Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Impact of Bleeding and Myocardial Infarction on Mortality in All-Comer Patients Undergoing Percutaneous Coronary Intervention

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BACKGROUND: Bleeding and myocardial infarction (MI) after percutaneous coronary intervention are independent risk factors for mortality. This study aimed to investigate the association of all-cause mortality after percutaneous coronary intervention with site-reported bleeding and MI, when considered as individual, repeated, or combined events.

METHODS: We used the data from the GLOBAL LEADERS trial (GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation), an all-comers trial of 15 968 patients undergoing percutaneous coronary intervention. Bleeding was defined as Bleeding Academic Research Consortium (BARC) 2, 3, or 5, whereas MI included periprocedural and spontaneous MIs according to the Third Universal Definition.

RESULTS: At 2-year follow-up, 1061 and 498 patients (6.64% and 3.12%) experienced bleeding and MI, respectively. Patients with a bleeding event had a 10.8% mortality (hazard ratio [HR], 5.97 [95% CI, 4.76–7.49]; $P<0.001$), and the mortality of patients with an MI was 10.4% (HR, 5.06 [95% CI, 3.72–6.90]; $P<0.001$), whereas the overall mortality was 2.99%. Albeit reduced over time, MI and even minor BARC 2 bleeding significantly influenced mortality beyond 1 year after adverse events (HR of MI, 2.32 [95% CI, 1.18–4.55]; $P=0.014$, and HR of BARC 2 bleeding, 1.79 [95% CI, 1.02–3.15]; $P=0.044$). The mortality rates in patients with repetitive bleeding, repetitive MI, and both bleeding and MI were 16.1%, 19.2%, and 19.0%, and their HRs for 2-year mortality were 8.58 (95% CI, 5.63–13.09; $P<0.001$), 5.57 (95% CI, 2.53–12.25; $P<0.001$), and 6.60 (95% CI, 3.44–12.65; $P<0.001$), respectively. De-escalation of antiplatelet therapy at the time of BARC 3 bleeding was associated with a lower subsequent bleeding or MI rate, compared with continuation of antiplatelet therapy (HR, 0.32 [95% CI, 0.11–0.92]; $P=0.034$).

CONCLUSIONS: The fatal impact of bleeding and MI persisted beyond one year. Additional bleeding or MIs resulted in a poorer prognosis. De-escalation of antiplatelet therapy at the time of BARC 3 bleeding could have a major safety merit. These results emphasize the importance of considering the net clinical benefit including ischemic and bleeding events.

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Key Words: bleeding ■ myocardial infarction

Dual antiplatelet therapy (DAPT) in patients undergoing percutaneous coronary intervention (PCI) reduces residual ischemic risk but increases the risk of bleeding. In an effort to reduce ischemic events without increasing bleeding events, P2Y12 inhibitor monotherapy after PCI has been proposed.[1] It has been recently shown

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WHAT IS KNOWN

- Major bleeding and myocardial infarction after percutaneous coronary intervention are independent risk factors for mortality.

WHAT THE STUDY ADDS

- Myocardial infarction and even minor Bleeding Academic Research Consortium 2 bleeding after percutaneous coronary intervention significantly influenced mortality beyond one year after adverse events.
- Additional bleeding or myocardial infarction events resulted in an even poorer prognosis.
- De-escalation of antiplatelet therapy at the time of Bleeding Academic Research Consortium 3 bleeding was associated with a lower rate of subsequent bleeding or myocardial infarction when compared with continuation of antiplatelet therapy.

Nonstandard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
DAPT	dual antiplatelet therapy
HR	hazard ratio
MI	myocardial infarction
PCI	percutaneous coronary intervention

that both bleeding and myocardial infarction (MI) after PCI are independent risk factors for mortality and the risk of major bleeding is comparable to, or sometimes even greater thans that of MI.[2–5] Bleeding and MI can sometimes occur repeatedly, although both can also occur in the same patient.[2,3] Notably, the impact on mortality of these secondary (repetitive) bleeding or MI events, after the first bleeding or MI event, has not been fully evaluated.

We aimed to investigate the association of all-cause mortality with any site-reported bleeding or MI, when occurring as individual, repeated, or combined events after PCI using the GLOBAL LEADERS trial (GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation) database.

METHODS

The authors declare that all supporting data are available within the article.

Study Design and Participants

The GLOBAL LEADERS trial was a prospective randomized, open-label trial, designed to compare 23-month ticagrelor monotherapy following one-month DAPT and 12-month DAPT followed by 12-month aspirin monotherapy after PCI in an all-comers population.[6] The details of antiplatelet therapy are described in Methods in the Data Supplement. The study enrolled 15991 patients, and a total of 15968 patients remained in the study because 23 patients withdrew consent and requested data deletion from the database. The survival status of the patients lost to follow-up was obtained through public civil registry and 99.95% of the vital status at 2 years was available.[6] All patients provided informed consent. The trial was approved by the institutional review board at each center and followed the ethical principles of the Declaration of Helsinki.

End Points

All-cause mortality, which is a reliable end point that does not require adjudication, was used as the end point of interest for the present analysis. The association of all-cause mortality with any site-reported Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding,[7] MI, and their repetition and combination during the 2-year follow-up was evaluated. MI included both periprocedural and spontaneous MI according to the Third universal definition of MI.[8] BARC 2, 3, or 5 bleeding was categorized into periprocedural or spontaneous bleeding, and periprocedural bleeding was defined as bleeding within 2 days of PCI. Regarding antiplatelet therapy, de-escalation of antiplatelet therapy was defined as a switch from a potent antiplatelet agent (ticagrelor or prasugrel) to clopidogrel/aspirin, or a stop of any antiplatelet agent for >5 days, within 2 days from the onset of the adverse event.

