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Characterization of the Average Daily Ischemic and Bleeding Risk After Primary PCI for STEMI

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ABSTRACT

BACKGROUND The risk of recurrent ischemic and bleeding events after primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) may not be uniform over time, which may affect the benefit-to-risk ratio of guideline-recommended antithrombotic therapies in different intervals.

OBJECTIVES This study sought to characterize the average daily ischemic rates (ADIRs) and average daily bleeding rates (ADBRs) within the first year after primary PCI for STEMI.

METHODS Among 3,602 patients with STEMI who were enrolled in the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, all ischemic and bleeding events, including recurrent events, were classified according to the timing of their occurrence as acute (≤24 h after PCI), subacute (1 day to 30 days), and late (30 days to 1 year). Patients were treated with aspirin and clopidogrel for the entire year. ADIRs included cardiac death, reinfarction, and definite stent thrombosis. ADBRs included non–coronary artery bypass graft–related Thrombolysis In Myocardial Infarction major and minor bleeding. ADIRs and ADBRs were calculated as the total number of events divided by the number of patient-days of follow-up in each interval assuming a Poisson distribution. Generalized estimating equations were used to test the absolute least square mean differences (LSMD) between ADIRs and ADBRs.

RESULTS The ADIR and ADBR both exponentially decreased from the acute to the late periods ($p < 0.0001$). Although there were no significant differences in ADIR and ADBR in the acute phase (LSMD: +0.11%; 95% confidence interval [CI]: −0.35% to 0.58%; $p = 0.63$), the ADBR was greater than the ADIR in the subacute phase (LSMD: −0.39%; 95% CI: −0.58% to −0.20%; $p < 0.0001$). In the late phase, the ADIR exceeded the ADBR (LSMD: +1.51%; 95% CI: 1.04% to 1.98%; $p < 0.0001$).

CONCLUSIONS After primary PCI, the ADIR and ADBR both markedly decreased over time. Although the rates for bleeding exceeded those for ischemia within 30 days, the daily risk of ischemia significantly exceeded the daily risk of bleeding beyond 30 days, supporting the use of intensified platelet inhibition during the first year after STEMI.
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Patients with ST-segment elevation myocardial infarction (STEMI) who are undergoing primary percutaneous coronary intervention (PCI) are at high risk for ischemic and bleeding events, both of which strongly affect subsequent morbidity and mortality (1–4). The selection of optimal antithrombotic agents in the acute and chronic phases after STEMI, in terms of their potency and duration, requires a careful evaluation of the offsetting risks of ischemia and bleeding (5–7). Although the predictors and impact of ischemic and hemorrhagic events after primary PCI in STEMI have been investigated (1,2), their absolute and relative rates over time remain uncertain. In this regard the risk for recurrent ischemic and bleeding events may not be uniform over time, a consideration that may influence the benefit-to-risk ratio of guideline-recommended antithrombotic therapies. For example, because the highest rate of ischemic events occurs in the first few days or weeks after STEMI (8,9), a strategy of potent platelet inhibition could be considered during the first month after the patient's presentation, if the bleeding risk is not excessive in this period. Thereafter, down-titrating to a less potent regimen could offer a favorable balance of ischemic protection versus bleeding avoidance. Such considerations rely on understanding the relative risks of ischemia and bleeding in different risk periods.

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All adverse outcomes (including recurrent events) must be considered for the true burden of ischemic and bleeding complications to be fully appreciated. However, conventional time-to-event analyses censor patients after the first endpoint event is experienced, thereby masking subsequent recurrent adverse events, reducing statistical power, and diminishing appreciation for the potential benefit (or harm) of preventative therapies (10). We therefore determined the average daily rate (ADR) of all ischemic and bleeding events in the first year after primary PCI in patients enrolled in the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, to characterize the total and temporal-related burden of adverse outcomes after STEMI.

METHODS

STUDY DESIGN AND OBJECTIVES. The study design of the HORIZONS-AMI trial has been previously described (11,12). Briefly, HORIZONS-AMI was a multicenter, international, open-label, 2×2 factorial randomized controlled trial that enrolled 3,602 patients presenting with STEMI within 12 h from onset of symptoms. Eligible patients were randomized 1:1 to unfractionated heparin (UFH) plus a glycoprotein IIb/IIIa inhibitor (GPI) versus bivalirudin. A total of 3,202 eligible patients were then randomized again in a 3:1 ratio to implantation of either a paclitaxel-eluting stent or a bare metal stent. Aspirin, 324 mg chewed or 500 mg intravenously, was given before PCI, and 75 to 81 mg orally once a day was prescribed indefinitely after discharge. A loading dose of clopidogrel (300 or 600 mg per investigators' discretion) was administered pre-PCI, followed by 75 mg orally once a day for at least 1 year. Clinical follow-up was performed at 30 days, 1 year, 2 years, and 3 years following the index procedure. The study was approved by an Institutional Review Board and/or ethical committee at each center participating in the study. All enrolled patients provided informed written consent.

The objectives of the present study were as follows: 1) to determine the average daily ischemic rate (ADIR) and average daily bleeding rate (ADBR) within different time intervals and overall within the first year following primary PCI for STEMI (the time period for which aspirin and clopidogrel were prescribed for all patients); 2) to examine the extent to which recurrent events contributed to the total burden of adverse outcomes; and 3) to determine whether randomized intraprocedural antithrombotic treatment (bivalirudin monotherapy vs. UFH plus GPI) affected these relative and absolute rates.

