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# The Impact of Timing of Ischemic and Hemorrhagic Events on Mortality After Percutaneous Coronary Intervention

## The ADAPT-DES Study

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## ABSTRACT

**OBJECTIVES** The aim of this study was to understand the impact of the timing of ischemic and hemorrhagic events after percutaneous coronary intervention (PCI) with drug-eluting stents on subsequent mortality.

**BACKGROUND** These events have been strongly associated with subsequent death.

**METHODS** In the multicenter, prospective ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug Eluting Stents) study, patients at 11 clinical sites with successful PCI with drug-eluting stents underwent assessment of platelet function and were followed for 2 years. Events occurring after PCI—definite or probable stent thrombosis (ST), myocardial infarction (MI) not related to ST, and clinically relevant bleeding (CB)—were classified as early (≤30 days), late (31 to 365 days), or very late (>365 days). Mortality within 30 days of each event was estimated by Kaplan-Meier methodology. Cox regression multivariate modeling was used to analyze the relationship between each event (as a time-updated variable) and mortality over the entire study period.

**RESULTS** Among 8,582 patients, 1,060 (12.4%) had events—691 (8.1%) had CB, 294 (3.4%) had MI, and 75 (0.9%) had ST—and 7,522 (87.6%) had no events. The highest risk was associated with early ST (38.5% mortality at 30 days after the event), whereas very late MI (7.5%) and late CB (7.3%) were less dangerous. By multivariate analysis, each event was independently predictive of death, with hazard ratios of 2.4, 1.8, and 11.4, respectively ($p < 0.0001$).

**CONCLUSIONS** Approximately 1 in 8 patients successfully undergoing PCI with drug-eluting stents had CB, MI, or ST during the ensuing 2 years. These events are associated with an increased hazard of mortality, particularly within the first 30 days following the event, warranting efforts to prevent their occurrence. (J Am Coll Cardiol Intv 2016;9:1450–7)
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After successful percutaneous coronary intervention (PCI) with drug-eluting stents (DES), patients may experience ischemic events (myocardial infarction [MI], stent thrombosis [ST], or repeat target vessel revascularization), as well as clinically relevant bleeding (CB). Both ischemic and hemorrhagic complications have been associated with an increased risk for subsequent death compared with patients not experiencing these events (1,2). The relationship between the timing of each of these events relative to the index procedure and subsequent risk for death is less well understood.

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To examine this issue, we analyzed the large, multicenter and contemporary ADAPT-DES (Assessment of Dual Antiplatelet Therapy with Drug Eluting Stents) registry to clarify the impact of ST, MI not related to ST, and CB on mortality within 30 days after each event according to time of event occurrence relative to index PCI: early (≤30 days), late (31 to 365 days), or very late (>365 days).

## METHODS

The design and principal results of ADAPT-DES have been described in detail (3). In brief, patients undergoing successful PCI with DES at 11 centers in the United States and Germany were enrolled in a prospective multicenter study in which aspirin and clopidogrel inhibition of platelet aggregation after standard loading doses of dual-antiplatelet therapy were tested. Consecutive patients undergoing successful PCI were enrolled as long as early coronary artery bypass graft surgery was not planned; there were no other clinical or anatomic exclusion criteria. Platelet reactivity was tested with the VerifyNow point-of-care assay (Accumetrics, San Diego, California), and in the context of clopidogrel effect, high platelet reactivity (HPR) was defined as >208 $P2Y_{12}$ reaction units (4,5). Dual-antiplatelet therapy was recommended for at least 1 year, whereas aspirin was continued indefinitely. The study was powered to detect significant differences in ST between patients with and those without HPR.

Patients were followed by office or phone visits at 30 days, 1 year, and 2 years after the index PCI. ST was adjudicated according to the Academic Research Consortium (6), with definite or probable ST meeting study criteria. MI was adjudicated according to the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial definitions (7) and was categorized as ST-related or non- ST-related. Finally, CB was adjudicated as bleeding meeting any of the major criteria according to the TIMI (Thrombolysis In Myocardial Infarction), GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), or ACUITY scale, as well as any other bleeding after hospital discharge requiring medical attention. All instances of death, MI, and ST were adjudicated independently by a panel blinded to platelet testing results, whereas CB and target vessel revascularization were site reported.