Statistical Analysis

The effect of experiencing bleeding or MI on all-cause death was quantified through hazard ratios (HRs) with 95% CIs on the basis of Cox proportional hazards regression. In these analyses, the time of the index procedure was treated as time 0. To investigate the associations of bleeding and MI events with the incidence and timing of all-cause mortality, bleeding and MI events were treated as time-updated binary covariates.[4] In the analysis for repeated or combined events, these were also treated as time-updated binary covariates. Prespecified baseline characteristics (age >75, sex, body mass index, impaired renal function, geographic region, hypertension, hypercholesterolemia, diabetes mellitus, previous MI, previous PCI, previous coronary artery bypass grafting, previous stroke, established peripheral vascular disease, chronic obstructive pulmonary disease, previous bleeding)[6] were included in adjustment covariates. To further evaluate the time-dependent risk of bleeding and MI on mortality, additional Cox proportional models were developed with different time-updated binary covariates for discrete time intervals (ie, 0–30 days, 31–365 days, and 366–730 days after the event). Antiplatelet therapy status was categorized as on DAPT or off DAPT. Patients who were receiving aspirin and P2Y12 antagonist were included in on DAPT, and those who were receiving antiplatelet monotherapy (either aspirin or ticagrelor) or not receiving an antiplatelet agent were categorized to off DAPT. In Cox proportional hazards regression analyses comparing the rates of subsequent bleeding or MI associated with de-escalation or continuation of antiplatelet therapy at the time of the first bleeding, the time of the first bleeding was treated as time 0.

The cumulative incidence of all-cause death at 2 years was calculated using the Kaplan-Meier method, in which the time of the index procedure was treated as time 0.

Kaplan-Meier survival curves were analyzed using the log-rank test and the Holm test for pairwise multiple comparisons. Continuous variables were expressed as mean±SD and were compared using Student *t* test or Mann-Whitney *U* test. Categorical variables were reported as numbers and percentages and were compared using χ^2 or Fisher exact test as appropriate. A 2-sided $P<0.05$ was considered statistically significant. Analyses were performed using JMP Pro14 (SAS Institute, Cary, NC) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In the GLOBAL LEADERS trial, there were 1804 bleeding (BARC 2, 3, or 5) or MI events in 1501 patients (9.40%). The number of patients experiencing bleeding was 1061 (6.64%), whereas 498 (3.12%) experienced an MI (Figure 1A and 1B). The patient and procedural characteristics, according to the occurrences of bleeding and MI, are shown in Table I in the Data Supplement. Patients with bleeding and those with MI had more frequently lower left ventricular ejection fraction, impaired renal function, peripheral vascular disease, and acute coronary syndrome at presentation. Patients who experienced bleeding were older, were more frequently women and current smokers, and were likely to have a history of chronic obstructive pulmonary disease and major bleeding compared with those without bleeding, whereas patients who experienced MI events were likely to have a history of diabetes mellitus, MI, PCI, and coronary artery bypass grafting compared with those without MI. Antiplatelet therapy strategy randomly assigned in the GLOBAL LEADERS trial was not significantly different neither in patients with/without bleeding nor in patients with/without MI (Table I in the Data Supplement).

All-Cause Mortality Following Bleeding or MI

Overall, 477 patients (2.99%) died during the 2-year follow-up (Figure 1B). Of the 1061 patients who experienced BARC 2, 3, or 5 bleeding, 114 (10.8%) died, whereas 52 out of the 498 patients having an MI died (10.4%, Figure 2A and 2B). Bleeding (BARC 2, 3, or 5) and MI were associated with HRs for subsequent mortality of 5.97 (95% CI, 4.76–7.49; $P<0.001$) and 5.06 (95% CI, 3.72–6.90; $P<0.001$), respectively (Figure 2C). Both periprocedural and spontaneous bleeding and MI events were significantly associated with mortality (Figure 2C). HRs of mortality risks within the first 30 days after bleeding (BARC 2, 3, or 5) and MI were 34.92 (95% CI, 25.27–48.26; $P<0.001$) and 27.68 (95% CI, 18.09–42.35; $P<0.001$), respectively, and the mortality risk after experiencing a bleeding or MI event was significantly sustained beyond 1 year after the adverse events (HR, 2.85 [95% CI, 1.84–4.42]; $P<0.001$ and HR, 2.32 [95% CI, 1.18–4.55]; $P=0.014$, respectively, Figure 2D). Even BARC 2 bleeding significantly influenced mortality beyond 1 year (HR, 1.79 [95% CI, 1.02–3.15]; $P=0.044$).

Regarding the impact of bleeding, 146 (13.8%) patients required a blood transfusion among 1061 patients experiencing bleeding. Bleeding with or without transfusion was significantly associated with all-cause mortality, and bleeding with transfusion was associated with a higher mortality risk than bleeding without transfusion (HR, 9.03 [95% CI, 6.04–13.50]; $P<0.001$, and HR, 5.38 [95% CI, 4.18–6.91]; $P<0.001$, respectively; *P* for interaction, 0.021; Figure 3A and 3B). As far as bleeding events were concerned, the following sites, intracranial, cardiac, gastrointestinal, urogenital, and access-site, were significantly associated with all-cause mortality (Figure 3C). Among these sites, gastrointestinal bleeding (32.7%) was the most frequent source (Figure 3C). At the time of bleeding, ≈40% of patients were receiving DAPT with aspirin plus ticagrelor, and the type of antiplatelet treatment before the bleeding was not different between gastrointestinal bleeding and bleeding from other sites/causes (Table II in the Data Supplement).

Impact of Additional Bleeding or MI

Numbers of subsequent events after the first bleed or MI during 2-year follow-up are shown in Table III in the Data Supplement. During 2-year follow-up, among the 1061 patients with bleeding (BARC 2, 3, or 5), 150 (14.1%) experienced >1 bleeding event, and these patients had a significantly higher all-cause mortality rate, compared with patients experiencing only one bleed (16.1% versus 9.9%, $P=0.027$, Figure 4A). Of the 498 patients with an MI during follow-up, 47 (9.44%) experienced >1 MI, and similarly, these patients also had a higher all-cause mortality rate, compared with those experiencing only one MI during 2-year follow-up (19.2% versus 9.5%, $P=0.05$, Figure 4B). In addition, there were 58 patients (3.86%) experiencing both bleeding and MI among the 1501 patients with bleeding or MI, and those patients tended to have a poorer prognosis than patients experiencing either only bleeding or only an MI (Figure 4C). Adjusted HRs for repeated bleeding, repeated MI, and combination of bleeding and MI were 8.58 (95% CI, 5.63–13.09; $P<0.001$), 5.57 (95% CI, 2.53–12.25; $P<0.001$), and 6.60 (95% CI, 3.44–12.65; $P<0.001$), respectively (Figure 2C).

