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Incidence of Death and Acute Myocardial Infarction Associated With Stopping Clopidogrel After Acute Coronary Syndrome

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RANDOMIZED CONTROLLED trials have established the efficacy of clopidogrel therapy following hospitalization for acute coronary syndrome (ACS) for patients treated either medically or with percutaneous coronary intervention (PCI).¹⁻³ The average duration of clopidogrel treatment in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial was 9 months following hospital discharge.¹ Current cardiology guidelines recommend clopidogrel therapy for at least 1 month and ideally up to 1 year for patients treated medically or with a bare metal stent, and at least 1 year for patients treated with a drug-eluting stent following hospitalization for ACS.⁴ These recommendations are categorized as class IA, indicating the highest level of evidence support.

While clopidogrel has been shown to be efficacious for patients with ACS, we sought to evaluate whether there may be a “rebound effect” or concentration of thrombotic events shortly after stopping treatment with clopidogrel.

Context It is unknown whether patients are at increased short-term risk for adverse events following clopidogrel cessation.

Objective To assess the rates of adverse events after stopping treatment with clopidogrel in a national sample of patients with acute coronary syndrome (ACS).

Design, Setting, and Patients Retrospective cohort study of 3137 patients with ACS discharged from 127 Veterans Affairs hospitals between October 1, 2003, and March 31, 2005, with posthospital treatment with clopidogrel.

Main Outcome Measure Rate of all-cause mortality or acute myocardial infarction (AMI) after stopping treatment with clopidogrel.

Results Mean (SD) follow-up after stopping treatment with clopidogrel was 196 (152) days for medically treated patients with ACS without stents (n = 1568) and 203 (148) days for patients with ACS treated with percutaneous coronary intervention (PCI) (n = 1569). Among medically treated patients, mean (SD) duration of clopidogrel treatment was 302 (151) days and death or AMI occurred in 17.1% (n = 268) of patients, with 60.8% (n = 163) of events occurring during 0 to 90 days, 21.3% (n = 57) during 91 to 180 days, and 9.7% (n = 26) during 181 to 270 days after stopping treatment with clopidogrel. In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90-day interval after stopping treatment with clopidogrel was associated with a significantly higher risk of adverse events (incidence rate ratio [IRR], 1.98; 95% confidence interval [CI], 1.46-2.69 vs the interval of 91-180 days). Similarly, among PCI-treated patients with ACS, mean (SD) duration of clopidogrel treatment was 278 (169) days and death or AMI occurred in 7.9% (n = 124) of patients, with 58.9% (n = 73) of events occurring during 0 to 90 days, 23.4% (n = 29) during 91 to 180 days, and 6.5% (n = 8) during 181 to 270 days after stopping clopidogrel treatment. In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90-day interval after stopping clopidogrel treatment was associated with a significantly higher risk of adverse events (IRR, 1.82; 95% CI, 1.17-2.83).

Conclusions We observed a clustering of adverse events in the initial 90 days after stopping clopidogrel among both medically treated and PCI-treated patients with ACS, supporting the possibility of a clopidogrel rebound effect. Additional studies are needed to confirm the clustering of events after stopping clopidogrel, including associations with cardiovascular mortality and reasons for stopping clopidogrel, as well as to determine the mechanism of this phenomenon, and to identify strategies to reduce early events after clopidogrel cessation.

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Several factors raise this hypothesis. First, a clustering of adverse events has previously been reported after cessation of long-term aspirin therapy as well as after cessation of heparin therapy in patients with ACS.⁵⁻¹⁴ The proposed mechanism for these events is thought to be a transient hyperthrombotic state after stopping drug therapy.⁶ Similarly, there have been reports of thrombotic events after thienopyridine cessation among patients receiving coronary stents, particularly drug-eluting stents.¹⁵⁻¹⁷ Yet these events have largely been attributed to stent-related mechanisms, particularly incomplete neointimal repair with a drug-eluting stent rather than a rebound hypercoagulable state.¹⁵ To date, we are unaware of any prior studies of possible clopidogrel rebound event clustering among patients not receiving a coronary stent.

Accordingly, we assessed the incidence and timing of mortality or acute myocardial infarction (AMI) after stopping treatment with clopidogrel in a national cohort of patients with ACS. Specifically, we evaluated for clustering of events after stopping treatment with clopidogrel in medically treated patients with ACS without stents. For comparison, we also assessed the incidence and timing of death or AMI among those patients with ACS who received PCI. Finally, we assessed the association between duration of clopidogrel therapy and event rates after stopping treatment with clopidogrel.

