to calculate mortality risks in relation to time after either event. To address the former, we generated categorical time-dependent covariates for both CTE and AB with different levels corresponding to whether a patient was on or off DAPT at the time of the adverse event. Statistical heterogeneity in mortality risk according to DAPT status was assessed by including interaction terms between the main effects of adverse event (CTE or AB) and DAPT status. For the latter, we generated additional binary time-dependent covariates corresponding to discrete time intervals after CTE or AB (1 to 30 days, 31 days to 1 year, >1 year). Finally, we tabulated the proportion of all deaths in the following time intervals after CTE or AB: 1 to 7, 8 to 30, and >30 days.

RESULTS

Baseline clinical and procedural parameters are presented in Tables 1 and 2, respectively. Over the 2-year study period, 289 patients experienced CTE, whereas AB occurred in 391. Periprocedural CTE occurred in 87 patients (30.1%), whereas nonperiprocedural MI and nonperiprocedural ST occurred in 139 (48.1%) and 63 (21.8%) patients, respectively. Most occurrences of ST (n = 47 [66%]) presented as MI. Analogously, periprocedural AB, nonperiprocedural BARC type 2 bleeding, and nonperiprocedural BARC type 3 bleeding occurred in 32 (8.2%), 190 (48.6%), and 169 patients (43.2%), respectively. Patients with AB were older and more often female and anemic with lower body mass index compared with those not experiencing either type of adverse event (n = 4,404) or CTE. In contrast, the prevalence of diabetes mellitus requiring insulin, current smoking, and prior PCI was higher among patients with CTE. With respect to procedural parameters, stent diameter was smallest and the frequency of lesions with final TIMI flow grade <3 was highest among patients with CTE.

TABLE 1 Baseline Characteristics by Coronary Thrombotic Events and Actionable Bleeding

	No CTE (n = 4,729)	CTE (n = 289)	p Value	No AB (n = 4,627)	AB (n = 391)	p Value
Age, yrs	63.7 ± 11.3	64.4 ± 11.8	0.57	63.6 ± 11.3	68.1 ± 11.4	<0.001
Female	1,199 (25.4)	80 (27.7)	0.38	1,136 (24.6)	143 (36.6)	<0.001
Body mass index, kg/m^2	29.3 ± 5.6	29.4 ± 6.0	0.56	29.3 ± 5.6	28.8 ± 5.9	0.09
Diabetes mellitus requiring insulin	485 (10.3)	60 (20.8)	<0.001	490 (10.6)	55 (14.1)	0.03
Chronic kidney disease	893 (20.7)	85 (31.0)	<0.001	859 (20.4)	119 (32.1)	<0.001
Anemia	716 (16.9)	66 (25.1)	0.001	673 (16.3)	109 (31.4)	<0.001
Hypertension	3,771 (79.7)	238 (82.4)	0.28	3,686 (79.7)	323 (82.6)	0.16
Dyslipidemia	3,580 (75.7)	221 (76.5)	0.77	3,515 (75.9)	286 (73.2)	0.21
Current smoking	912 (19.3)	69 (23.9)	0.06	912 (19.7)	69 (17.7)	0.32
Prior MI	1,122 (23.7)	92 (31.8)	0.002	1,116 (24.1)	98 (25.1)	0.67
Prior CABG	625 (13.2)	60 (20.8)	<0.001	619 (13.4)	66 (16.9)	0.05
Prior PCI	1,842 (38.9)	128 (44.3)	0.07	1,815 (39.2)	155 (39.6)	0.87
PVD	364 (7.7)	28 (9.7)	0.22	361 (7.8)	31 (7.9)	0.93
Prior stroke	156 (3.3)	17 (5.9)	0.02	153 (3.3)	20 (5.1)	0.06
Acute coronary syndrome			0.09			0.11
Troponin negative	1,361 (28.7)	94 (32.5)		1,331 (28.8)	124 (31.7)	
Troponin positive	563 (11.8)	38 (13.2)		550 (11.9)	51 (13.0)	
Educational level			0.89			0.19
Less than secondary school	544 (11.8)	49 (17.1)		543 (12.0)	50 (13.0)	
Secondary school	2,351 (50.5)	132 (45.9)		2,279 (50.4)	204 (52.9)	
PPI use	1,103 (23.3)	71 (24.5)	0.63	1,084 (23.4)	90 (23.0)	0.85
Triple therapy	292 (6.2)	22 (7.6)	0.33	247 (5.3)	67 (17.1)	<0.001

Values are mean ± SD or n (%).