ENDPOINT AND TIME INTERVAL DEFINITIONS. ADIR events were defined as cardiac death, myocardial infarction (MI), and definite stent thrombosis (ST). ADBR events were defined as Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding unrelated to coronary

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ADBR = average daily bleeding rate

ADIR = average daily ischemic rate

ADR = average daily rate

GPI = glycoprotein IIb/IIIa inhibitor

LSMD = least square mean difference

MI = myocardial infarction

PCI = percutaneous coronary intervention

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

UFH = unfractionated heparin

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TABLE 1 Number of Patients With Discrete Events Within Each Time Period and During the Total 1-Year Study Period

Endpoint	Acute (Day 0 to Day 1)	Subacute (Day 1 to Day 30)	Late (Day 30 to Day 365)	Overall (Day 0 to Day 365)
Cardiac death, reinfarction, or definite stent thrombosis				
Total events	37	129	113	279
Patients with 1 event	37	106	83	220
Patients with 2 events	–	10	10	21
Patients with 3 events	–	1	2	3
Patients with 4 events	–	–	1	2
Death				
Total events	20	73	54	147
Patients with 1 event	20	73	54	147
Noncardiac death				
Total events	1	8	33	42
Patients with 1 event	1	8	33	42
Cardiac death				
Total events	19	65	21	105
Patients with 1 event	19	65	21	105
Reinfarction				
Total events	14	58	85	157
Patients with 1 event	14	47	70	127
Patients with 2 events	–	4	4	7
Patients with 3 events	–	1	1	4
Patients with 4 events	–	–	1	1
Definite stent thrombosis				
Total events	21	47	32	100
Patients with 1 event	21	37	26	82
Patients with 2 events	–	5	3	6
Patients with 3 events	–	–	–	2
TIMI major and minor bleeding				
Total events	33	213	25	271
Patients with 1 event	33	197	22	228
Patients with 2 events	–	5	–	17
Patients with 3 events	–	2	1	3

TIMI = Thrombolysis In Myocardial Infarction.

artery bypass graft (CABG) procedures. The definition of MI in the periprocedural and nonprocedural periods has been previously described (9,10). ST was defined according to the Academic Research Consortium criteria (13). Net adverse clinical events were defined as death, MI, definite ST, and TIMI major and minor bleeding. The ADRs for ischemic and bleeding events were categorized according to the timing of their occurrence in the following time intervals: acute phase (≤24 h), subacute phase (day 1 to day 30), early phase (0 to 30 days), and late phase (day 30 to day 365). To account for the sometimes delayed recognition and diagnosis of bleeding events, ADRs were also examined using an alternative cutoff between the acute and the subacute phases, specifically: day 0 to day 3 (modified acute phase) and day 3 to day 30 (modified subacute phase). A clinical events committee blinded to treatment group allocation independently adjudicated all endpoint events through original source document evaluation.

STATISTICAL ANALYSES. The events of death (all-cause, cardiac, and noncardiac), MI, definite ST, and TIMI major and minor bleeding unrelated to CABG were examined in all 3,602 patients randomized to bivalirudin monotherapy versus UFH plus GPI. For this analysis, all events per patient were tabulated, as opposed to only the first event per patient, as is typically reported in time-to-first-event analyses. For example, a single patient could have 1 ST, 2 MIs, and 2 episodes of bleeding during the follow-up period. However, these had to be discrete, unrelated events. For example, if an ST directly resulted in an MI, this was coded as only as a single ischemic event in the composite ADIR endpoint. However, if an ischemic event led to a bleeding event (or vice versa), these were considered as 2 separate discrete events (i.e., a major bleeding episode led to development of an MI, or an ST led to PCI with subsequent periprocedural major bleeding).

TABLE 2 Relationships Between Ischemic and Bleeding Events

Primary Event	Secondary Event	0 to 7 Days	7 to 30 Days	0 to 30 Days	30 Days to 1 Year	0 to 1 Year
Bleeding (N = 271)	Ischemia (N = 43)	20/271 (7.4)	10/271 (3.7)	30/271 (11.1)	13/271 (4.8)	43/271 (15.9)
	MI or ST (n = 18)	5/271 (1.8)	4/271 (1.5)	9/271 (3.3)	9/271 (3.3)	18/271 (6.6)
	Cardiac death (n = 25)	15/271 (4.8)	6/271 (2.2)	21/271 (7.0)	4/271 (1.5)	25/271 (9.2)
Ischemia (N = 279)	Bleeding (N = 22)	13/279 (4.7)	9/279 (3.2)	22/279 (7.9)	0/279 (0.0)	22/279 (7.9)

Values are the number of recurrent events/number of primary bleeding or ischemic events (%). Proportion of ischemic and bleeding events occurring within 365 days following a bleeding (upper rows) or ischemic event (lower row), respectively.

MI = myocardial infarction; ST = stent thrombosis.

The ADR for a given interval was defined as the total number of events in that interval divided by the total number of patient-days of follow-up (number of patients multiplied by how many days each patient was at risk in that given period). Generalized estimating equations were used to test the least square mean differences (LSMDs) among the acute, subacute, and late time periods, with the patient as a repeated measure and assuming a Poisson distribution. The latter analysis compared the average rates per patient and produced the LSMD, 95% confidence intervals (CIs), and p values for the pairwise comparisons. Generalized estimating equations were also used to test the LSMD between the average rates for ischemia and bleeding within each specific interval. Because the definition of ABDR does not contain noncardiac death, as a sensitivity analysis we also calculated the LSMD between ischemia and bleeding after exclusion of cardiac death from the composite AIDR endpoint (i.e., with AIDR comprising only MI or definite ST). For descriptive purposes, instantaneous daily rates, calculated as the number of events on a given day divided by the number of patients at risk on that day (censoring only deaths and patients lost to follow-up), were also determined; that is, if on day 15 after PCI, 4 MIs occurred in 300 patients alive and at risk on that day, the instantaneous daily rate would be 1.3% (4 of 300). All analyses were then repeated in the randomized groups to determine the impact of procedural antithrombotic treatment with bivalirudin versus UFH plus GPI on the ADRs in different time intervals, according to the intention-to-treat principle. All statistical tests were 2-sided. A p value lower than 0.05 was considered statistically significant for hypothesis testing. Statistical analyses were performed with SAS software version 9.4 (SAS Institute, Cary, North Carolina).