Categorical variables were compared using chi-square or Fisher exact tests. Continuous variables are presented as mean ± SD and were compared using analysis of variance. Adverse events were categorized as early, late, or very late, and their relationships with subsequent mortality within 30 days were modeled using Kaplan-Meier methods and compared using the log-rank test. The stepwise multivariate Cox regression model included each of the events as time-updated covariates along with age, sex, diabetes mellitus (none, oral treatment only, or insulin treatment), previous MI (>7 days before PCI), history of chronic kidney disease (defined as creatinine clearance <60 ml/min), current smoking, ST-segment elevation or non-ST-segment elevation MI (vs. stable or unstable angina) at presentation, baseline hemoglobin, baseline platelet count, baseline white blood cell count, baseline creatinine clearance, hypertension, hyperlipidemia, multivessel coronary disease, and HPR. Patients were categorized in an event group on the basis of first event to occur after PCI, even if multiple events occurred over the study period. A 2-sided alpha level of 0.05 was used for all testing. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

### ABBREVIATIONS AND ACRONYMS

**CB** = clinically relevant bleeding
**CI** = confidence interval
**DES** = drug-eluting stent(s)
**HPR** = high platelet reactivity
**HR** = hazard ratio
**MI** = myocardial infarction
**PCI** = percutaneous coronary intervention
**ST** = stent thrombosis

## RESULTS

Among the 8,582 patients enrolled in ADAPT-DES, 1,060 (12.4%) had events—691 (8.1%) had CB (261 of which occurred before hospital discharge), 294 (3.4%)

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**TABLE 1 Baseline and Procedural Characteristics of Patients With and Without Events**