Influence of Antiplatelet Therapy Status at the Time of Events

Influences of bleeding and MI on mortality were significant irrespective of antiplatelet therapy status at the time of the adverse event (Figure 5). When experiencing recurrent bleeding, the mortality risk was much higher in patients off DAPT (HR, 16.09 [95% CI, 9.74–26.57] $P<0.001$) than in those on DAPT (HR, 3.65 [95% CI, 1.62–8.21];

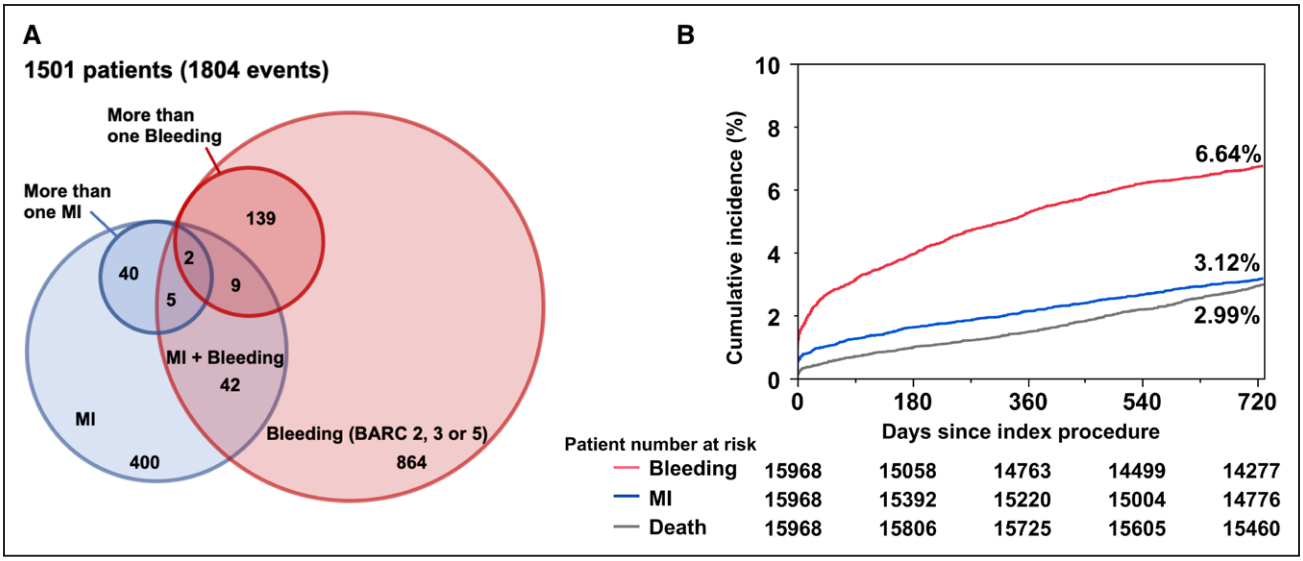


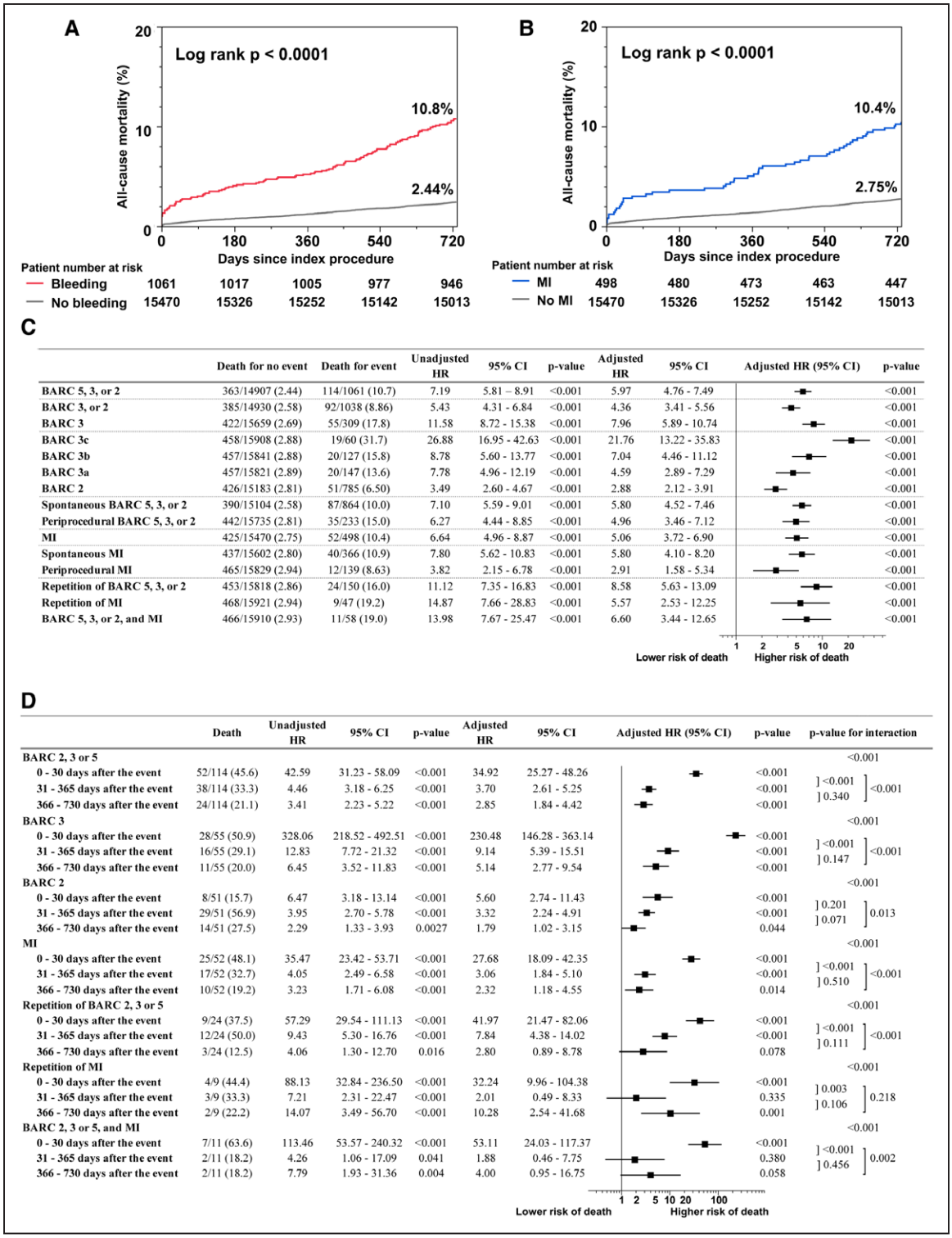
Figure 1. Incidence of bleeding (Bleeding Academic Research Consortium [BARC] 2, 3, or 5) and myocardial infarction (MI). **A**, The Venn diagram shows patients experiencing BARC 2, 3, or 5 bleeding (in red) and MI (in blue). Dark smaller circles represent patients experiencing >1 event during follow-up. The intersection represents patients experiencing both bleeding and MI during follow-up. Figures described in the Venn diagram refer to the numbers of patients. **B**, Cumulative incidence of BARC 2, 3, or 5 bleeding, MI, and all-cause death.