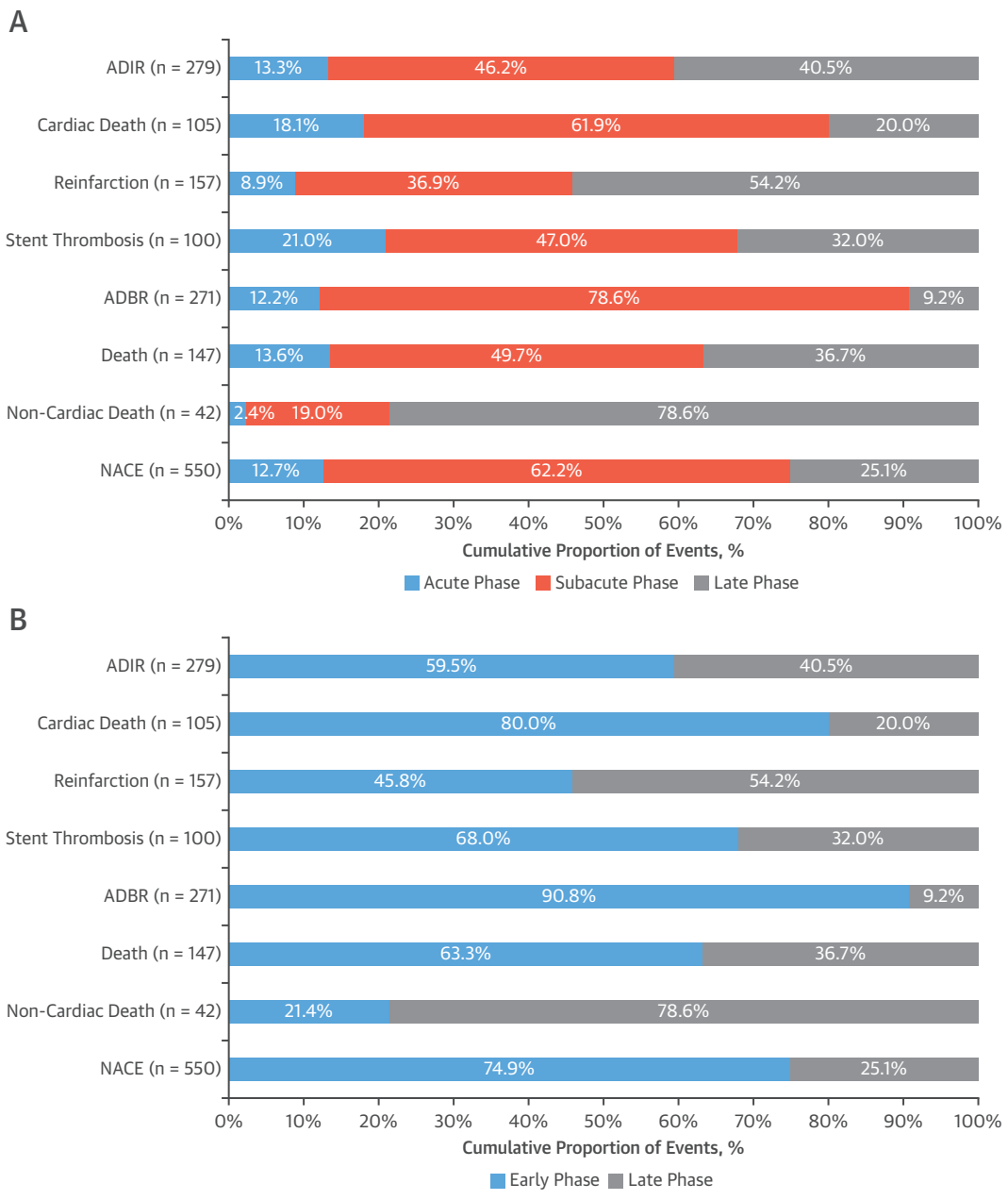
RESULTS

Among the 3,602 patients presenting with STEMI within 12 h of symptom onset who were enrolled in HORIZONS-AMI, 279 discrete ischemic events (cardiac death, MI, and definite ST) and 271 non-CABG-related TIMI major and minor bleeding events occurred within the first year following primary PCI for STEMI. Of these, 59 of 279 (21.1%) ischemic events and 43 of 271 (15.9%) bleeding events were recurrent and unrelated (**Table 1**). Conversely, most ischemic and bleeding events were not temporally related (**Table 2**). Only 22 of the 279 ischemic events (7.9%) were followed by a bleeding event, all occurring within 30 days. Following the 271 bleeding events, an ischemic event occurred in only 43 cases (15.9%), most (30 of 43; 69.8%) within 30 days.

The proportion of ischemic and bleeding events occurring in the acute, subacute, and late time intervals is illustrated in **Figure 1**. Most of the bleeding events (90.8%) occurred in the early phase. Conversely, only 59.5% of ischemic events occurred within 30 days, whereas 40.5% of ischemic events occurred between 30 days and 1 year. The absolute number of ischemic and bleeding events occurring each day over the 1-year follow-up period is shown in Online Figure 1, demonstrating the rapid and exponential reduction in the ADRs of both ischemic and bleeding events after PCI in STEMI.

AVERAGE DAILY ISCHEMIC AND BLEEDING RATES WITHIN 1 YEAR. The ADIR and ADBR up to 30 days, after 30 days, and within the entire first year are shown in **Figure 2**. The ADIR peaked in the first 24 h, and the ADBR peaked between day 2 and 3 (Online Table 1). The ADIR and ADBR in the acute, subacute, early and late phases are shown in **Figure 3, Table 3,** Online Table 2 (using the 3-day modified acute and subacute definitions), and Online Table 3 (examining the in-hospital and out-of-hospital periods). Highly significant reductions in both ADIR (**Table 4, Figure 3A**) and ADBR (**Table 4, Figure 3B**) were observed as the patients transitioned from the acute to the subacute to the late period ($p < 0.0001$ for both ADIR and ADBR, across all time intervals). Results were consistent in the modified acute and subacute intervals (Online Table 4). The daily rates for ischemic and bleeding events are shown in Online Figure 2.