| | MI (n = 294) | ST (n = 75) | CB (n = 691) | No MI, ST, or CB (n = 7,522) | p Value |
|---|---|---|---|---|---|
| Age, yrs | 64.6 ± 11.2 (294) | 62.1 ± 12.0 (75) | 66.9 ± 10.5 (691) | 63.3 ± 10.8 (7,522) | <0.0001 |
| Male | 73.8% (217/294) | 72.0% (54/75) | 68.9% (476/691) | 74.6% (5,610/7,522) | 0.10 |
| Diabetes | 44.2% (130/294) | 48.0% (36/75) | 33.7% (233/691) | 31.7% (2,384/7,522) | <0.0001 |
| Insulin treated | 22.4% (66/294) | 20.0% (15/75) | 13.3% (92/691) | 11.0% (825/7,522) | <0.0001 |
| History of peripheral arterial disease | 19.0% (56/294) | 18.7% (14/75) | 14.3% (99/691) | 9.4% (707/7,522) | <0.0001 |
| History of congestive heart failure | 13.9% (41/294) | 5.3% (4/75) | 12.3% (85/691) | 7.6% (569/7,522) | <0.0001 |
| Previous MI | 33.7% (99/294) | 38.7% (29/75) | 26.2% (181/691) | 24.7% (1,855/7,522) | 0.0002 |
| Previous CABG | 28.9% (85/294) | 20.0% (15/75) | 18.2% (126/691) | 16.5% (1,242/7,522) | <0.0001 |
| Previous PCI | 50.7% (149/294) | 53.3% (40/75) | 46.3% (320/691) | 42.1% (3,169/7,522) | 0.001 |
| History of dialysis | 3.1% (9/294) | 5.3% (4/75) | 3.0% (21/691) | 1.4% (104/7,522) | <0.0001 |
| Hypertension | 84.7% (249/294) | 86.7% (65/75) | 86.0% (594/691) | 78.8% (5,925/7,522) | <0.0001 |
| Hyperlipidemia | 79.9% (235/294) | 74.7% (56/75) | 79.6% (550/691) | 73.6% (5,539/7,522) | 0.0008 |
| Cigarette smoking | 55.4% (163/294) | 68.0% (51/75) | 54.1% (374/691) | 56.4% (4,241/7,522) | 0.13 |
| Current (within 1 month) | 21.4% (63/294) | 32.0% (24/75) | 20.0% (138/691) | 22.8% (1,715/7,522) | 0.08 |
| Acute coronary syndrome | 59.5% (175/294) | 64.0% (48/75) | 42.7% (295/691) | 52.0% (3,915/7,522) | <0.0001 |
| Unstable angina | 31.6% (93/294) | 28.0% (21/75) | 22.7% (157/691) | 27.9% (2,099/7,522) | 0.02 |
| Non-ST-segment elevation | 23.1% (68/294) | 17.3% (13/75) | 14.2% (98/691) | 14.2% (1,070/7,522) | 0.0003 |
| ST-segment elevation | 4.8% (14/294) | 18.7% (14/75) | 5.8% (40/691) | 9.9% (746/7,522) | <0.0001 |
| Killip class II–IV at time of PCI | 2.7% (8/294) | 0.0% (0/75) | 2.6% (18/691) | 2.1% (155/7,522) | 0.38 |
| Anemia | 29.3% (86/294) | 25.3% (19/75) | 29.4% (203/691) | 20.9% (1,564/7,486) | <0.0001 |
| Creatinine clearance <60 ml/min | 24.0% (70/292) | 20.0% (15/75) | 25.9% (179/690) | 15.2% (1,138/7,486) | <0.0001 |
| Degree of coronary artery disease | | | | | |
| 1 vessel | 21.8% (64/294) | 32.0% (24/75) | 30.5% (211/691) | 39.7% (2,984/7,522) | <0.0001 |
| 2 vessels | 36.4% (107/294) | 36.0% (27/75) | 32.9% (227/691) | 32.9% (2,474/7,522) | 0.60 |
| 3 vessels | 41.8% (123/294) | 32.0% (24/75) | 36.6% (253/691) | 27.4% (2,064/7,522) | <0.0001 |
| Left main >50% stenosis | 3.7% (11/294) | 2.7% (2/75) | 5.2% (36/691) | 2.8% (208/7,522) | 0.004 |
| Ejection fraction <40% | 35.7% (105/294) | 38.7% (29/75) | 46.0% (318/691) | 28.2% (2,124/7,522) | <0.0001 |
| Radial access | 7.1% (21/294) | 6.7% (5/75) | 2.5% (17/691) | 4.4% (332/7,522) | 0.06 |
| Vessels treated per patient | 1.29 ± 0.54 (294) | 1.16 ± 0.40 (75) | 1.26 ± 0.52 (691) | 1.17 ± 0.41 (7,522) | <0.0001 |
| Lesions treated per patient | 1.69 ± 1.01 (294) | 1.47 ± 0.78 (75) | 1.60 ± 0.86 (691) | 1.49 ± 0.77 (7,522) | <0.0001 |
| Stents implanted per patient | 2.02 ± 1.32 (294) | 1.84 ± 1.21 (75) | 1.92 ± 1.14 (691) | 1.69 ± 0.99 (7,522) | <0.0001 |
| XIENCE/Promus | 67.7% (199/294) | 49.3% (37/75) | 59.2% (409/691) | 65.0% (4,893/7,522) | 0.0004 |
| Total stent length, mm | 39.5 ± 28.2 (294) | 36.4 ± 25.6 (75) | 36.4 ± 25.0 (691) | 31.8 ± 21.7 (7,522) | <0.0001 |
| Any GPI during index PCI | 4.1% (12/294) | 10.7% (8/75) | 3.6% (25/691) | 3.1% (231/7,522) | 0.002 |
| Time to VerifyNow from PCI, h | 19.11 (16.50–22.40) | 18.58 (15.58–23.30) | 19.73 (17.10–22.38) | 18.90 (16.20–21.67) | <0.0001 |
| ARU | 400 (390–433) | 404 (390–426) | 399 (387–426) | 401 (388–424) | 0.48 |
| ≥550 ARU | 5.2% (15/291) | 5.3% (4/75) | 5.2% (36/686) | 5.7% (423/7,474) | 0.95 |
| PRU | 215 (125–285) | 233 (158–299) | 173 (92–250) | 187.50 (115–260) | <0.0001 |
| >208 PRU | 52.4% (151/288) | 61.3% (46/75) | 38.9% (262/673) | 42.5% (3,150/7,412) | <0.0001 |
| Both ≥550 ARU and >208 PRU | 1.8% (5/285) | 5.3% (4/75) | 2.4% (16/668) | 2.5% (188/7,373) | 0.37 |
| No aspirin at discharge | 0.3% (1/292) | 1.4% (1/73) | 1.0% (7/689) | 0.8% (59/7,522) | 0.68 |
| Daily aspirin without discontinuation for 2 yrs | 78.6% (231/294) | 77.3% (58/75) | 60.6% (419/691) | 82.4% (6,200/7,522) | <0.0001 |
| No clopidogrel at discharge | 0.3% (1/292) | 0.0% (0/73) | 1.2% (8/689) | 0.2% (17/7,522) | 0.0003 |
| Daily clopidogrel without discontinuation for 1 yr | 70.4% (207/294) | 65.3% (49/75) | 55.0% (380/691) | 77.8% (5,854/7,522) | <0.0001 |
| Daily clopidogrel without discontinuation for 2 yrs | 50.7% (149/294) | 44.0% (33/75) | 25.9% (179/691) | 51.2% (3,855/7,522) | <0.0001 |

Values are mean ± SD (N), % (n/N), or median (interquartile range). Patients were analyzed according to first event.