P=0.002), with evidence of interaction (*P* for interaction, 0.002, Figure 5). In addition, we investigated the impact of antiplatelet therapy management at the time of first BARC 2 or 3 bleeding on subsequent MI and BARC 2, 3, or 5 bleeding. Statuses of antiplatelet therapy pre and post first BARC 2 or 3 bleeding were available in 1011 patients (99.1%; Table IV in the Data Supplement). Of 256 patients with BARC 3 bleeding, 48 patients (18.8%) de-escalated antiplatelet therapy, whereas, among the 755 patients with BARC 2 bleeding, 69 patients (9.1%) de-escalated their antiplatelet therapy. The types of antiplatelet treatment before a BARC 3 bleeding were not different between patients who de-escalated their antiplatelet therapy and those who continued their antiplatelet therapy after a BARC 3 bleeding. Among patients who de-escalated their antiplatelet therapy after a BARC 2 bleeding, over 70% were receiving DAPT with aspirin plus ticagrelor. De-escalation of antiplatelet therapy at the time of BARC 3 bleeding was associated with a lower rate of subsequent BARC 2, 3, or 5 bleeding, or MI, when compared with continuation of antiplatelet therapy (HR, 0.32 [95% CI, 0.11–0.92]; *P*=0.034), and did not result in subsequent MI (Figure 6). De-escalation at the time of BARC 2 bleeding did not change the rate of subsequent BARC 2, 3, or 5 bleeding, or MI. Among these patients with de-escalation of antiplatelet therapy for a BARC 2 bleeding, only one patient who had stopped ticagrelor monotherapy suffered a subsequent MI.

DISCUSSION

The main findings of this study are that the occurrence of MI and even minor BARC 2 bleeding after PCI substantially impact on mortality beyond 1 year and that serial bleeding or MI results in an even poorer prognosis. Furthermore, de-escalation of antiplatelet therapy at the time of BARC 3 bleeding is associated with a lower rate of subsequent bleeding or MI events, when compared to continuation of antiplatelet therapy.

MI and bleeding occurring after PCI have been consistently demonstrated to have a direct correlation with mortality.[4,9] In addition, periprocedural and spontaneous MI and bleeding have been implicated as independent risk factors for mortality.[5,10] The lethality of either bleeding or MI was shown not only in acute coronary syndrome patients but also in the all-comers population and real-world clinical practice.[2–4] In the present analysis from the all-comers GLOBAL LEADERS trial, the time-dependent adjusted hazard ratios of BARC 2, 3, or 5 bleeding and MI were 5.97 (95% CI, 4.76–7.49) and 5.06 (95% CI, 3.71–6.90), respectively. The significant effects of bleeding and MI on mortality in the GLOBAL LEADERS trial confirm previous reports from all-comers trials and real-world clinical practice.[2–4] We also evaluated the effects of different categories of bleeding as per the BARC criteria (BARC 2, BARC 3a, BARC 3b, BARC 3c) as previous performed in the TRACER trial (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome).[5] The time-dependent adjusted hazard ratios of bleeding for subsequent death were in order of severity of bleeding and BARC 2 minor bleeding demonstrated significant effect on mortality (HR, 2.88 [95% CI, 2.12–2.91]; *P*<0.001), which were consistent with the TRACER trial.[5] Regarding the lethality of MI and bleeding, both spontaneous and periprocedural events were associated with mortality. This result was also consistent with previous reports.[3,4,10] When analyzing the impact of