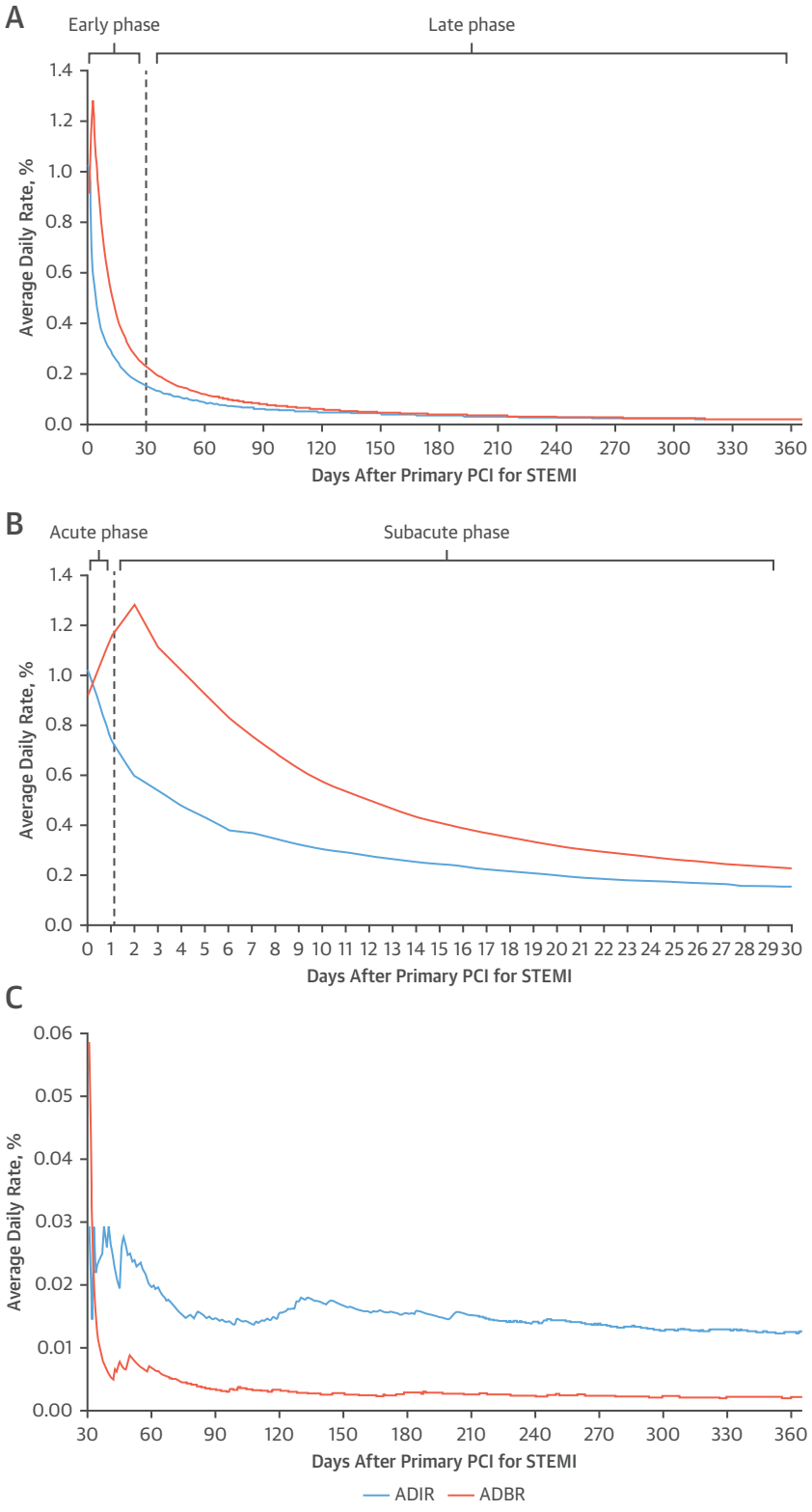
FIGURE 1 Adverse Event Proportions During the First Year After Primary PCI for STEMI



(A) Proportion of adverse events occurring in the acute (≤24 h), subacute (day 1 to day 30), and late (day 30 to day 365) periods. **(B)** Proportion of adverse events occurring in the early (day 0 to day 30) and late (day 30 to day 365) periods. ADBR = average daily bleeding rate; ADIR = average daily ischemic rate; NACE = net adverse clinical events; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