ARU = aspirin reaction units; CABG = coronary artery bypass grafting; CB = clinically relevant bleeding; GPI = glycoprotein IIb/IIIa receptor inhibitor; MI = myocardial infarction; PCI = percutaneous coronary intervention; PRU = $P2Y_{12}$ reaction units; ST = stent thrombosis.

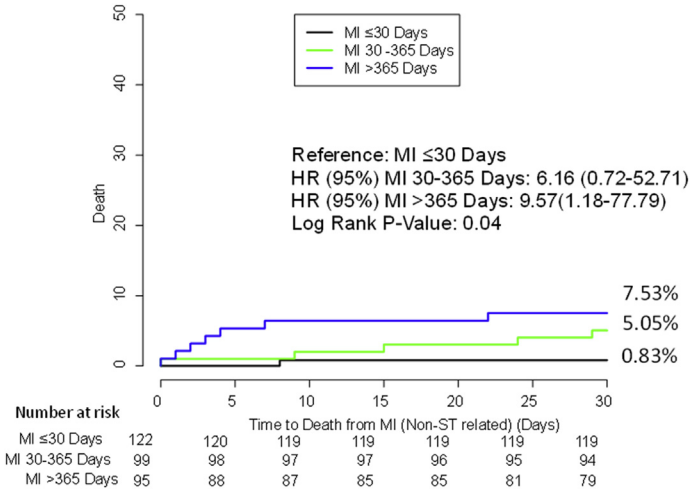
had MI not related to ST (107 of which occurred before hospital discharge and were periprocedural MI), and 75 (0.9%) had ST (8 of which occurred before hospital discharge)—and 7,522 (87.6%) had no events. Key baseline and procedural characteristics of the 4 groups are shown in Table 1. There were multiple and important differences in baseline characteristics between the groups, with more risk factors for coronary artery disease present in patients with events, particularly in those with MI or ST. Significantly more stents were implanted in patients with subsequent events than in those without events.