METHODS

Data for this study were collected as part of the Department of Veterans Affairs (VA) Veterans Health Administration Cardiac Care Follow-up Clinical Study, which uses national data from the Veterans Health Administration External Peer Review Program for quality monitoring for a variety of medical conditions and procedures, including AMI and unstable angina.

Starting in 2003, the records of all patients discharged from a VA hospital with AMI or unstable angina were abstracted as part of a national VA cardiac care initiative. All patients with *In-*

ternational Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes 410.xx and 411.xx were identified from the VA Patient Treatment File, and their records were manually abstracted by trained abstractors using standard reporting forms. Additional details of the study methods have been published.¹⁸

Patient Population

All patients with AMI or unstable angina as documented by standard electrocardiographic criteria, elevated troponin levels, and other clinical evidence, who were discharged with posthospital treatment with clopidogrel from any 1 of 127 VA medical centers between October 1, 2003, and March 31, 2005, and who remained event-free during clopidogrel treatment were included. We excluded patients who had an adverse event while receiving clopidogrel therapy; these events were not related to a potential rebound phenomenon because clopidogrel therapy had not been stopped. Patients admitted with other primary medical conditions but who developed AMI during their hospitalization or who had a perioperative MI were included if they survived to hospital discharge and were prescribed clopidogrel at discharge. Patients who were transferred into VA hospitals from other medical facilities were excluded because important baseline data, PCI procedural details, or both were not available. Since 2003, race and ethnicity data have been collected by the VA and are self-reported by the patient. Patient self-report has been found to have high agreement with observer-recorded race/ethnicity data.¹⁹

Clopidogrel Use and Clopidogrel Cessation

Clopidogrel use was assessed using the Veterans Health Administration Pharmacy Benefits Management database, which records the date dispensed and the number of days supplied for each dispensed medication. In our primary analysis, the last day of clopidogrel use was based on the date of the last pre-

scription refill plus the number of days supplied for that refill. Therefore, duration of clopidogrel therapy was calculated from the day of hospital discharge to the last clopidogrel refill date plus the number of days supplied for that last refill.^{20,21}

Outcomes

The primary outcome was the combined end point of all-cause mortality or AMI hospitalization following cessation of clopidogrel therapy. The VA vital status file was used to determine vital status after stopping treatment with clopidogrel.^{22,23} This file has 98.3% sensitivity and 97.6% exact agreement with dates when compared with the National Death Index.²² The AMI outcome was based on a primary discharge *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code of 410.XX for any hospitalization within the VA after stopping treatment with clopidogrel.²⁴ Vital status information was available after hospital discharge on all patients through January 31, 2007.

Statistical Methods

The primary objective of the analysis was to assess the incidence and timing of adverse events after stopping treatment with clopidogrel among medically treated ACS patients without stents. First, unadjusted incidence rates for all-cause mortality or AMI were calculated for each 90-day interval after stopping treatment with clopidogrel. Differences in incidence rates between time intervals (eg, 0-90, 91-180, and 181-270 days) were evaluated using the Fisher exact test. Pharmacy data on clopidogrel use were available until September 30, 2005, and patients still taking clopidogrel at that time were censored because we were unable to determine the exact clopidogrel stop date.

Second, we constructed multivariable Cox regression models, adjusting for total duration of clopidogrel treatment and all other covariates listed in TABLE 1 to obtain risk-adjusted instantaneous incidence rates using kernel hazard functions.

Third, to assess the association between time interval after stopping treatment with clopidogrel and risk of adverse events, we used Poisson regression to calculate incidence rate ratios (IRRs), adjusting for all Table 1 variables including duration of clopidogrel treatment. In these models, the primary independent variable of interest was the risk of adverse events in the first interval of 0 to 90 days after stopping treatment with clopidogrel compared with the interval of 91 to 180 days.

To further assess the robustness of our findings, we performed a series of additional analyses. First, we assessed the in-

cidence of the AMI outcome only to assess whether the clustering of events after stopping treatment with clopidogrel was specifically associated with cardiac events. Second, we assessed the association between time interval after stopping treatment with clopidogrel and outcomes in prespecified subgroups: (1) patients taking clopidogrel for 3 months or less, 6 months or less, and at least 9 months following ACS; and (2) patients with diabetes because a prior *in vitro* platelet study demonstrated rebound platelet activity in individuals with diabetes and coronary disease following clopidogrel withdrawal.^{1,25} Third, due

to concerns that medication adherence behavior could explain in part any association between medication use via pharmacy refill data and outcomes, we included adherence to statin medications as a covariate in our multivariable models. Statin adherence was calculated using the method of the proportion of days covered and adherence was categorized as high (≥ 0.80), intermediate (0.60-0.79), and low (< 0.60).²⁰