AB = actionable bleeding; CABG = coronary artery bypass graft; CTE = coronary thrombotic event(s); MI = myocardial infarction; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; PVD = peripheral vascular disease; ST = stent thrombosis.

TABLE 2 Procedural Parameters by Coronary Thrombotic Events and Actionable Bleeding

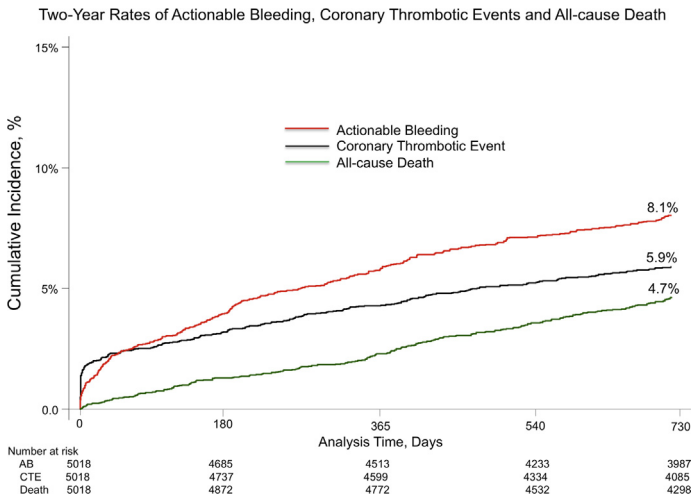
	No CTE (n = 4,729)	CTE (n = 289)	p Value	No AB (n = 4,627)	AB (n = 391)	p Value
Vessel treated						
Left main	149 (3.2)	9 (3.1)	0.97	139 (3.0)	19 (4.9)	0.04
LAD	2,190 (46.3)	134 (46.4)	0.99	2,160 (46.7)	164 (41.9)	0.07
RCA	1,657 (35.0)	103 (35.6)	0.84	1,609 (34.8)	151 (38.6)	0.13
LCx	1,486 (31.0)	82 (28.4)	0.34	1,423 (30.8)	127 (32.5)	0.48
Bifurcation lesion	562 (11.9)	33 (11.4)	0.81	545 (11.8)	50 (12.8)	0.55
CTO lesion	180 (3.8)	4 (1.4)	0.03	172 (3.7)	12 (3.1)	0.51
Thrombotic lesion	390 (8.3)	25 (8.7)	0.81	387 (8.4)	28 (7.2)	0.41
Baseline TIMI flow grade 0/1	521 (11.4)	29 (10.6)	0.69	513 (11.5)	37 (10.0)	0.38
Final TIMI flow grade <3	23 (0.5)	5 (1.8)	0.01	26 (0.6)	2 (0.5)	0.92
Maximal stent diameter, mm	3.1 ± 0.5	3.0 ± 0.5	0.05	3.1 ± 0.5	3.1 ± 0.5	0.34
Stent type						
BMS	810 (17.1)	74 (25.6)	<0.001	786 (16.9)	98 (25.1)	<0.001
First-generation DES	635 (13.4)	39 (13.5)	0.97	629 (13.6)	45 (11.5)	0.25
Second-generation DES	3,479 (73.6)	190 (65.7)	0.004	3,400 (73.5)	269 (68.8)	0.045
Number of stents implanted			0.24			0.11
1	2,635 (55.7)	147 (50.9)		2,585 (55.9)	197 (50.4)	
2	1,328 (28.1)	87 (30.1)		1,292 (27.9)	123 (31.5)	
>2	766 (16.2)	55 (19.0)		750 (16.2)	71 (18.2)	

Values are n (%) or mean ± SD.