**TABLE 2 Adjudicated Ischemic Clinical Events Up to 2 Years**

| | MI (n = 294) | ST (n = 75) | CB (n = 691) | No MI, ST, or CB (n = 7,522) | p Value |
|---|---|---|---|---|---|
| All events | | | | | |
| Cardiac death/MI/definite/probable ST | 100% (294) | 100% (75) | 9.44% (62) | 1.42% (100) | <0.0001 |
| Death/MI/ischemic TVR | 100% (294) | 98.67% (74) | 27.33% (186) | 10.05% (718) | <0.0001 |
| Death/MI | 100% (294) | 91.76% (68) | 15.36% (104) | 2.66% (190) | <0.0001 |
| Cardiac death/MI | 100% (294) | 91.76% (68) | 9.30% (61) | 1.42% (100) | <0.0001 |
| Death | 12.43% (35) | 27.15% (20) | 10.54% (71) | 2.66% (190) | <0.0001 |
| Cardiovascular | 9.61% (27) | 27.15% (20) | 5.85% (38) | 1.58% (112) | <0.0001 |
| Noncardiovascular | 3.12% (8) | 0.00% (0) | 4.99% (33) | 1.10% (78) | <0.0001 |
| MI | 100.00% (294) | 90.14% (59) | 5.89% (38) | 0.00% (0) | <0.0001 |
| ST-related MI | 2.17% (6) | 86.97% (57) | 0.00% (0) | 0.00% (0) | <0.0001 |
| Non-ST-related MI | 63.05% (179) | 0.00% (0) | 3.83% (24) | 0.00% (0) | <0.0001 |
| Periprocedural MI | 38.21% (112) | 2.67% (2) | 2.06% (14) | 0.00% (0) | <0.0001 |
| Definite/probable ST | 5.68% (16) | 100.00% (75) | 0.29% (2) | 0.00% (0) | <0.0001 |
| Early (30 days) | | | | | |
| Cardiac death/MI/definite/probable ST | 38.44% (113) | 48.00% (36) | 1.88% (13) | 0.00% (0) | <0.0001 |
| Death/MI/ischemic TVR | 39.12% (115) | 48.00% (36) | 2.90% (20) | 0.32% (24) | <0.0001 |
| Death/MI | 38.44% (113) | 46.67% (35) | 2.17% (15) | 0.03% (2) | <0.0001 |
| Cardiac death/MI | 38.44% (113) | 46.67% (35) | 1.74% (12) | 0.00% (0) | <0.0001 |
| Death | 0.34% (1) | 16.00% (12) | 0.58% (4) | 0.03% (2) | <0.0001 |
| Cardiovascular | 0.34% (1) | 16.00% (12) | 0.29% (2) | 0.01% (1) | <0.0001 |
| Noncardiovascular | 0.00% (0) | 0.00% (0) | 0.29% (2) | 0.01% (1) | 0.19 |
| MI | 38.44% (113) | 36.17% (26) | 1.74% (12) | 0.00% (0) | <0.0001 |
| ST-related MI | 0.34% (1) | 33.45% (24) | 0.00% (0) | 0.00% (0) | <0.0001 |
| Non-ST-related MI | 1.72% (5) | 0.00% (0) | 0.15% (1) | 0.00% (0) | <0.0001 |
| Periprocedural MI | 36.39% (107) | 2.67% (2) | 1.59% (11) | 0.00% (0) | <0.0001 |
| Definite/probable ST | 0.34% (1) | 48.00% (36) | 0.29% (2) | 0.00% (0) | <0.0001 |
| Late (>30 days to 1 yr) | | | | | |
| Cardiac death/MI/definite/probable ST | 34.47% (100) | 43.53% (27) | 4.16% (28) | 0.59% (43) | <0.0001 |
| Death/MI/ischemic TVR | 39.98% (116) | 45.15% (28) | 15.96% (109) | 5.69% (417) | <0.0001 |
| Death/MI | 34.12% (99) | 34.25% (21) | 7.18% (49) | 1.23% (90) | <0.0001 |
| Cardiac death/MI | 34.12% (99) | 34.25% (21) | 4.16% (28) | 0.59% (43) | <0.0001 |
| Death | 5.86% (17) | 4.87% (3) | 5.42% (37) | 1.23% (90) | <0.0001 |
| Cardiovascular | 5.18% (15) | 4.87% (3) | 2.81% (19) | 0.68% (50) | <0.0001 |
| Noncardiovascular | 0.71% (2) | 0.00% (0) | 2.68% (18) | 0.55% (40) | <0.0001 |
| MI | 33.55% (97) | 32.02% (19) | 1.95% (13) | 0.00% (0) | <0.0001 |
| ST-related MI | 0.70% (2) | 28.65% (17) | 0.00% (0) | 0.00% (0) | <0.0001 |
| Non-ST-related MI | 31.97% (92) | 0.00% (0) | 1.81% (12) | 0.00% (0) | <0.0001 |
| Periprocedural MI | 1.06% (3) | 0.00% (0) | 0.15% (1) | 0.00% (0) | <0.0001 |
| Definite/probable ST | 3.48% (10) | 39.95% (24) | 0.00% (0) | 0.00% (0) | <0.0001 |
| Very late (>1 to 2 yrs) | | | | | |
| Cardiac death/MI/definite/probable ST | 37.34% (99) | 33.31% (19) | 3.81% (23) | 0.83% (57) | <0.0001 |
| Death/MI/ischemic TVR | 42.91% (114) | 38.58% (22) | 11.65% (73) | 4.90% (332) | <0.0001 |
| Death/MI | 38.31% (102) | 33.31% (19) | 6.90% (43) | 1.43% (98) | <0.0001 |
| Cardiac death/MI | 37.34% (99) | 33.31% (19) | 3.81% (23) | 0.83% (57) | <0.0001 |
| Death | 6.66% (17) | 8.84% (5) | 4.86% (30) | 1.43% (98) | <0.0001 |
| Cardiovascular | 4.34% (11) | 8.84% (5) | 2.84% (17) | 0.89% (61) | <0.0001 |
| Noncardiovascular | 2.43% (6) | 0.00% (0) | 2.08% (13) | 0.54% (37) | <0.0001 |
| MI | 36.86% (97) | 32.01% (18) | 2.53% (15) | 0.00% (0) | <0.0001 |
| ST-related MI | 1.14% (3) | 28.45% (16) | 0.00% (0) | 0.00% (0) | <0.0001 |
| Non-ST-related MI | 31.38% (82) | 0.00% (0) | 1.88% (11) | 0.00% (0) | <0.0001 |
| Periprocedural MI | 0.75% (2) | 0.00% (0) | 0.33% (2) | 0.00% (0) | <0.0001 |
| Definite/probable ST | 1.89% (5) | 30.22% (17) | 0.00% (0) | 0.00% (0) | <0.0001 |