Fourth, we performed several sensitivity analyses around the clopidogrel stop date by drawing (1) a 10% random sample and changing the date by ± 15 days from the stop date used in the primary analyses; (2) a 10% random sample and changing the stop date by ± 30 days; and (3) a 20% random sample and changing the stop date by ± 15 days. The findings of these sensitivity analyses around the stop date did not change our primary results and therefore are not reported further. Fifth, because bleeding events have been associated with higher rates of adverse events and can be associated with clopidogrel cessation, we excluded patients who had any outpatient or inpatient code for bleeding following their index ACS hospitalization (follow-up through September 30, 2005).

Sixth, to further address potential patient characteristic differences between those who took longer vs shorter courses of clopidogrel, we performed a matched propensity analysis based on the characteristics in Table 1 between those who took clopidogrel for 6 months or less or more than 6 months. We then evaluated the rate of adverse events in the time intervals after clopidogrel cessation (ie, first 90-day interval after stopping treatment with clopidogrel compared with the interval of 91-180 days) among patients who took clopidogrel for 6 months or less and for more than 6 months in the propensity-matched cohort. Finally, because the rate of death or AMI during treatment with clopidogrel can serve as a reference, we compared the rate of adverse events following index ACS discharge while patients were taking clopidogrel with the rate of adverse events after stopping treatment with clopidogrel.

Table 1. Baseline Characteristics of the Study Cohort

Variables	All (n = 3137)	Medical Therapy (n = 1568)	PCI (n = 1569)
Demographics			
Age, y			
Mean (SD)	66.0 (11.7)	68.5 (11.7)	63.5 (11.1)
Median (range)	65 (57-76)	70 (60-79)	62 (56-73)
Male sex, No. (%)	3080 (98.2)	1543 (98.4)	1537 (98.0)
White race, No. (%)	1669 (53.2)	853 (54.4)	816 (52.0)
Comorbidities, No. (%)			
Heart failure	715 (22.8)	487 (31.1)	228 (14.5)
Diabetes	659 (21.0)	376 (24.0)	283 (18.0)
Prior myocardial infarction	809 (25.8)	485 (30.9)	325 (20.7)
PCI within prior 6 mo	272 (8.7)	98 (6.2)	174 (11.1)
Prior CABG	710 (22.6)	449 (28.6)	261 (16.6)
Cerebrovascular disease	228 (7.3)	153 (9.8)	75 (4.8)
Peripheral vascular disease	805 (25.7)	518 (33.0)	287 (18.3)
Renal disease	504 (16.1)	338 (21.6)	166 (10.6)
COPD	472 (15.1)	290 (18.5)	182 (11.6)
Dementia	358 (11.4)	225 (14.4)	133 (8.5)
Cancer	202 (6.4)	123 (7.8)	79 (5.0)
Current smoker	1068 (34.0)	468 (29.9)	600 (38.2)
Medications, No. (%)			
Prior clopidogrel use	620 (19.8)	452 (28.8)	168 (10.7)
Aspirin at discharge	2866 (91.4)	1381 (88.1)	1485 (94.7)
β -Blocker at discharge	2907 (92.7)	1439 (91.8)	1468 (93.6)
ACE inhibitor at discharge	2365 (75.4)	1111 (70.9)	1254 (79.9)
Statin at discharge	2540 (81.0)	1198 (76.4)	1342 (85.5)
ACS presentation factors			
TIMI risk score, mean (SD)	3.2 (1.3)	3.2 (1.3)	3.2 (1.3)
Left ventricular ejection fraction $< 40\%$, No. (%)	786 (25.1)	441 (28.1)	345 (22.0)
Unstable angina, No. (%)	402 (12.8)	326 (20.8)	76 (4.8)
ACS treatment, No. (%)			
Glycoprotein IIb/IIIa use	1437 (45.8)	408 (26.0)	1029 (65.6)
Duration receiving clopidogrel following hospital discharge, d			
Mean (SD)	290 (161)	278 (169)	302 (151)
Median (range)	298 (163-413)	281 (120-417)	310 (182-410)

Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Analyses evaluating the incidence and timing of events after stopping treatment with clopidogrel were then repeated in the PCI-treated patients with ACS to allow comparison of patterns of event clustering and magnitude of risk with the medically treated ACS patients after clopidogrel cessation. All analyses were conducted using Stata version 9.0 (StataCorp, College Station, Texas). The Cardiac Care Follow-up Clinical Study was approved by the University of Washington's human subjects committee and the Colorado Multiple Institutional Review Board.