	Death for no event	Death for event	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
BARC 5, 3, or 2	363/14907 (2.44)	114/1061 (10.7)	7.19	5.81 – 8.91	<0.001	5.97	4.76 - 7.49	<0.001
BARC 3, or 2	385/14930 (2.58)	92/1038 (8.86)	5.43	4.31 - 6.84	<0.001	4.36	3.41 - 5.56	<0.001
BARC 3	422/15659 (2.69)	55/309 (17.8)	11.58	8.72 - 15.38	<0.001	7.96	5.89 - 10.74	<0.001
BARC 3c	458/15908 (2.88)	19/60 (31.7)	26.88	16.95 - 42.63	<0.001	21.76	13.22 - 35.83	<0.001
BARC 3b	457/15841 (2.88)	20/127 (15.8)	8.78	5.60 - 13.77	<0.001	7.04	4.46 - 11.12	<0.001
BARC 3a	457/15821 (2.89)	20/147 (13.6)	7.78	4.96 - 12.19	<0.001	4.59	2.89 - 7.29	<0.001
BARC 2	426/15183 (2.81)	51/785 (6.50)	3.49	2.60 - 4.67	<0.001	2.88	2.12 - 3.91	<0.001
Spontaneous BARC 5, 3, or 2	390/15104 (2.58)	87/864 (10.0)	7.10	5.59 - 9.01	<0.001	5.80	4.52 - 7.46	<0.001
Periprocedural BARC 5, 3, or 2	442/15735 (2.81)	35/233 (15.0)	6.27	4.44 - 8.85	<0.001	4.96	3.46 - 7.12	<0.001
MI	425/15470 (2.75)	52/498 (10.4)	6.64	4.96 - 8.87	<0.001	5.06	3.72 - 6.90	<0.001
Spontaneous MI	437/15602 (2.80)	40/366 (10.9)	7.80	5.62 - 10.83	<0.001	5.80	4.10 - 8.20	<0.001
Periprocedural MI	465/15829 (2.94)	12/139 (8.63)	3.82	2.15 - 6.78	<0.001	2.91	1.58 - 5.34	<0.001
Repetition of BARC 5, 3, or 2	453/15818 (2.86)	24/150 (16.0)	11.12	7.35 - 16.83	<0.001	8.58	5.63 - 13.09	<0.001
Repetition of MI	468/15921 (2.94)	9/47 (19.2)	14.87	7.66 - 28.83	<0.001	5.57	2.53 - 12.25	<0.001
BARC 5, 3, or 2, and MI	466/15910 (2.93)	11/58 (19.0)	13.98	7.67 - 25.47	<0.001	6.60	3.44 - 12.65	<0.001

	Death	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value	p-value for interaction
BARC 2, 3 or 5								<0.001
0 - 30 days after the event	52/114 (45.6)	42.59	31.23 - 58.09	<0.001	34.92	25.27 - 48.26	<0.001	] <0.001
31 - 365 days after the event	38/114 (33.3)	4.46	3.18 - 6.25	<0.001	3.70	2.61 - 5.25	<0.001	] 0.340] <0.001
366 - 730 days after the event	24/114 (21.1)	3.41	2.23 - 5.22	<0.001	2.85	1.84 - 4.42	<0.001	
BARC 3								<0.001
0 - 30 days after the event	28/55 (50.9)	328.06	218.52 - 492.51	<0.001	230.48	146.28 - 363.14	<0.001	] <0.001
31 - 365 days after the event	16/55 (29.1)	12.83	7.72 - 21.32	<0.001	9.14	5.39 - 15.51	<0.001	] 0.147] <0.001
366 - 730 days after the event	11/55 (20.0)	6.45	3.52 - 11.83	<0.001	5.14	2.77 - 9.54	<0.001	
BARC 2								<0.001
0 - 30 days after the event	8/51 (15.7)	6.47	3.18 - 13.14	<0.001	5.60	2.74 - 11.43	<0.001	] 0.201
31 - 365 days after the event	29/51 (56.9)	3.95	2.70 - 5.78	<0.001	3.32	2.24 - 4.91	<0.001	] 0.071] 0.013
366 - 730 days after the event	14/51 (27.5)	2.29	1.33 - 3.93	0.0027	1.79	1.02 - 3.15	0.044	
MI								<0.001
0 - 30 days after the event	25/52 (48.1)	35.47	23.42 - 53.71	<0.001	27.68	18.09 - 42.35	<0.001	] <0.001
31 - 365 days after the event	17/52 (32.7)	4.05	2.49 - 6.58	<0.001	3.06	1.84 - 5.10	<0.001	] 0.510] <0.001
366 - 730 days after the event	10/52 (19.2)	3.23	1.71 - 6.08	<0.001	2.32	1.18 - 4.55	0.014	
Repetition of BARC 2, 3 or 5								<0.001
0 - 30 days after the event	9/24 (37.5)	57.29	29.54 - 111.13	<0.001	41.97	21.47 - 82.06	<0.001	] <0.001
31 - 365 days after the event	12/24 (50.0)	9.43	5.30 - 16.76	<0.001	7.84	4.38 - 14.02	<0.001	] 0.111] <0.001
366 - 730 days after the event	3/24 (12.5)	4.06	1.30 - 12.70	0.016	2.80	0.89 - 8.78	0.078	
Repetition of MI								<0.001
0 - 30 days after the event	4/9 (44.4)	88.13	32.84 - 236.50	<0.001	32.24	9.96 - 104.38	<0.001	] 0.003
31 - 365 days after the event	3/9 (33.3)	7.21	2.31 - 22.47	<0.001	2.01	0.49 - 8.33	0.335	] 0.106] 0.218
366 - 730 days after the event	2/9 (22.2)	14.07	3.49 - 56.70	<0.001	10.28	2.54 - 41.68	0.001	
BARC 2, 3 or 5, and MI								<0.001
0 - 30 days after the event	7/11 (63.6)	113.46	53.57 - 240.32	<0.001	53.11	24.03 - 117.37	<0.001	] <0.001
31 - 365 days after the event	2/11 (18.2)	4.26	1.06 - 17.09	0.041	1.88	0.46 - 7.75	0.380	] 0.456] 0.002
366 - 730 days after the event	2/11 (18.2)	7.79	1.93 - 31.36	0.004	4.00	0.95 - 16.75	0.058	

Figure 2. Influence of experiencing bleeding or myocardial infarction (MI) on mortality risk.
A and **B**, Kaplan-Meier estimates of all-cause mortality for the patients who experienced Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding (**A**) and MI (**B**). **C**, Hazard ratios (HRs) for all-cause mortality after bleeding and MI. Rates of death were reported as numbers and percentages. **D**, HRs for all-cause mortality according to the time interval after bleeding and MI.

bleeding, it appeared that blood transfusion was associated with a higher mortality risk when compared with bleeding without transfusion. Although adjusted hazards for mortality of bleeding with/without transfusion were similar in the ADAPT-DES study (Assessment of Dual Antiplatelet Therapy With Drug Eluting Stents),[2] impact of blood transfusion after PCI on mortality was subsequently demonstrated by a meta-analysis.[11] These results