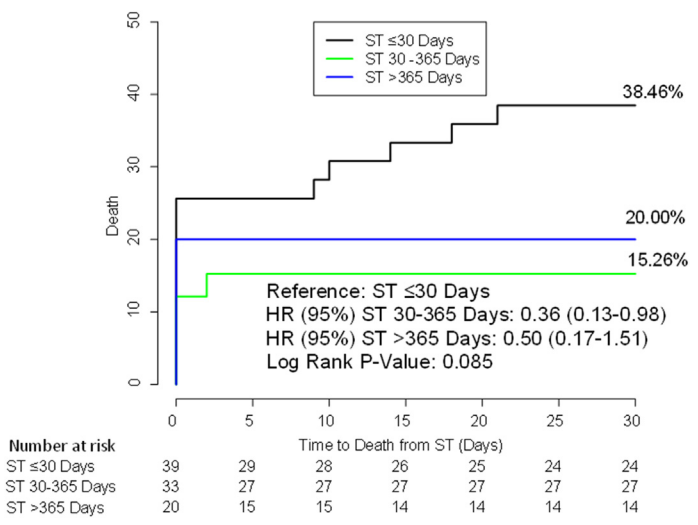
Values are 2-year Kaplan-Meier event rate (number of events). Percentages refer to the proportion of patients with each adverse event.
TVR = target vessel revascularization; other abbreviations as in Table 1.

**FIGURE 1 Time to Death (Within 30 Days or to Study End) After a Non-Stent Thrombosis-Related Myocardial Infarction, According to Timing of Myocardial Infarction Relative to Index Percutaneous Coronary Intervention (Unadjusted Hazard Ratios)**




The cumulative rates of death within 30 days of a non-stent thrombosis (ST)-related myocardial infarction (MI), in patients who had MI occur within 30 days of percutaneous coronary intervention (PCI) **(black line)**, 30 to 365 days after PCI **(green line)**, and more than 1 year after PCI **(blue line)** are shown with respective hazard ratios (HRs) compared with the reference of MI within 30 days of PCI.

**FIGURE 2 Time to Death (Within 30 Days or to Study End) After Definite or Probable Stent Thrombosis, According to Timing of Stent Thrombosis Relative to Index Percutaneous Coronary Intervention (Unadjusted Hazard Ratios)**




The cumulative rates of death within 30 days of definite or probable stent thrombosis (ST), in patients who had ST occur within 30 days of percutaneous coronary intervention (PCI) **(black line)**, 30 to 365 days after PCI **(green line)**, and more than 1 year after PCI **(blue line)** are shown with respective hazard ratios (HRs) compared with the reference of ST within 30 days of PCI.

Uninterrupted dual-antiplatelet therapy, as expected, was substantially less common among patients with CB at 1 and 2 years.

Adjudicated ischemic clinical events up to 2 years are shown in Table 2. All-cause (and cardiovascular) death was significantly more common in patients with ST than in any other group (27.2%), whereas those without any events had the lowest mortality rate (2.7%) ($p < 0.0001$). It is notable that the incidence of definite or probable ST after CB was only 0.29%, and there was no MI in this cohort.

Figures 1 to 3 depict time to death in the 30 days after MI, ST, or CB, according to the timing of each event relative to index PCI (unadjusted hazard ratios [HRs]). The graphs depict the total number of each type of event, including additional events in patients with multiple events. As such, in total, there were 316 MIs not related to ST, 92 definite or probable ST events, and 739 CB events. There were very few (1 CB and 5 MI) events in the last 30 days of the study, and these patients had thus incomplete 30-day follow-up beyond the occurrence of these events. For MI, the very late events were associated with the highest death rate at 30 days: a 10-fold increase compared with early MI and an absolute rate of 7.5%. In contrast, early ST carried the highest risk in this category, with an absolute rate of death of 38.5%, whereas later ST was associated with roughly one-half to one-third of that mortality rate. CB was associated with mortality rates similar to MI, with the lowest observed for early bleeding. It is notable that for patients with CB, one-half of the mortality, roughly, was noncardiovascular.

The significant predictors of 2-year death by stepwise multivariate modeling, including events after PCI as time-updated variables, are shown in Table 3. The highest risk was conferred by ST, whereas bleeding and MI (not related to ST) had smaller but similar contributions to risk for death. Notably, presentation with MI (vs. stable or unstable angina), non- insulin-treated diabetes mellitus (vs. no diabetes), and HPR were not independent predictors of death.