RESULTS

Medically Treated Patients With ACS

Of 8095 patients hospitalized for ACS during the study period and who received medical therapy only (ie, no PCI), there was documentation in the chart that 3425 patients (42.3%) were to be discharged with posthospital treatment with clopidogrel. Of these patients, 2475 (72.3%) filled their prescription for clopidogrel through the VA outpatient pharmacy. Refill prescription data were available for all of these patients. During follow-up, 1568 patients stopped treatment with clopidogrel and were event-free prior to stopping, yielding the medically treated patient cohort for the study.

Baseline characteristics of the medically treated patients are shown in Table 1. The mean (SD) age was 66.0 (11.7) years, and these patients had a high prevalence of cardiac history and other chronic medical conditions. The mean (SD) duration of clopidogrel therapy following hospital discharge among the medically treated patients was 302 (151) days and the median was 310 days, with 80.1% of patients taking clopidogrel for more than 3 months, 66.2% taking clopidogrel for more than 6 months, 52.1% taking clopidogrel for more than 9 months, and 34.8% taking clopidogrel for more than 12 months.

Mean (SD) follow-up after stopping treatment with clopidogrel among the medically treated patients was 196

(152) days; median was 155 (interquartile range, 98-254) days. All-cause mortality ($n=155$) or AMI ($n=113$) occurred in 17.1% ($n=268$) of patients, with 60.8% ($n=163$) of events occurring during 0 to 90 days, 21.3% ($n=57$) occurring during 91 to 180 days, and 9.7% ($n=26$) occurring during 181 to 270 days after stopping treatment with clopidogrel (FIGURE and TABLE 2).

The incidence rate per 1000 patient-days of follow-up during each 90-day interval after stopping treatment with clopidogrel was 1.31 (95% confidence interval [CI], 1.12-1.53 for 0-90 days), 0.69 (95% CI, 0.53-0.89 for 91-180 days), and 0.64 (95% CI, 0.44-0.94 for 181-270 days) ($P<.001$ for comparison between the 3 time intervals). In multivariable analysis, including adjustment for total duration of clopidogrel treatment, the interval of 0 to 90 days was associated with significantly increased risk of adverse events after stopping treatment with clopidogrel compared with the interval of 91 to 180 days (IRR, 1.98; 95% CI, 1.46-2.69) (TABLE 3).

The findings of an increased risk of adverse events associated with the interval of 0 to 90 days were similar when the AMI outcome alone was evaluated (IRR, 2.39; 95% CI, 1.50-3.82). In addition, the increased risk for 0 to 90 days also was consistent among patients taking clopidogrel for 3 months or less, 6 months or less, 9 months or less, or more than 9 months after ACS hospital discharge (Table 3). Moreover, the findings were consistent for patients with and without diabetes (Table 3).

The majority of patients had high (36.2%) or intermediate (43.3%) levels of statin adherence; and the findings of increased adverse events associated with the interval of 0 to 90 days after stopping treatment with clopidogrel was consistent even after adjusting for statin adherence. A total of 326 patients (20.8%) had 1 or more outpatient or inpatient codes for bleeding during follow-up after their index ACS admission. In sensitivity analysis excluding these patients, the increased

event rate in the initial 90-day interval after stopping treatment with clopidogrel remained consistent. Further, in the propensity-matched cohort ($n=1018$) analysis, the rate of increased adverse events associated in the initial 90-day interval following clopidogrel cessation compared with adverse events in the subsequent interval of 91 to 180 days was consistent with the primary findings among patients who took clopidogrel for 6 months or less or for more than 6 months.

In addition, for the entire cohort of patients taking clopidogrel after hospital discharge, the rate of adverse events was 1.20 per 1000 patient-days in the initial 90 days, which then decreased to a background rate of approximately 0.50 per 1000 patient-days for the interval of 91 to 360 days. In comparison, there was an increase in the rate of adverse events following clopidogrel cessation (1.31 per 1000 patient-days for the interval of 0-90 days) among patients who were event-free prior to stopping treatment with clopidogrel. Therefore, the rate of adverse events in the initial 90 days after stopping treatment with clopidogrel was higher than both the initial and background rates of adverse events for patients still taking clopidogrel, further supporting a clustering of events after clopidogrel cessation.