BMS = bare-metal stent(s); CTO = chronic total occlusion; DES = drug-eluting stent(s); LCx = left circumflex coronary artery; LAD = left anterior descending coronary artery; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

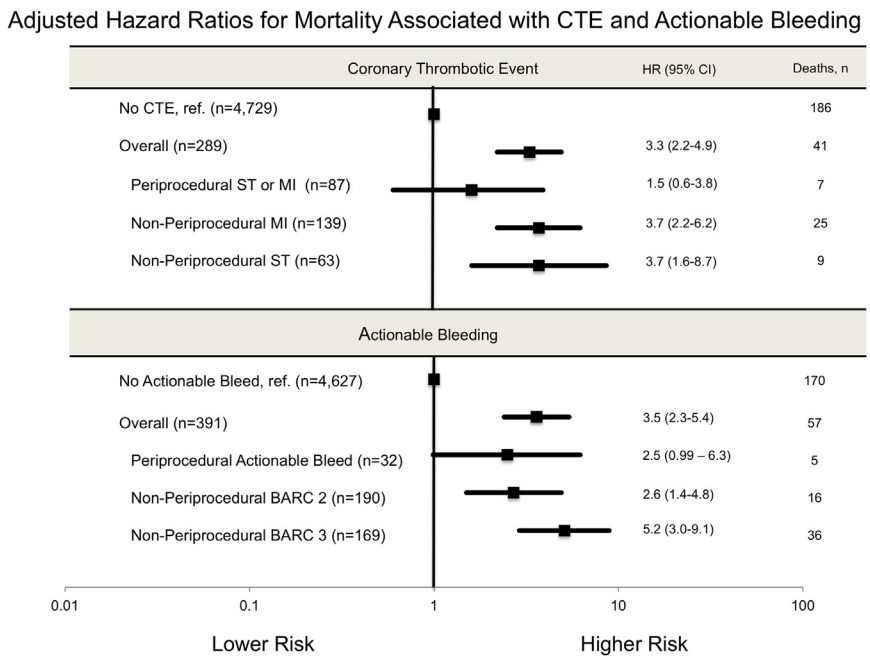
Over the 2-year study period, a total of 340 patients (6.8%) were lost to follow-up. The crude incidence of CTE, AB, and all-cause mortality at 2 years is depicted in Figure 1. The number of patients and corresponding Kaplan-Meier estimate for each event were 289 (5.9%), 391 (8.1%), and 227 (4.7%), respectively. Median follow-up after CTE and AB was similar (1.2 and 1.3 years, respectively). Adjusted HR for CTE and AB, overall and in relation to PCI timing and the severity of each event, are displayed in Figure 2. Mortality HR for any CTE and AB were 3.3 (95% confidence interval [CI]: 2.2 to 4.9) and 3.5 (95% CI: 2.3 to 5.4), respectively, point estimates that were statistically comparable to each other ($p = 0.83$ for the effect size of CTE vs. AB). To account for possible heterogeneity in mortality associations related to participating region, analyses were repeated with region included as either a random effect or a stratification variable, yielding almost identical results to our primary findings (data not shown). Periprocedural CTE were associated with a nonsignificant 1.5-fold higher risk for mortality, whereas the corresponding estimate for AB was 2.5 (95% CI: 0.99 to 6.3). Nonperiprocedural ST and MI were each

FIGURE 1 Cumulative Incidence of Coronary Thrombotic Events, Actionable Bleeding, and All-Cause Death Over 2 Years



Incidence was calculated as Kaplan-Meier estimate of time to first event. Curves are presented for descriptive purposes only, as groups are not mutually exclusive. AB = actionable bleeding; CTE = coronary thrombotic event(s).

FIGURE 2 Forest Plot Demonstrating Adjusted Hazard Ratios and 95% Confidence Intervals for 2-Year Mortality Associated With Coronary Thrombotic Events and Actionable Bleeding



Associations are displayed according to the timing (periprocedural and nonperiprocedural) and severity of each event. BARC = Bleeding Academic Research Consortium; CI = confidence interval; CTE = coronary thrombotic event(s); HR = hazard ratio; MI = myocardial infarction; ST = stent thrombosis.

associated with mortality risks of comparable magnitude, whereas nonperiprocedural BARC type 3 bleeding was associated with an approximate 2-fold higher risk compared with BARC type 2 bleeding. All other parameters with significant associations with 2-year mortality are presented in Online Table 1.