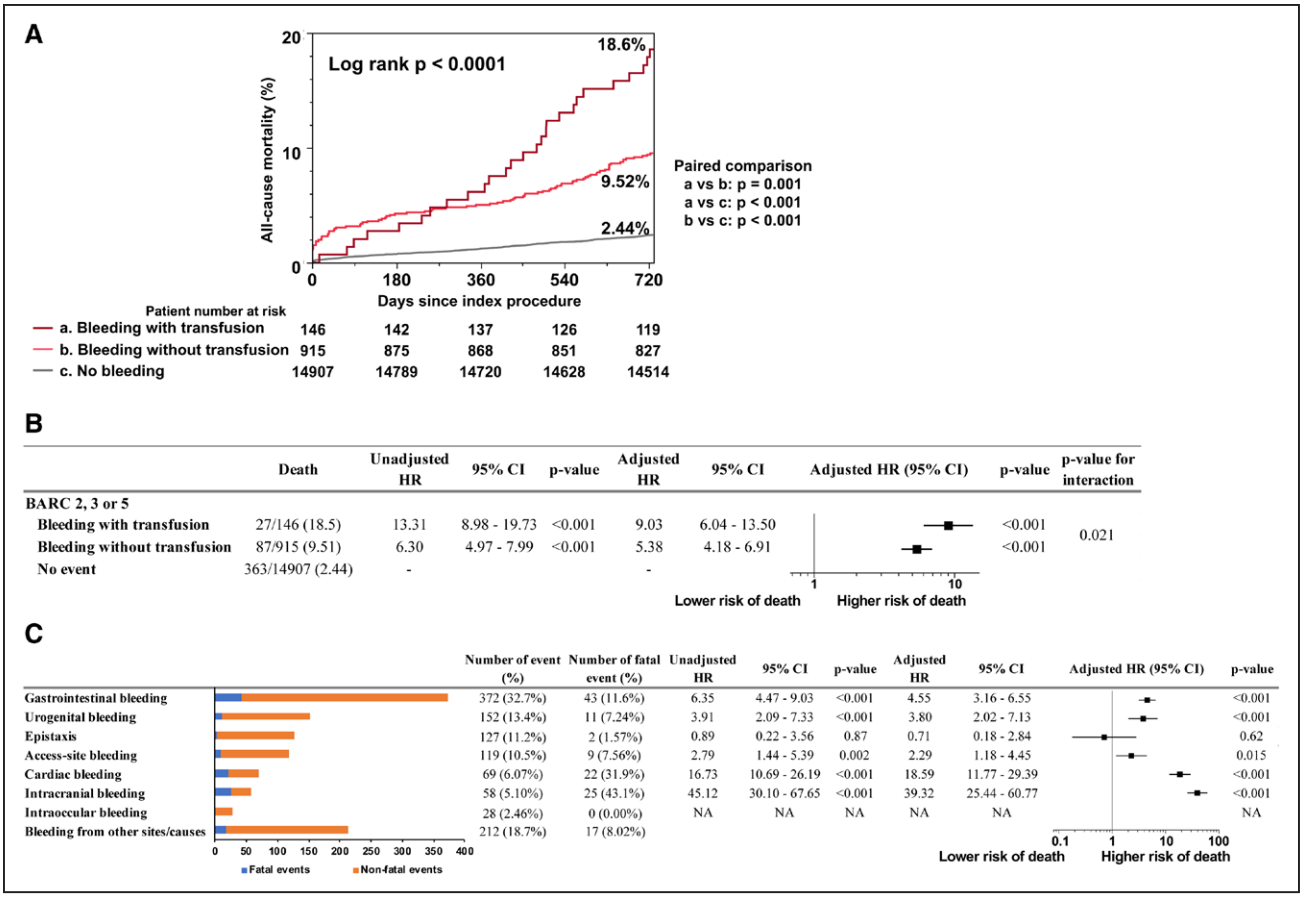


Figure 3. Mortality risk according to the characteristics of bleeding (Bleeding Academic Research Consortium [BARC] 2, 3, or 5). **A**, Kaplan-Meier estimates of all-cause mortality according to BARC 2, 3, or 5 bleeding with or without transfusion. **B**, Hazard ratios (HRs) for all-cause mortality according to BARC 2, 3, or 5 bleeding with or without transfusion. **C**, Incidence and impact on all-cause mortality of bleeding according to bleeding sites. NA indicates not applicable.

suggest that higher-risk patients tend to receive transfusion, and bleeding which requires transfusion could be a marker of higher-risk patients. Among the bleeding sites, gastrointestinal bleeding was the leading cause (Figure 3C), which is consistent with previous reports albeit the rate of events was smaller.[2,3] At the time of gastrointestinal bleeding, ≈40% of patients were receiving DAPT with aspirin plus ticagrelor, a rate higher than the rate estimated from the protocol design of the GLOBAL LEADERS trial. Aspirin was associated with a 59% relative increase of gastrointestinal bleeding in a systematic review.[12] The gastrointestinal bleeding risk was not different between the aspirin and ticagrelor arms in the SOCRATES study (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes).[13] Both aspirin and ticagrelor increase the risk for gastrointestinal bleeding, therefore DAPT with aspirin plus ticagrelor should increase the gastrointestinal bleeding risk compared with aspirin monotherapy or ticagrelor monotherapy. A meta-analysis of the gastrointestinal bleeding risk comparing potent P2Y12 inhibitors (ticagrelor or prasugrel) to clopidogrel demonstrated that potent P2Y12 inhibitors were associated with a higher risk.[14] Taken together, it seems plausible that the predominant type of antiplatelet strategy at the time of gastrointestinal bleeding was DAPT with aspirin plus ticagrelor, although the same assumption applied to bleeding other than gastrointestinal bleeding. Gastrointestinal bleeding was significantly associated with mortality, a fact that has encouraged us to discriminate the high gastrointestinal bleeding risk patients (eg, patients with previous gastrointestinal bleeding, patients with abnormal findings on gastroscopy and colonoscopy) and treat them appropriately (eg, proton pump inhibitors, short DAPT).