PCI-Treated Patients With ACS

Of the 2805 patients hospitalized for ACS and who received PCI, there was documentation in the chart that 2634 patients (93.9%) were to be discharged with posthospital treatment with clopidogrel. Of these patients, 2303 (87.4%) filled their prescription for clopidogrel through the VA outpatient pharmacy. Clopidogrel refill prescription data was available on all of these patients. During follow-up, 1569 stopped clopidogrel and were event-free prior to stopping treatment with clopidogrel, yielding the PCI-treated patient cohort for the study.

The mean (SD) age of the PCI-treated patients was 63.5 (11.1) years, and a sizeable proportion had a prior car-

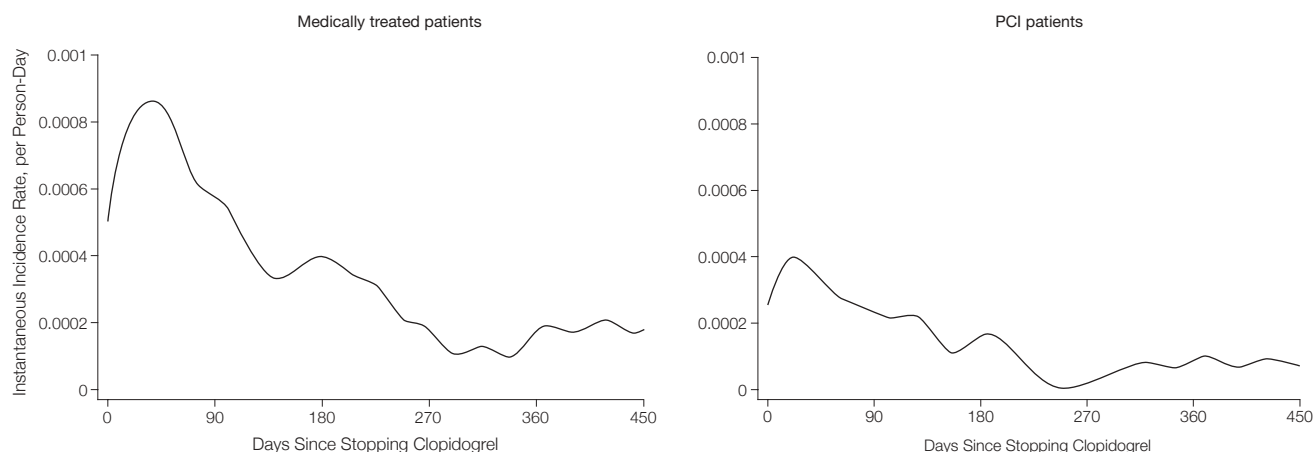
diac history and coexisting chronic conditions (Table 1). Approximately two-thirds of these patients (n=984; 62.7%) received a bare metal stent while one-third (n=585; 37.3%) received a drug-eluting stent. The majority of patients received a bare metal stent because the study period spanned the time when the drug-eluting stent was first introduced into clinical practice. The mean (SD) duration of clopidogrel therapy following hospital discharge was 278 (169) days and the median was 281 days, with 87.9% of the patients taking clopidogrel for more than 3 months, 75.5% taking clopidogrel for more than 6 months, 59.5% taking clopidogrel for more than 9 months, and 36.8% taking clopidogrel for more than 12 months.

Among the PCI-treated patients, the mean (SD) follow-up after stopping treatment with clopidogrel was 203 (148) days; median was 160 (interquartile range, 109-262) days. The combined end point of all-cause mortality (n=68) or AMI (n=56) occurred in 7.9% (n=124) of the patients, with 58.9% (n=73) of the events occurring during 0 to 90 days, 23.4% (n=29) occurring during 91 to 180 days, and 6.5% (n=8) occurring during 181 to 270 days after stopping treatment with clopidogrel (Figure and Table 2). The incidence rate per 1000 patient-days of follow-up during each 90-day interval after stopping treatment with clopidogrel was 0.57 (95% CI, 0.45-0.72 for 0-90 days), 0.33 (95% CI, 0.23-0.47 for 91-

180 days), and 0.19 (95% CI, 0.09-0.37 for 181-270 days) ($P < .001$ for comparison between the 3 time intervals).

In multivariable analysis, including adjustment for total duration of clopidogrel treatment following hospital discharge, the interval of 0 to 90 days after stopping treatment with clopidogrel was associated with a significantly increased risk of adverse events compared with the interval of 91 to 180 days (IRR, 1.82; 95% CI, 1.17-2.83) among PCI-treated patients with ACS. Because the study spanned the time when drug-eluting stents were first introduced, only a minority of patients had received a drug-eluting stent and there was a small number of events after stop-

Figure. Risk-Adjusted Instantaneous Incidence Rates of Death or AMI Over Time After Stopping Treatment With Clopidogrel Among Medically Treated and PCI-Treated Patients With ACS Using Multivariable Cox Regression Models



ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention.