Associations among CTE, AB, and 2-year mortality across different clinical subgroups are shown in **Figure 3**. In general, both CTE and AB were associated with similar mortality hazards, without evidence of statistical interaction.

Table 3 shows the results of analyses relating the influence of DAPT status and time interval on mortality risk associated with CTE and AB. Among the 289 patients with CTE, most (n = 227 [79%]) occurred while on DAPT. Risk after CTE was much higher for patients on (HR: 3.9; 95% CI: 2.6 to 5.9) versus off (HR: 1.3; 95% CI: 0.5 to 3.1) DAPT at the time of thrombosis, with evidence of interaction ($p_{int} = 0.02$). In contrast, mortality risks associated with AB were nondifferential by DAPT status ($p_{int} = 0.55$). As shown in the bottom half of **Table 3**, mortality risks in the first 30 days, 31 days to 1 year, and 1 to 2 years after CTE were 13.3 (95% CI: 7.1 to 25.0), 2.5 (95% CI: 1.4 to 4.3), and 1.9 (95% CI: 0.9 to 4.2), respectively ($p_{trend} < 0.001$). A similar temporal gradient in mortality risk was observed for AB.

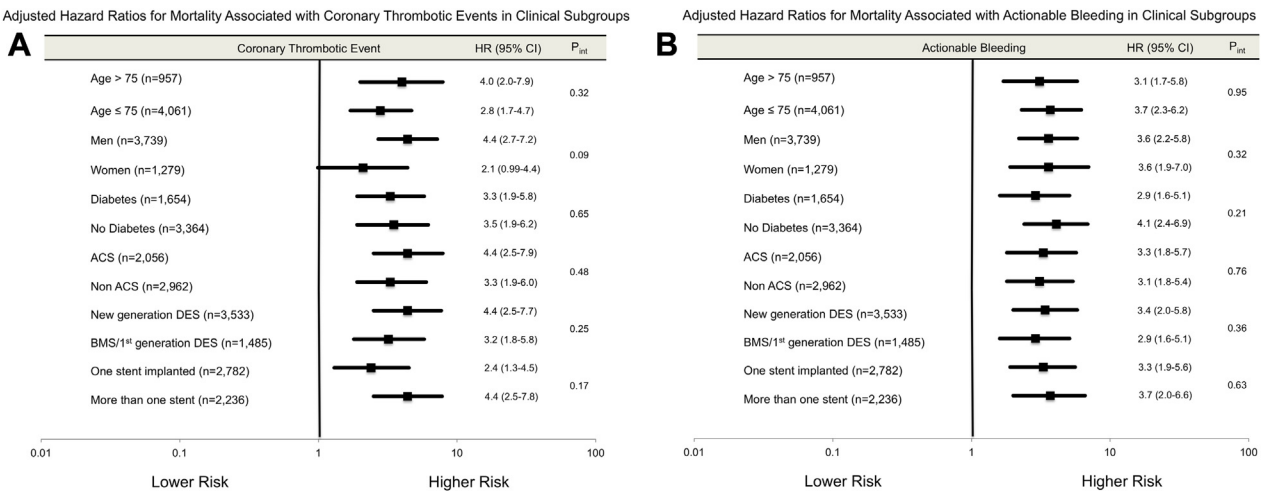
As shown in Online Figure 1, most deaths after CTE or AB occurred at least 30 days after the index event (59.0% and 72.0%). Additional sensitivity analyses after excluding patients with both CTE and AB (n = 66) or using cardiac death as the dependent outcome are shown in Online Tables 2 and 3, with similar results to our primary analyses.

DISCUSSION

In the present study, comprising more than 5,000 patients undergoing PCI, we found substantial, independent, and comparable risks for mortality over 2 years subsequent to an episode of BARC type 2 or 3 bleeding or coronary thrombosis. Nonperiprocedural events were associated with greater risk compared with those occurring at the time of PCI, with the highest mortality hazard related to out-of-hospital BARC type 3 bleeds. Results remained consistent after multivariate adjustment and across different clinical subgroups. In addition, we observed that DAPT status modified CTE-related risk, with an accentuated mortality hazard associated with thrombotic events occurring while patients were on as opposed to off DAPT. In aggregate, these results reinforce the importance of DAPT adherence to mitigate the impact of early thrombosis and highlight the role of bleeding beyond the early post-procedural period as a correlate of mortality risk after PCI.