Next, we evaluated the time-association between bleeding or MI events and death. The impact of bleeding or MI on mortality was greatest in the first 30 days after the event and then decreased. However, the impact of bleeding and MI on mortality persisted beyond 1 year. Of note, although BARC 2 bleeding is regarded as minor, it has a significant impact on death which persists beyond 1 year. The duration of the detrimental effects on mortality after bleeding or MI is still a matter of debate,[5,9] and the mortality effect after bleeding or MI beyond 1 year was especially not fully evaluated. In a meta-analysis of randomized control trials comparing short to longer

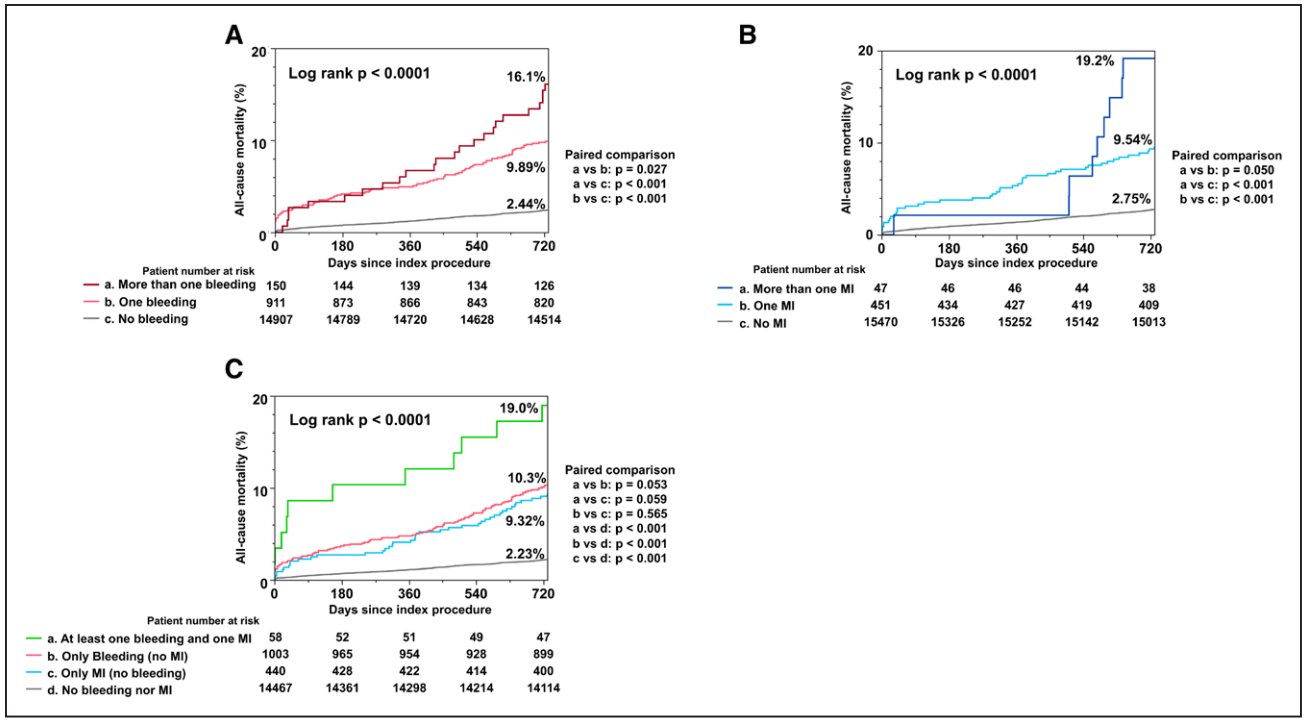


Figure 4. Cumulative mortality rates according to the number of bleeding (Bleeding Academic Research Consortium [BARC] 2, 3, or 5) and myocardial infarction (MI) events.
A, **B**, and **C**, Kaplan-Meier estimates of all-cause mortality according to the number of BARC 2, 3, or 5 bleeding events (**A**), the number of MI events (**B**), and experiencing BARC 2, 3, or 5 bleeding or MI events (**C**).

durations of DAPT after PCI, bleeding and MI were predictors of all-cause mortality occurring within 1 year, but not beyond 1 year, after adverse events.[9] In the PARIS registry (Patterns of Non-Adherence to Antiplatelet Regimens in Stented Patients), BARC 2 or 3 bleeding was impacted on death beyond 1year, but thrombosis was not.[4] These discrepancies may be due to differences in populations and definitions of events. A large number

	Death	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value	p-value for interaction
BARC 2, 3 or 5								
Event on DAPT	71/666 (10.7)	6.12	4.74 - 7.91	<0.001	5.30	4.07 - 6.92	<0.001	0.203
Event off DAPT	39/380 (10.2)	9.51	6.80 - 13.31	<0.001	7.06	4.93 - 10.12	<0.001	
No event	363/14907 (2.44)	-			-			
MI								
Event on DAPT	26/302 (8.81)	4.79	3.22 - 7.13	<0.001	4.07	2.70 - 6.13	<0.001	0.206
Event off DAPT	21/175 (12.0)	9.39	6.04 - 14.59	<0.001	6.02	3.72 - 9.73	<0.001	
No event	425/15470 (2.75)	-			-			
Repetition of BARC 2, 3 or 5								
Event on DAPT	6/69 (8.70)	4.71	2.10 - 10.55	<0.001	3.65	1.62 - 8.21	0.002	0.002
Event off DAPT	17/78 (21.8)	20.08	12.31 - 32.74	<0.001	16.09	9.74 - 26.57	<0.001	
No event	453/15818 (2.86)	-			-			
Repetition of MI								
Event on DAPT	4/31 (12.9)	8.77	3.27 - 23.50	<0.001	4.42	1.41 - 13.89	0.011	0.806
Event off DAPT	4/15 (27.7)	27.58	10.27 - 74.03	<0.001	5.45	1.58 - 18.80	0.007	
No event	468/15921 (2.94)	-			-			
BARC 2, 3 or 5, and MI								
Event on DAPT	6/30 (20.0)	12.54	5.60 - 28.09	<0.001	11.62	5.15 - 26.22	<0.001	0.054
Event off DAPT	4/24 (16.7)	13.50	5.04 - 36.20	<0.001	3.17	1.10 - 9.15	0.033	
No event	466/15910 (2.93)	-			-			

Figure 5. Influence of antiplatelet therapy status on mortality risk associated with bleeding (Bleeding Academic Research Consortium [BARC] 2, 3, or 5) or myocardial infarction (MI).
Hazard ratios (HRs) for all-cause mortality associated with antiplatelet therapy status and clinical events. Rates of death were reported as numbers and percentages. DAPT indicates dual antiplatelet therapy.