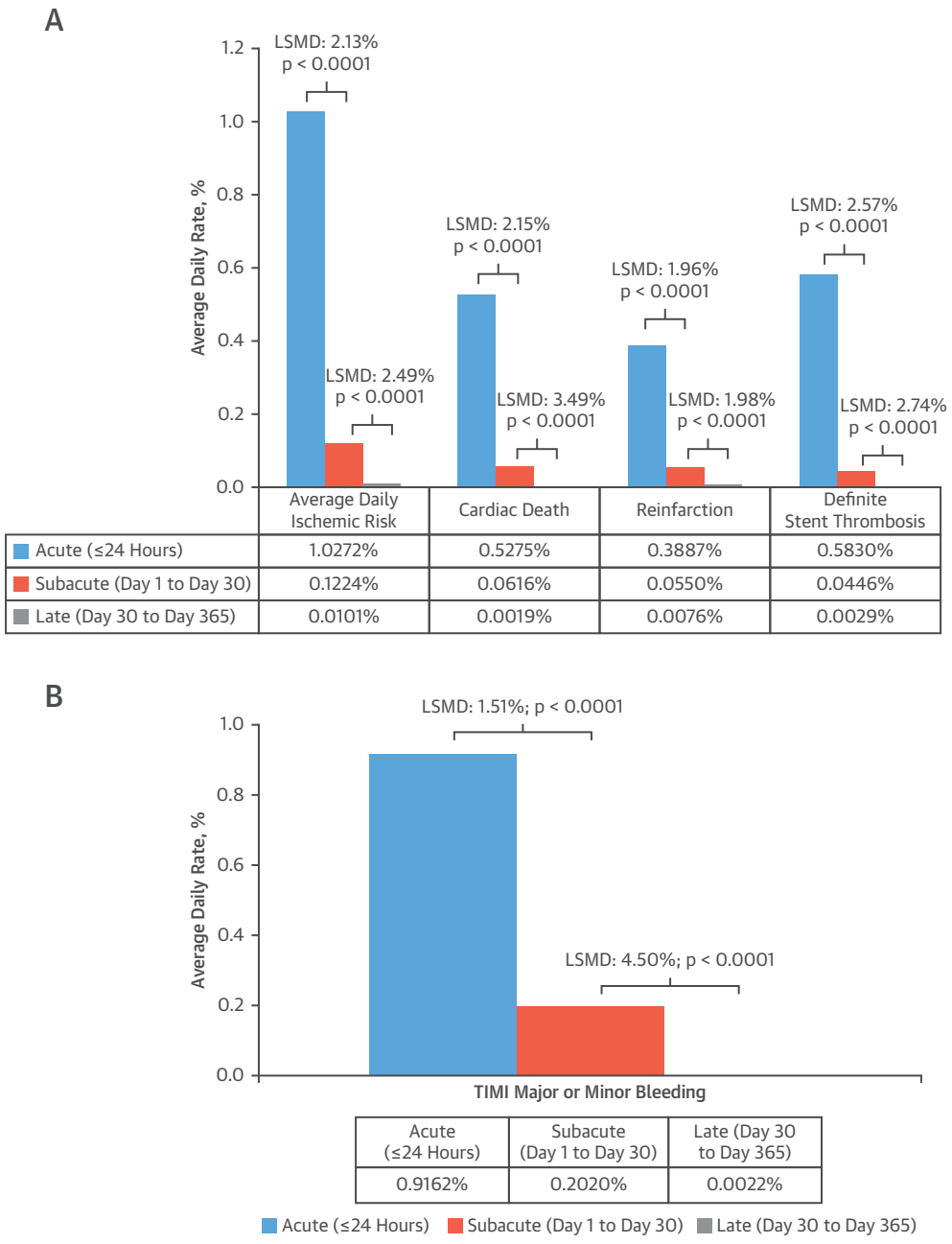
DIFFERENCES BETWEEN AVERAGE DAILY ISCHEMIC AND BLEEDING RATES AT 1 YEAR. LSMDs between ADIRs and ADBRs across time intervals are shown in the Central Illustration. ADBRs significantly exceeded ADIRs in the early phase (day 0 to 30 days; LSMD: −0.39%; 95% CI: −0.58% to −0.20%; $p < 0.0001$). Within the early phase, there was no significant difference between ADIR and ADBR in the

FIGURE 2 **Average Daily Ischemic and Bleeding Rates Within 1 Year After Primary PCI for STEMI**



(A) From day 0 to day 365. **(B)** From day 0 to day 30. **(C)** From day 30 to day 365. Abbreviations as in Figure 1.

FIGURE 3 Reductions in Average Daily Ischemic and Bleeding Rates From the Acute to the Subacute to the Late Periods After Primary PCI for STEMI



(A) Ischemic rate. **(B)** Bleeding rate. LSMD = least square mean differences; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Figure 1.

acute (0 to 1 day) phase, whereas ADBR exceeded ADIR in the subacute (day 1 to 30) phase. Using the alternative 3-day cutoff (Online Figure 3), ADBR exceeded ADIR in the acute (day 0 to 3) phase, with no significant differences between ADIR and ADBR in the subacute (day 3 to 30) phase. Finally, ADIR significantly exceeded ADBR in the late phase (30 days to 1 year; LSMD: 1.51%; 95% CI: 1.04% to 1.98%; $p < 0.0001$). Results

TABLE 3 Average Daily Rates for Adverse Events in the Acute, Subacute, Early, and Late Periods

Endpoint	Acute (≤24 h)	Subacute (Day 1 to Day 30)	Early (Day 0 to Day 30)	Late (Day 30 to Day 365)
Average daily ischemic rate*	37/3,602 (1.0272)	129/105,435 (0.1224)	166/109,037 (0.1522)	113/1,116,866 (0.0101)
Cardiac death	19/3,602 (0.5275)	65/105,435 (0.0616)	84/109,037 (0.0770)	21/1,116,866 (0.0019)
Reinfarction	14/3,602 (0.3887)	58/105,435 (0.0550)	72/109,037 (0.0660)	85/1,116,866 (0.0076)
Definite stent thrombosis	21/3,602 (0.5830)	47/105,435 (0.0446)	68/109,037 (0.0624)	32/1,116,866 (0.0029)
Average daily bleeding rate†	33/3,602 (0.9162)	213/105,435 (0.2020)	246/109,037 (0.2256)	25/1,116,866 (0.0022)
Average daily mortality rate	20/3,602 (0.5552)	73/105,435 (0.0692)	93 /109,037 (0.0853)	54/1,116,866 (0.0048)
Noncardiac death	1/3,602 (0.0278)	8/105,435 (0.0076)	9/109,037 (0.0083)	33/1,116,866 (0.0030)
Average daily net adverse clinical events rate‡	70/3,602 (1.9434)	342/105,435 (0.3244)	412/109,037 (0.3779)	138/1,116,866 (0.0124)

Values are the number of events/patient-day of follow-up (average daily rate, %) in each time-period. *Defined as cardiac death, reinfarction and definite stent thrombosis. †Defined as non-coronary artery bypass graft [CABG]-related Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding. ‡Defined as any death, reinfarction, definite stent thrombosis, and non-CABG-related TIMI major and minor bleeding.

were consistent after excluding cardiac death from the composite ischemic endpoint (Online Figure 4).