Although several studies have examined mortality associations between thrombotic or bleeding complications after PCI (1,2,4,20-26), several of these were limited by the inclusion of select populations

FIGURE 3 Forest Plot Showing Adjusted Hazard Ratios and 95% Confidence Intervals for 2-Year Mortality Associated With Coronary Thrombotic Events and Actionable Bleeding in Different Clinical Subgroups



(A) Coronary thrombotic events (CTE) and **(B)** actionable bleeding (AB). ACS = acute coronary syndrome; BMS = bare-metal stent(s); CI = confidence interval; DES = drug-eluting stent(s); HR = hazard ratio.

TABLE 3 Influence of Dual-Antiplatelet Therapy Status and Time Period on Mortality Risk Associated With Coronary Thrombotic Events and Actionable Bleeding

	HR (95% CI)	Deaths	p_{int}
Risk with CTE and AB according to DAPT status at time of event			
CTEs			
On DAPT (n = 227)	3.9 (2.6–5.9)	35	0.02
Off DAPT (n = 62)	1.3 (0.5–3.1)	6	
AB			
On DAPT (n = 281)	2.4 (1.6–3.7)	37	0.55
Off DAPT (n = 110)	5.7 (3.3–9.9)	20	
Time-dependent mortality risks associated with CTE and AB*			
CTEs			
1–30 days	13.3 (7.1–25.0)	17	<0.001
31 days to 1 yr	2.5 (1.4–4.3)	16	
1–2 yrs	1.9 (0.9–4.2)	8	
AB			
1–30 days	11.0 (5.9–20.8)	16	<0.001
31 days to 1 yr	2.3 (1.3–3.9)	23	
1–2 yrs	3.6 (1.9–6.6)	18	

*Point estimates represent adjusted hazards for mortality in discrete time intervals after CTE or AB. p values for trend are displayed in lower half of table.

CI = confidence interval; DAPT = dual-antiplatelet therapy; HR = hazard ratio; other abbreviations as in Table 1.

(1,2,22,24), focusing on just in-hospital events (20,25), or modeling risks after 1 type of adverse event alone (20,22,23). These distinctions are clinically meaningful because the merits of prolonging DAPT warrant a simultaneous appraisal of both ischemic and hemorrhagic complications that might accrue during the short- or long-term phase of therapy. In this regard, a retrospective analysis by Kazi et al. (21) from a large administrative claims database showing comparable mortality risks associated with MI and bleeding is consistent with our findings. Nevertheless our results, from a prospective registry with independent event adjudication, extend these earlier observations to a more contemporary cohort primarily treated with second-generation drug-eluting stent(s).

We also assessed the influence of antiplatelet therapy status at the time of thrombosis or bleeding as a modifier of mortality risk related to each event. We found that the mortality hazard associated with CTE was substantially higher among patients on versus off DAPT at the time of thrombosis. This result is consistent with the "aspirin paradox," wherein risk for recurrent adverse events in patients with acute coronary syndrome is higher among those on versus off aspirin at the time of acute coronary syndrome (27). We now extend this concept to a contemporary PCI cohort treated with DAPT. The occurrence of thrombosis despite ongoing platelet inhibition may reflect a state of enhanced blood thrombogenicity, generalized platelet hyperreactivity, or resistance to either aspirin or clopidogrel (i.e., biological effect) (28). Alternatively, ongoing treatment with DAPT in a real-world population may be a marker of higher risk patients vis-à-vis confounding by indication, thereby accounting for the differential risk as a function of DAPT status (i.e., an epiphenomenon). Nevertheless, the small number of deaths occurring after CTE in off-DAPT patients, coupled with the possibility of residual confounding, renders these results speculative and requiring substantiation in external cohorts.