	Continuation	De-escalation	Log-rank p-value	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	Adjusted HR (95% CI)	p-value
1st bleeding: BARC 3	n=208	n=48								
Subsequent BARC 2, 3 or 5, or MI	48 (23.1)	4 (8.3)	0.040	0.36	0.13 - 1.00	0.049	0.32	0.11 - 0.92		0.034
Subsequent BARC 2, 3, or 5	43 (20.7)	4 (8.3)	0.074	0.41	0.15 - 1.13	0.084	0.37	0.13 - 1.08		0.068
Subsequent MI	7 (3.4)	0 (0.0)	0.220	NA	NA	NA	NA	NA		NA
1st bleeding: BARC 2	n=686	n=69								
Subsequent BARC 2, 3 or 5, or MI	108 (15.7)	8 (11.6)	0.359	0.72	0.35 - 1.47	0.361	0.87	0.41 - 1.83		0.709
Subsequent BARC 2, 3, or 5	96 (14.0)	7 (10.1)	0.382	0.71	0.33 - 1.53	0.384	0.85	0.38 - 1.88		0.687
Subsequent MI	16 (2.3)	1 (1.5)	0.626	0.63	0.08 - 4.59	0.630	0.91	0.11 - 7.27		0.915

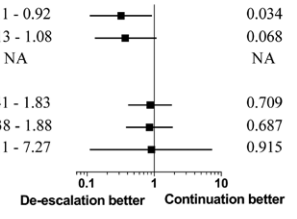


Figure 6. Hazard ratios (HRs) for subsequent bleeding or myocardial infarction (MI) associated with de-escalation of antiplatelet therapy at the time of bleeding.
Patients with subsequent adverse events were reported as numbers and percentages. BARC indicates Bleeding Academic Research Consortium; and NA, not applicable.

of patients were enrolled in the all-comers GLOBAL LEADERS trial, and the fact that MI and even minor bleeding (BARC 2) impacted on death beyond 1 year after adverse events clearly indicated that patients with adverse events have to be carefully followed-up beyond 1 year after adverse events.

Furthermore, we evaluated the influence of additional bleeding and MI events on subsequent mortality. The mortality rates in patients experiencing repeated events were higher than patients without additional events, especially in the analysis of bleeding events. The number of cases with repetitive bleeding and MI events was small, and the follow-up time relatively short to fully evaluate the effect on mortality of repeated events. Further research is required to confirm the impact of additional events on mortality.

Finally, we investigated the impact of antiplatelet therapy at the time of bleeding or MI. There was no significant effect on mortality between patients who were on or off DAPT at the time of their first bleeding or MI event, but the mortality risk was much higher in patients off DAPT when experiencing recurrent bleeding (Figure 5). In the PARIS registry and CHARISMA trial, patients off DAPT at the time of bleeding had a higher risk of mortality than those on DAPT.[4,15] Taken together, recurrent bleeding in the setting of off DAPT was a marker of higher-risk patients. Regarding the management of the antiplatelet therapy at the time of bleeding, the number of subsequent events was small; however, de-escalation of antiplatelet therapy at the time of BARC 3 bleeding was associated with a low rate of subsequent bleeding or MI and did not result in subsequent MI (Figure 6), a fact that suggests that de-escalation of antiplatelet therapy at the time of BARC 3 bleeding could have a major safety merit and should be considered in the decision making of the physician.

Limitations

Bleeding and MI events were site-reported, as the trial did not have a central clinical adjudication committee for serious adverse events due to limited financial resources. However, 7 on-site monitoring visits were performed in each participating center, and 20% of the reported events were checked according to source documents. In addition, the trial was monitored for event under-reporting and event definition consistency. Furthermore, the GLASSY (GLOBAL LEADERS Adjudication Sub-Study) was performed to implement an independent adjudication process of reported as well as unreported potential end points, in a representative sample of patients from the 20 top-enrolling participating sites in the GLOBAL LEADERS trial.[16] The GLASSY demonstrated that there were no significant differences between site-reported and adjudicated rates of MI (3.47% versus 3.20%, *P*=0.061) and BARC 3 or 5 bleeding (2.21% versus 2.48%, *P*=0.052).[16] One of the reasons for these nonsignificant different rates is different definitions used for periprocedural MI. The GLOBAL LEADERS trial used the Third Universal Definition,[8] and the GLASSY used the definition from the Society for Cardiovascular Angiography and Interventions.[17] In the GLOBAL LEADERS trial, periprocedural MI was reported categorically, and there was no specific information about the value of cardiac enzyme.[16] Finally, in the Kaplan-Meier estimates for mortality, bleeding and MI were treated as time-invariant variables. Death could occur after bleeding or MI in patients with bleeding or MI; in other words, they were free from death until bleeding or MI occurred. Therefore, their cumulative mortality rates and accordingly log-rank *P* values obtained by the comparison between patients with bleeding or MI and those who had no adverse events could be underestimated.

Conclusions

In the all-comer GLOBAL LEADERS trial, both bleeding and MI after PCI significantly influenced mortality, and additional bleeding or MI events were associated with an even poorer prognosis. MI and even minor BARC 2 bleeding significantly impacted on mortality beyond one year after adverse events, although the impact was less. Regarding the management for bleeding, de-escalation of antiplatelet therapy at the time of BARC 3 bleeding

was associated with a lower rate of subsequent bleeding or MI, when compared with continuation of antiplatelet therapy. The strong relationship between both MI and bleeding and subsequent mortality emphasizes the importance of including ischemic and bleeding events in the assessment of net clinical benefit.

ARTICLE INFORMATION

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