AVERAGE DAILY ISCHEMIC AND BLEEDING RATES ACCORDING TO THE ANTITHROMBOTIC TREATMENT. Differences in ADRs between bivalirudin-treated and UFH plus GPI-treated patients are illustrated in Online Table 5 (using a cutoff of ≤24 h for the acute phase) and Online Table 6 (using a cutoff of ≤3 days for the acute phase). At 30 days, bivalirudin was associated with lower rates of bleeding and mortality, with no significant differences observed in ADIR. Conversely, there were no significant differences in ADIR and ADBR between the 2 groups beyond 30 days. LSMDs between ADIR and ADBR in the bivalirudin arm and in the UFH plus GPI arm are shown in Online Figures 5 and 6, respectively. In patients treated with bivalirudin, there were no significant differences between ADIR and ADBR within the first 30 days, whereas in patients treated with UFH + GPI, ADBR exceeded ADIR in the early period. ADIR significantly exceeded ADBR in the late phase (30 days to 1 year) for both antithrombotic regimens.

DISCUSSION

The main findings from the present analysis, in which the absolute and relative daily and interval rates of ischemic and bleeding events were characterized in the first year after primary PCI in 3,602 patients with STEMI who were maintained on a dual antiplatelet regimen of aspirin and clopidogrel, are as follows: 1) the ADRs for both ischemic and bleeding events, including recurrent events, were highest early after the procedure and then rapidly declined over time; 2) in the early period (0 to 30 days), the absolute rates of bleeding exceeded those of ischemia and were influenced by the type of intraprocedural anticoagulation; and 3) in the late period (30 days to 1 year), the ADR of ischemic events exceeded that of bleeding; in this period the rates of ischemia and bleeding were unaffected by the procedural anticoagulation regimen. These novel findings elucidate the time-related differences in the offsetting rates of ischemia and bleeding after primary PCI, and they have implications for the use of more potent $P2Y_{12}$ inhibitors and other bleeding avoidance strategies during various intervals after mechanical reperfusion therapy in STEMI.

The current analysis from the HORIZONS-AMI trial extends the findings from prior studies in which the competing daily rates of ischemia and bleeding have been examined. Previously, Bhatt et al. (14), in a post hoc analysis from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, estimated the daily instantaneous hazard of ischemic and bleeding events at 3 years in stable patients who were taking aspirin plus placebo or clopidogrel. However, conventional time-to-event analyses (e.g., Kaplan-Meier methods and Cox proportional hazard models) are limited by the fact that patients are censored after the occurrence of the first endpoint event. This approach does not allow evaluation of multiple or recurrent events over time, and therefore it impedes full appreciation of the overall disease burden and effects of concomitant treatments (15). For example, in trials of heart failure therapies, as many as 50% of heart failure re-hospitalizations are recurrent events occurring in single participants (16,17). Application of time-to-first-event analysis for such endpoints results in a substantial loss of information and statistical power (18). In the present study, we examined the daily risk of discrete first-time and recurrent ischemic and bleeding events over 1 year after primary PCI for STEMI. Approximately 21% of all ischemic events and

TABLE 4 Differences in Average Daily Rates for Adverse Events in the Acute, Subacute, Early, and Late Periods