Table 2. Incidence of Death or Acute Myocardial Infarction Among Patients With Acute Coronary Syndrome Medically Treated or Treated With Percutaneous Coronary Intervention (PCI) After Stopping Treatment With Clopidogrel

Period, d ^a	Medically Treated Patients			PCI-Treated Patients		
	No. at Risk	No. of Events	Incidence Rate per 1000 Patient-Days (95% CI)	No. at Risk	No. of Events	Incidence Rate per 1000 Patient-Days (95% CI)
0-90	1568	163	1.31 (1.12-1.53)	1569	73	0.57 (0.45-0.72)
91-180	1212	57	0.69 (0.53-0.89)	1279	29	0.33 (0.23-0.47)
181-270	582	26	0.64 (0.44-0.94)	630	8	0.19 (0.09-0.37)
271-360	363	5	0.19 (0.08-0.45)	366	5	0.18 (0.08-0.44)
361-450	238	8	0.46 (0.23-0.93)	237	4	0.24 (0.09-0.63)

Abbreviation: CI, confidence interval.

^aThere were 9 events and 5 events in the medically treated and PCI-treated groups, respectively, in the time interval of more than 450 days.

ping treatment with clopidogrel among patients with a drug-eluting stent ($n=42$), limiting the ability to perform multivariable subgroup analysis; however, there was a similar trend of increased adverse events ($n=23$) in the 0 to 90 days after stopping treatment with clopidogrel for patients with a drug-eluting stent. Among the patient subgroup with a bare metal stent, the findings of increased risk of adverse events in the interval of 0 to 90 days after stopping treatment with clopidogrel were consistent with the overall results (IRR, 2.14; 95% CI, 1.23-3.74).

COMMENT

To our knowledge, this is the first study to evaluate patterns of adverse events after clopidogrel cessation in a national cohort of patients with ACS. In particular, we were able to study medically treated ACS patients, allowing for assessment of adverse events after stopping treatment with clopidogrel without the confounding factor of a coronary stent. We found a clustering of significantly higher risk of death or AMI in the initial 90-day period after stopping treatment with clopidogrel compared with later follow-up intervals. These findings were consistent among patient subgroups including those who took shorter vs longer durations of clopidogrel therapy, among patients with and without diabetes, as well as among PCI-treated ACS patients. In addition, the rate of adverse events in the initial 90-day interval after stopping treatment with clopidogrel was higher than the rate of adverse events following hospital discharge while patients were still taking clopidogrel. These findings support the hypothesis of a rebound hyperthrombotic period after stopping treatment with clopidogrel and highlight the need for additional studies to confirm these findings, to better understand the pathophysiology of this phenomenon, and to identify strategies to attenuate this effect.

There is *in vitro* and physiological evidence to support a short-term increase in platelet activation and associated thrombotic risk immediately after stop-

Table 3. Adjusted Incidence Rate Ratios From Multivariable Regressions for the Outcome of Death or Acute Myocardial Infarction Comparing the Periods of 0 to 90 Days vs 91 to 180 Days After Stopping Treatment With Clopidogrel

	No. of Patients	Adjusted Incidence Rate Ratio (95% CI) ^a
Medically treated	1568	1.98 (1.46-2.69)
Clopidogrel ≤ 90 d	312	2.13 (1.36-3.32)
Clopidogrel ≤ 180 d	530	2.20 (1.49-3.26)
Clopidogrel ≤ 270 d	751	2.00 (1.41-2.85)
Clopidogrel > 270 d	817	1.79 (0.96-3.34)
Diabetes	376	2.37 (1.34-4.19)
No diabetes	1192	1.75 (1.22-2.52)
Acute myocardial infarction outcome only	158	2.39 (1.50-3.82)
Treated with percutaneous coronary intervention	1568	1.82 (1.17-2.83)
Bare metal stent	984	2.14 (1.23-3.74)

Abbreviation: CI, confidence interval.

^aAdjusted for variables listed in Table 1.

ping antiplatelet therapy. Serebruany et al²⁶ noted increases in platelet activity as assessed by conventional aggregometry, Ultegra analyzer readings, expression of glycoprotein IIb/IIIa, P-selectin, and platelet endothelial cell adhesion molecules following withdrawal of nonsteroidal anti-inflammatory drugs and cyclooxygenase 2 inhibitors. In addition, 2 other studies found significant increases in prothrombotic and proinflammatory platelet activity following cessation of clopidogrel or prasugrel among patients receiving dual antiplatelet therapy.^{25,27} While additional studies are warranted to confirm the mechanism, our study provides epidemiological evidence consistent with current physiological data of rebound platelet activation following clopidogrel withdrawal.