## DISCUSSION

The principal findings of this study can be summarized as follows: 1) the risk for death is increased by post-PCI ischemic and hemorrhagic events; 2) early ST and very late spontaneous MI carry the highest risk for subsequent short-term death, whereas early bleeding appears least dangerous; and 3) bleeding and non- ST-related MI increase the risk for death to a similar and lower extent than ST. Early MIs portended a low risk for death, as many of these events were

peri-procedural events, which appear to lack prognostic significance (8).

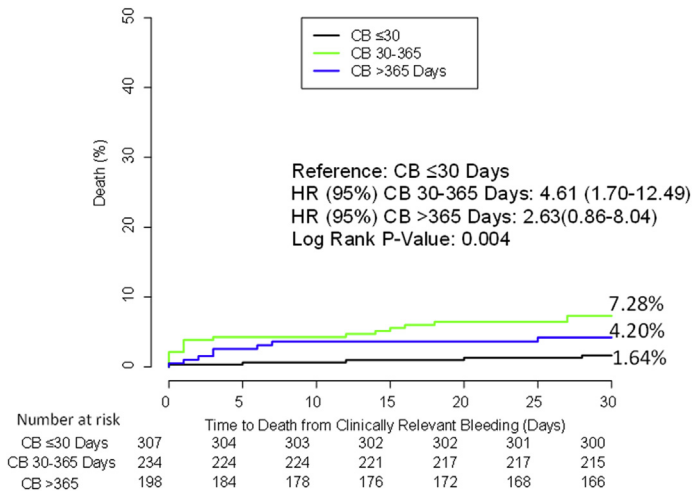
Ndrepepa et al. (9) culled 5,384 patients from 4 studies of PCI with glycoprotein IIb/IIIa receptor inhibitor or placebo and showed that bleeding (all events, TIMI criteria) within 30 days after PCI was an independent predictor of 1-year mortality (HR: 2.96; 95% confidence interval [CI]: 1.96 to 4.48; $p < 0.001$), similar to the effect of early MI (HR: 2.29; 95% CI: 1.52 to 3.46; $p < 0.001$). Their report included only early events, but the HRs were similar to those found in this analysis of a larger population followed for a longer duration including stricter definitions for significant bleeding and separating MI from episodes of ST.

Stone et al. (10) evaluated the relative impact of major bleeding and reinfarction on 3-year cardiac mortality in 3,602 patients with ST-segment elevation MI enrolled in the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction). They found that major bleeding (HR: 2.53; 95% CI: 1.61 to 3.98; $p < 0.001$) and reinfarction (HR: 7.88; 95% CI: 4.62 to 13.42; $p < 0.001$) carried significant prognostic information. Our data extend these observations in a more diverse cohort of patients and add granularity to the information by including ST and analyzing the different intervals from PCI to the ischemic or hemorrhagic event.

Pocock et al. (11) performed an analysis of the effects of CB or MI in the first 30 days after acute coronary syndromes on 1-year mortality in the ACUITY study. In a time-updated Cox regression model, each of these complications significantly increased mortality (HR: 2.93; 95% CI: 2.29 to 3.74; $p < 0.001$; and HR: 2.66; 95% CI: 2.06 to 3.43; $p < 0.001$, respectively). Of the 77 deaths occurring after MI, two-thirds happened within 30 days of MI, and the rest occurred within 1 year. In another analysis from ACUITY, the risk for death after MI was particularly high early on, whereas the contribution of bleeding to death was more constant over 1 year of follow-up (12). Our data, again, extend these observations to patients without acute coronary syndromes also and included events occurring at any point in the ADAPT-DES trial, not just in the first 30 days after hospitalization. Moreover, we separated the impact of spontaneous MI from that of ST.

Genereux et al. (13) evaluated the significance of post-hospital discharge bleeding in ADAPT-DES (two-thirds of all the bleeding events) and showed that after multivariate adjustment, it was associated with significantly higher 2-year mortality (HR: 5.03; $p < 0.0001$), with an effect size greater than that of post-discharge MI. The present analysis adds granularity to these data and shows that the increased mortality was not related to ST or MI resulting from the possible interruption of antithrombotic therapy. In this respect, our data reinforce the possibility that CB is a marker of comorbidity and not necessarily a direct cause of death, as one-half the mortality was non-cardiovascular, closely resembling the distribution of death causes among patients without any adverse events.