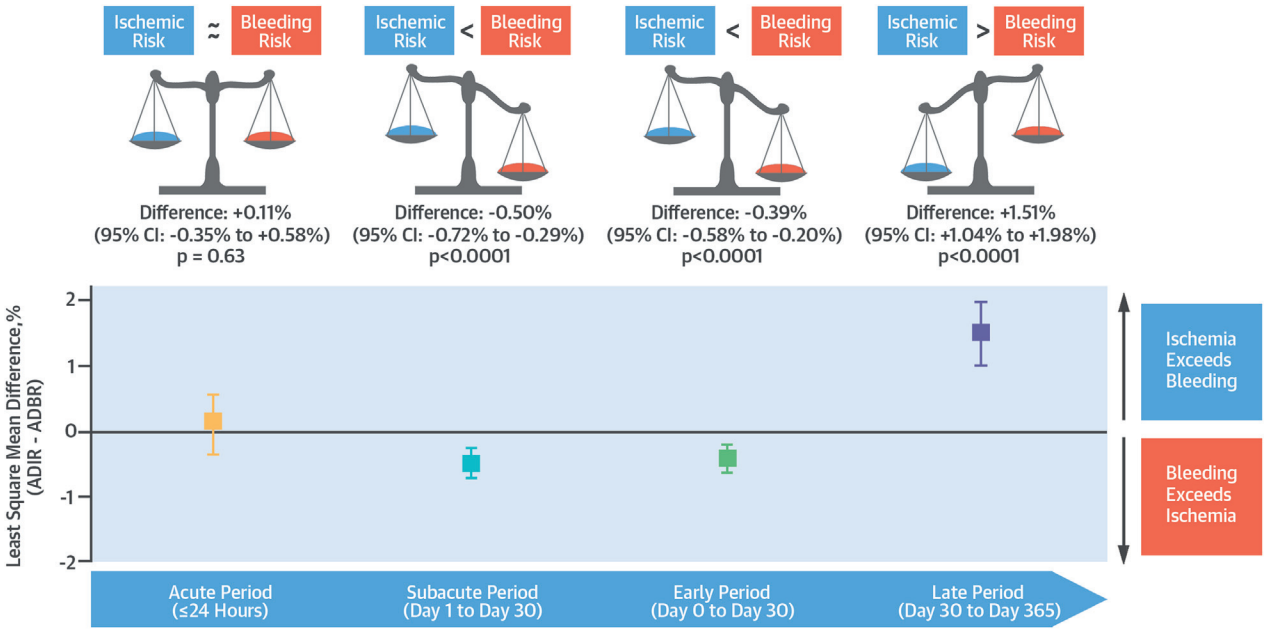
	Acute vs. Subacute Period			Acute vs. Late Period		
	Difference (%)	95% CI	p Value	Difference (%)	95% CI	p Value
Average daily ischemic rate	2.13	1.75 to 2.50	<0.0001	4.62	4.24 to 5.00	<0.0001
Cardiac death	2.15	1.64 to 2.66	<0.0001	5.64	5.02 to 6.26	<0.0001
Reinfarction	1.96	1.36 to 2.55	<0.0001	3.93	3.37 to 4.50	<0.0001
Definite stent thrombosis	2.57	2.04 to 3.10	<0.0001	5.32	4.77 to 5.87	<0.0001
Average daily bleeding rate	1.51	1.15 to 1.87	<0.0001	6.01	5.48 to 6.55	<0.0001
Average daily mortality rate	2.08	1.59 to 2.58	<0.0001	4.74	4.23 to 5.26	<0.0001
Noncardiac death	1.30	−0.78 to 3.38	0.22	2.24	0.25 to 4.23	0.03
Average daily net adverse clinical events rate	1.79	1.54 to 2.04	<0.0001	5.06	4.76 to 5.35	<0.0001
	Subacute vs. Late Period			**Early vs. Late Period**		
	Difference (%)	95% CI	p Value	Difference (%)	95% CI	p Value
Average daily ischemic rate	2.49	2.21 to 2.78	<0.0001	2.71	2.44 to 2.98	<0.0001
Cardiac death	3.49	3.00 to 3.98	<0.0001	3.71	3.23 to 4.19	<0.0001
Reinfarction	1.98	1.61 to 2.35	<0.0001	2.16	1.82 to 2.50	<0.0001
Definite stent thrombosis	2.74	2.26 to 3.23	<0.0001	3.08	2.64 to 3.52	<0.0001
Average daily bleeding rate	4.50	4.05 to 4.95	<0.0001	4.62	4.18 to 5.07	<0.0001
Average daily mortality rate	2.66	2.31 to 3.01	<0.0001	2.87	2.53 to 3.21	<0.0001
Noncardiac death	0.94	0.17 to 1.72	0.02	1.03	0.29 to 1.76	0.006
Average daily net adverse clinical events rate	3.27	3.04 to 3.50	<0.0001	3.42	3.20 to 3.64	<0.0001

CI = confidence interval.

16% of all bleeding events occurring within 1 year were recurrent events. Moreover, by detailed chart review we examined the interrelationship of ischemic and bleeding events. For example, it could be envisioned that many episodes of major bleeding during follow-up arise from PCI treatment of ischemic complications (e.g., ST) or that many ischemic events arise after discontinuation of antiplatelet agents or other therapies to treat major bleeding. However, in contrast to this expectation, only a few adverse ischemic and bleeding events were temporally related to bleeding and ischemic events, respectively. These findings place into perspective the total burden of adverse events that occur within the first year after primary PCI for STEMI (in patients treated with a dual antiplatelet regimen of aspirin and clopidogrel), and emphasize the relative independence of ischemic and bleeding complications in these high-risk patients.

The absolute risk for ischemic events was highest early after the PCI procedure, and then it exponentially decayed over time. This finding emphasizes that the early period (especially the first few days after primary PCI) is the interval in which more potent antiplatelet agents may have the greatest utility in improving prognosis. However, the absolute rate of bleeding was also greatest in this early period, and as such more potent agents may also produce harm in this interval. Such a trade-off is evidenced by procedural anticoagulation with bivalirudin rather than UFH plus GPI, which in the first 24 h results in greater rates of ST but less major bleeding. These offsetting risks can be favorably affected by routine use of a post-procedural bivalirudin infusion at 1.75 mg/kg/h for 3 to 4 h post-PCI, which may eliminate the excess acute risk of ST without increasing bleeding (19–21). Similarly, intensification of $P2Y_{12}$-receptor inhibition with intravenous cangrelor compared with clopidogrel during the PCI procedure and for the first 2 to 4 h thereafter favorably reduces the acute and 48-h rates of MI and ST without increasing major bleeding (22). In contrast, although the use of prasugrel rather than clopidogrel in patients with acute coronary syndromes (ACSs) was highly effective in reducing adverse ischemic events early after PCI, the excessive bleeding complications with this irreversible agent (including an increase in fatal and life-threatening bleeding) offset much of its benefit (23). Finally, given that in the first 30 days the overall burden of bleeding exceeded that of ischemia, bleeding avoidance strategies in this early high-risk period may be particularly effective in favorably shifting the benefit-to-risk equation. This finding possibly explains the early survival benefit seen in patients with STEMI who undergo primary PCI with radial artery access compared with femoral artery access, and with bivalirudin compared with UFH, with or without GPI, as intraprocedural antithrombotic therapy (24,25).

CENTRAL ILLUSTRATION **Temporal Differences in Ischemic and Bleeding Rates After Primary PCI for STEMI**



Giustino, G. et al. J Am Coll Cardiol. 2017;70(15):1846–57.