The results of this study add to the literature supporting a rebound phenomenon following antiplatelet agent withdrawal. In particular, the results compliment prior aspirin studies in which cessation of use was associated with an increased risk of cerebrovascular and cardiac events compared with continuous aspirin use.⁷⁻⁹ However, aspirin is generally recommended for indefinite use in cardiac patients whereas clopidogrel is recommended for a specific course of therapy, enhancing concern regarding a potential rebound effect.

The results of this study also complement the Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent vs Abciximab and Bare-Metal Stent in Myocardial Infarction (STRATEGY) study, which reported a clustering of death or nonfatal MI in the first 30 days after stopping thienopyridine therapy among patients treated with a drug-eluting stent or bare metal stent for ST-elevation MI, consistent with our data.¹⁷ Limitations of the STRATEGY study included small sample size ($n=175$), relatively short duration of thienopyridine treatment (approximately 6 months), and patients received a coronary stent, suggesting a mechanism related to the stents as the likely etiology of adverse events. Because we observed an increase in the incidence of adverse events following clopidogrel cessation among medically treated patients with ACS without a stent, a mechanism unrelated to stenting is implicated. Taken together, the findings of our study coupled with prior studies on aspirin, the STRATEGY study, and physiological studies support the hypothesis of a rebound phenomenon after stopping treatment with clopidogrel.

There are other potential explanations for the increased number of early adverse events after stopping treatment with clopidogrel noted in our study. For some patients, the clinician may have stopped clopidogrel early due

to clinical deterioration, other reasons such as bleeding, or both. These patients still could have unstable plaques following recent ACS hospitalization and withdrawal of effective anti-platelet therapy could lead to increased thrombotic risk. However, this is unlikely the case for the majority of patients in our study because more than 80% of patients took clopidogrel for at least 3 months. Moreover, secondary analysis excluding patients with bleeding events after index ACS hospitalization did not alter the primary findings. Furthermore, the magnitude of risk in the initial 90 days following clopidogrel withdrawal was consistent whether patients took clopidogrel for 3, 6, 9, or more than 9 months, supporting that the association was independent of the clopidogrel treatment duration. Finally, patient nonadherence to therapy may potentially explain increased events following clopidogrel withdrawal. However, we adjusted for statin adherence in our multivariable analyses and the increased event rate in the interval of 0 to 90 days after stopping treatment with clopidogrel was consistent, further reinforcing the primary study findings.

Limitations

There are important considerations in interpreting the results of this study. Ascertainment of clopidogrel use was based on pharmacy dispensing data. However, we had detailed pharmacy use data for the majority of patients; and pharmacy dispensing data are a validated measure of medication adherence and is strongly correlated with a broad range of patient outcomes.^{28,29} Second, our cohort was predominantly male veterans and our findings should be replicated in other cohorts. However, this was a real-world cohort for a large integrated health care delivery system. Third, we did not have data on cause-specific mortality or recurrent MI events outside the VA. However, we had complete ascertainment of vital status, and the association between increased MI events and the interval of 0 to 90 days after stopping

treatment with clopidogrel was consistent with our mortality findings, supporting a cardiac-specific cause for the events. Moreover, we would expect that recurrent hospitalizations for MI outside the VA would tend to bias the results toward the null.

Fourth, we do not have information on reasons for stopping treatment with clopidogrel, but potential reasons include the end of the prescribed course—the expected reason for most of the patients—or the occurrence of complications from the medication, such as bleeding. When we excluded patients with bleeding in the secondary analyses, the results did not change. Future prospective studies should assess the reasons for clopidogrel cessation as well as determine the mechanisms of early adverse events. Future studies also should assess event rates after stopping treatment with clopidogrel among patients taking longer durations of therapy (eg, >12 months), and among patients with drug-eluting stents given the small proportion of patients with drug-eluting stents in our cohort.

Fifth, we excluded the small proportion of patients who had an event while receiving treatment with clopidogrel because these events were unrelated to a potential rebound effect. This exclusion may have resulted in a lower risk study population, but we did not have adequate numbers of these patients or follow-up (because such patients often start a new course of clopidogrel) to evaluate them as a subgroup. Finally, as with any retrospective cohort study design, we cannot conclude causality and suggest that additional studies are needed to confirm the association found in our study of an increase in adverse events after stopping treatment with clopidogrel.