**FIGURE 3 Time to Death (Within 30 Days or to study End) After Clinically Relevant Bleeding, According to Timing of Clinically Relevant Bleeding Relative to Index Percutaneous Coronary Intervention (Unadjusted Hazard Ratios)**




The cumulative rates of death within 30 days of a clinically relevant bleeding (CB) event, in patients who had CB occur within 30 days of percutaneous coronary intervention (PCI) **(black line)**, 30 to 365 days after PCI **(green line)**, and more than 1 year after PCI **(blue line)** are shown with respective hazard ratios (HRs) compared with the reference of CB within 30 days of PCI.

**TABLE 3 Significant Predictors of Death at 2 Years**

| | Hazard Ratio | 95% Confidence Interval | p Value |
|---|---|---|---|
| Age, yrs | 1.05 | 1.03–1.06 | <0.0001 |
| Male | 1.36 | 1.04–1.78 | 0.02 |
| Insulin-requiring diabetes mellitus | 1.78 | 1.32–2.40 | 0.0001 |
| Previous MI (>7 days before percutaneous coronary intervention) | 1.37 | 1.08–1.73 | 0.01 |
| Chronic kidney disease | 1.44 | 1.05–1.99 | 0.02 |
| Creatinine clearance | 0.99 | 0.99–1.00 | 0.04 |
| Cigarette smoking | 1.37 | 1.08–1.73 | 0.01 |
| Baseline hemoglobin | 0.82 | 0.75–0.89 | <0.0001 |
| Baseline white blood cell count | 1.10 | 1.06–1.14 | <0.0001 |
| Clinically relevant bleeding | 2.43 | 1.86–3.18 | <0.0001 |
| Stent thrombosis | 11.37 | 7.61–16.98 | <0.0001 |
| MI without stent thrombosis | 1.84 | 1.24–2.72 | 0.002 |

Other variables considered (but not found significant): MI versus stable or unstable angina at presentation, non- insulin-dependent diabetes, arterial hypertension, hyperlipidemia, high platelet reactivity, and multivessel coronary artery disease.

MI = myocardial infarction.

Why early ST is more likely to result in death than later ST remains unclear, although similar observations were made in the setting of PCI for acute ST-segment elevation MI (14) and elective PCI (15,16). Our data also echo the large analysis from the National Cardiovascular Data Registry CathPCI registry, which showed that among 7,315 cases of ST, the ones occurring early (with the same temporal definitions as in our study) were associated with 2-fold higher in-hospital mortality compared with those occurring late or very late (7.8% vs. 3.8% vs. 3.6%, respectively, $p < 0.001$) (17). It is possible that earlier events occur more abruptly, without previous restenosis leading to the formation of collateral channels.

**STUDY STRENGTHS AND LIMITATIONS.** The main strengths of the present analysis are the inclusion of all events, not just the early ones; their categorization according to interval from PCI; and the more extended follow-up in a diverse population. That being said, we also recognize important limitations. Significant bleeding in this analysis was on the basis of site reporting, without independent adjudication, and included a rather broad range of events, albeit in tune with the recent efforts to standardize bleeding definitions (18). ADAPT-DES included a population of patients who underwent successful PCI with DES and thus may not represent the entire universe of PCI patients.

## CONCLUSIONS

Despite these limitations, we conclude that 1 in every 8 patients treated with initially successful PCI with DES had an episode of ST or MI not related to ST or CB over a 2-year period. When these events occur, they substantially increase risk for death, particularly if early ST or very late spontaneous MI is considered. These data provide additional impetus to further attempt to eliminate early ST by improving PCI techniques and using adequate antithrombotic therapy and prevent the progression of coronary artery disease and plaque rupture with aggressive risk factor modification.

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### PERSPECTIVES

**WHAT IS KNOWN?** Ischemic or bleeding events after PCI adversely affect prognosis. Less well defined is the impact of timing of these events relative to PCI on prognosis.

**WHAT IS NEW?** This study confirms the negative impact of these complications on prognosis and identifies ST occurring within the first 30 days after PCI as the event with the highest subsequent mortality, followed by late spontaneous MI.

**WHAT IS NEXT?** Additional studies are needed to confirm the improved outcomes resulting from prevention of both early ST and late spontaneous MI in patients with prior PCI.

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**KEY WORDS** **bleeding, drug-eluting stent(s), ischemia, percutaneous coronary intervention, stent thrombosis**