Least square mean differences (LSMD) between the average daily ischemic and bleeding rates in the acute, subacute, early, and late periods. The x-axis displays time. The y-axis displays the LSMD between ischemia and bleeding, with LSMD >1 if ischemia exceeds bleeding and LSMD <1 if bleeding exceeds ischemia. In the early period (before 30 days), the rates of bleeding exceed those for ischemia. In the late period (from 30 days to 1 year), the average daily ischemic rate (ADIR) significantly exceeds the average daily bleeding rate (ADBR). CI = confidence interval; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

In contrast to the first 30 days, ischemic and bleeding rates were substantially lower after 30 days, and they were unaffected by the procedural anticoagulation regimen. However, in this period the absolute rate of ischemia was ~1.5% greater than the absolute rate of bleeding (representing a relative increase of ~50-fold) (**Central Illustration**), suggesting a particularly beneficial role in the late period for an agent able to reduce ischemia further (as long as major bleeding is not markedly increased). This finding may underlie those from the PLATO (Study of Platelet Inhibition and Patient Outcomes) trial, in which patients with STEMI and non-STEMI who were treated with aspirin plus ticagrelor rather than aspirin plus clopidogrel experienced a 1-year reduction in the rates of MI, ST, cardiac mortality, and noncardiac mortality, despite a modest increase in non-CABG-related major bleeding (26). Of note, the benefits of ticagrelor in this trial did not begin to emerge until several weeks after initiation, and they continued to diverge throughout the 1-year follow-up period, as predicted from the present study (26). Thus the current analysis confirms current guidelines supporting consistent and high-intensity platelet inhibition to ≥1 year after primary PCI in STEMI, thereby emphasizing the selection of agents and consideration of patients' comorbidities to ensure an optimal balance of ischemia suppression and bleeding risk (27).

The insights from the present study may also have bearing on the design of future randomized controlled trials for primary or secondary prevention in patients with ACS and in patients undergoing PCI. In particular, inclusion of recurrent events (i.e., reinfarction or re-hospitalization for cardiac causes) as a pre-specified primary outcome measure may increase the number of endpoint events facilitating studies of smaller sample size (affecting trial feasibility) or with greater power (10). Such an approach may also allow for a more accurate estimation of the impact of a given intervention on overall disease burden. However, the present study also underscores the time dependence of the absolute and relative risks of offsetting events in disease states, as well as

the potential risks versus benefits of applying different therapeutic approaches in different periods. A treatment that offers a favorable benefit-to- risk profile early after a patient's presentation may not provide net clinical benefit later on (or vice versa).

STUDY LIMITATIONS. The implications of our study findings should be assessed considering their strengths, limitations, and unknowns. This analysis was performed from a large, prospective, international, multicenter randomized controlled trial with complete monitoring and event adjudication, thereby providing robust findings. Only first-generation drug-eluting stents and bare metal stents were used, and we did not study a UFH-only arm, which some centers use in primary PCI. In addition, more than 90% of patients were treated by femoral access, which has been associated with a greater risk of bleeding and vascular complications than transradial access (24,25). However, in contemporary U.S. practice, femoral access and UFH and GPI are still used in up to 90% and 40% of STEMI cases, respectively (28). Novel, more potent $P2Y_{12}$-receptor inhibitors (ticagrelor, prasugrel, and cangrelor) were not available during study enrollment, and therefore our findings apply to an aspirin- and clopidogrel-treated population. These newer treatments may affect the absolute and relative risks of ischemia versus bleeding, although the general concepts still apply. Moreover, clopidogrel is still prescribed at hospital discharge in up to 60% to 70% of patients with ACS in the United States (29-31). The net effects of new strategies capable of suppressing ischemia but that may also increase bleeding depend on the following: 1) the absolute rates of these competing risks; 2) the relative reduction in ischemia versus increase in bleeding with the new therapy; and 3) the relative impact of ischemia versus bleeding on overall patient outcomes, for example as measured by their effect on mortality rates, a factor not considered in the present report but previously investigated in both acute (32) and more chronic settings (33). In this regard, in the HORIZONS-AMI trial, non-CABG-related protocol-defined bleeding was at least as strongly associated with all-cause mortality through 3-year follow-up as was reinfarction (adjusted HR: 3.44 vs. 2.88, respectively) (33). The observed peak for the rate of bleeding between days 2 and 3 may be related to ascertainment bias caused by the typical nadir in hemoglobin that occurs after a periprocedural hemorrhagic event. For this reason we presented a sensitivity analysis with acute events defined as those occurring within 3 days. Finally, in the current analysis we estimated ADRs in the overall trial population. Because the absolute rates of ischemia and bleeding may vary with individual patients' risk factors, further analyses are warranted to identify subgroups at relatively higher or lower risk for recurrent ischemic versus bleeding events who may differentially benefit from more intensive anti-ischemic therapies or bleeding avoidance approaches, respectively.

CONCLUSIONS

In the HORIZONS-AMI trial, in patients with STEMI treated with primary PCI on a background of aspirin and clopidogrel for 1 year, the daily risk for both adverse ischemic and bleeding events was highest early after the procedure and then dramatically declined over time. However, in contrast to the early period, beyond 30 days the absolute risk for ischemia exceeded the risk for bleeding. The current findings support the use of potent platelet inhibition continuing through at least 1 year to prevent both primary and recurrent ischemic events, especially in patients without excessive bleeding risk. Implementation of bleeding avoidance strategies is also essential, especially in the acute and subacute phases after primary PCI. Finally, substantial proportions of both ischemic and bleeding events that occurred during the 1-year follow-up period were discrete, recurrent events, although in most cases not related to each other; these considerations should be taken into account when evaluating the effect of pharmacotherapies for secondary prevention after STEMI.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: After primary PCI in patients with STEMI, the risk of first and recurrent ischemic and bleeding events is highest early after the procedure and declines over time. Although rates for bleeding exceeded those for ischemic events within the first 30 days, beyond this period the risk of recurrent ischemia exceeds the risk for bleeding.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to evaluate the overall burden of events, including recurrent adverse events, which are censored in conventional time-to-event analyses.

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KEY WORDS average daily rate, bleeding events, ischemic events, percutaneous coronary intervention, ST-segment elevation myocardial infarction

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