In contrast, we observed a directionally opposite result with regard to AB, with a higher mortality risk observed among those off versus on DAPT at the time of bleeding. Our findings are very similar to those previously reported by Berger et al. (29) from a post hoc analysis of a randomized cohort. In that study, the adjusted HR for mortality associated with bleeding among patients on aspirin alone and DAPT were 5.27 and 1.48, respectively, a gradient in risk that approximates our results. As suggested by Berger et al. (29), the excess risk with bleeding in the setting of aspirin alone may be due to bleeding sources that directly result in mortality or a marker of higher risk patients. The latter hypothesis is most consistent with our findings, as we excluded fatal bleeding events from our primary analysis. For example, we found that patients with bleeding complications were older and more often female with lower body mass index compared with their nonbleeding counterparts. In addition, most deaths after AB and CTE occurred at least 30 days after the event, a time interval that indicates that such nonfatal events may serve more as proxies or markers of risk rather than as direct and causal antecedents to mortality.

In addition to examining the impact of bleeding and CTE that occurred over the entire study period, we also evaluated associations after taking into account the timing and severity of each respective event. Periprocedural thrombotic events were much more common than bleeding complications, occurring in 30% and 8% of patients, respectively. Moreover, early bleeding was associated with a marginally higher mortality risk compared with periprocedural CTE, consistent with prior findings by Lindsey et al. (25). Whether this reflects a true difference in biological severity or is a consequence of a more sensitive criterion to classify periprocedural MI remains unclear. We found that BARC type 2 and 3 bleeding events were each independently related to mortality, although risk with type 3 bleeding was twice that of type 2 bleeding. In contrast, others have shown no excess risk with BARC type 2 bleeding (1,30). In a ST-segment elevation MI cohort, for example, Kikkert et al. (1) reported that risk with BARC bleeding was

primarily confined to those with type 3b or greater. These discrepancies may reflect differences in the underlying risks for bleeding, mortality, and background pharmacotherapy across populations.

The present findings also provide a real-world context and novel insight with respect to recently completed trials evaluating different durations of DAPT after PCI (5-7). In the DAPT trial, for example, Mauri et al. (6) found that a 30- versus 12-month provision of DAPT yielded significant reductions in thrombotic events, albeit at an excess risk for bleeding, with a numerically higher risk for all-cause mortality. Similarly, at least 2 other randomized comparisons of prolonging versus discontinuing DAPT after 1 year from PCI failed to show any differences in mortality (5,7). These results, coupled with our findings suggesting comparable mortality hazards associated with either bleeding or coronary thrombosis, highlight the need for decision support tools to inform clinical decision making surrounding the extension of DAPT. In contrast to most scales focused on periprocedural events, the recently introduced DAPT score may prove useful in identifying patients most likely to derive benefit, or alternatively experience harm, from a prolonged DAPT strategy (31).

STUDY LIMITATIONS. Among the limitations of our study include an observational design, which precludes causal inferences and introduces the possibility of residual confounding on our point estimates. Thrombotic events were restricted to coronary thrombosis, as we did not collect follow-up information on noncoronary ischemic events. Whether a broader definition of thrombosis may modify the associations we observed, therefore, warrants further investigation. In addition, as almost all PARIS participants were treated with clopidogrel, our findings may not be generalizable to the more potent $P2Y_{12}$ antagonists prasugrel and ticagrelor.

CONCLUSIONS

We found that AB and intracoronary thrombosis were associated with substantial and comparable risks for mortality over a 2-year period after PCI. These results highlight the importance of both ischemic and hemorrhagic complications in a contemporary cohort, findings that may provide clinically relevant insight on the risk/benefit calculations for decisions regarding the extension or discontinuation of DAPT after PCI.

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PERSPECTIVES

WHAT IS KNOWN? Both bleeding and thrombotic events after PCI are associated with mortality risk. Whether these associations are comparable with each other over time remains unclear.

WHAT IS NEW? In this report, we demonstrate that both nonfatal AB, defined as BARC type 2 or 3, and coronary thrombosis occurring over a 2-year period after PCI associate with all-cause mortality to a similar extent. Risk after both events was highest in the first 30 days, with attenuation thereafter.

WHAT IS NEXT? These findings support the development of stratification tools to refine long-term risk estimation for both bleeding and thrombosis after PCI.

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KEY WORDS bleeding, dual-antiplatelet therapy, mortality

APPENDIX For supplemental tables and a figure, please see the online version of this article.