Clinical Implications

There are several potential implications of this study. Even though the absolute event rates were low, the relative increase in adverse events in the early period after stopping treatment with clopidogrel was nearly 2-fold

higher than later periods. In addition, the absolute number of adverse events attributable to this event clustering is significant when extrapolated to a population level, considering the number of patients admitted with ACS and discharged with posthospital treatment with clopidogrel therapy both in the United States and worldwide.³⁰

These findings, however, do not necessarily offset the benefits of clopidogrel therapy. Rather, additional studies are needed to confirm the presence of the event clustering after cessation of clopidogrel and to better understand the pathophysiology of this phenomenon. If these findings are subsequently confirmed, guideline recommendations may need to be reconsidered in terms of duration of clopidogrel therapy and perhaps the means of drug cessation. One consideration would be to continue clopidogrel for an extended period or indefinitely, like aspirin, to avoid the potential rebound effect. However, such a recommendation would need to consider the increased risk of bleeding with prolonged dual antiplatelet therapy as well as the cost-effectiveness of such a strategy.^{31,32} Alternatively, various strategies could be evaluated to attenuate the rebound effect, such as tapering of clopidogrel therapy, bridging clopidogrel cessation with higher dose aspirin for a given period, or using alternative antiplatelet regimens such as ticlopidine.³³ All of these potential approaches would require formal study before any specific recommendation could be made.

In conclusion, we observed a higher incidence of death and AMI during the initial 90-day period after stopping treatment with clopidogrel in a national cohort of medically treated and PCI-treated patients with ACS. The findings of this study, coupled with prior physiological studies, support the hypothesis of a possible clopidogrel rebound effect from rebound platelet activation following clopidogrel withdrawal, although we did not have information on cardiovascular mortality or reasons for stopping treatment with clopidogrel. These results highlight the need for additional studies to confirm the cluster-

ing of events after stopping clopidogrel, to confirm the mechanism of this phenomenon, and if confirmed, to identify strategies to attenuate this effect.

Author Contributions: Drs Ho and Rumsfeld had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ho, Peterson, Wang, Fihn, Larsen, Jesse, Rumsfeld.

Acquisition of data: Wang, Fihn.

Analysis and interpretation of data: Ho, Peterson, Wang, Magid, Rumsfeld.

Drafting of the manuscript: Ho, Rumsfeld.

Critical revision of the manuscript for important in-

tellectual content: Ho, Peterson, Wang, Magid, Fihn, Larsen, Jesse, Rumsfeld.

Statistical analysis: Wang.

Obtained funding: Fihn.

Administrative, technical, or material support: Fihn, Jesse.

Study supervision: Fihn, Larsen, Jesse, Rumsfeld.

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patients had intermediate to high levels of statin adherence in our study. Also, we included a sensitivity analysis excluding patients with any bleeding complications (for whom aspirin as well as clopidogrel would likely have been discontinued) and found results similar to the main analysis. Finally, for the small group of patients filling aspirin prescriptions through the pharmacy at the VA Medical Center, we assessed the risk of events among those who continued aspirin after stopping clopidogrel ($n=532$). The risk of early adverse outcomes was similar to the overall cohort (incidence rate ratio, 1.98; 95% CI, 1.25-3.14), further supporting the main results.

Nonetheless, we view our findings as the first in a line of research, and future studies will need to specifically evaluate concomitant aspirin use. Such studies will likely need to be prospective because most pharmacy data do not adequately capture aspirin use given its wide availability over the counter.

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Looking Back on *The House of God*

To the Editor: I enjoyed the Literatim essay on *The House of God* by Dr Markel.¹ As a senior medical student in 1979, I also eagerly read this book. Its seemingly exaggerated perspective was disturbing, engaging, and entertaining.

As a first-year internal medicine resident at a large county medical center in 1980, I tried to reread *The House of God* but found it too painful. What I had perceived as exaggeration as a medical student now cut too close to the bone. The physical and emotional exhaustion I felt facing more than 100 hours per week on the wards, trying to manage too many patients with complex serious illnesses, experiencing deaths and losses without adequate time to grieve, transformed me into Roy Basch. Even now, it is hard to relive those experiences.

Privately, I too used derogatory terms to describe patients, and I believed on one level that "they could always hurt you more." But I also had the insight that this venting among peers was a reflexive and useful defense mechanism.

Humor has always been a key strategy for maintaining mental health in pathological situations. *The House of God* was written during a preresidency training reform era when sleep was a luxury. One vivid memory of internship is sitting with a fellow intern in the early morning hours of a bad call night, looking out the hospital windows to the parking

lot below, and hearing him say, "Thank God there's bars on these windows."

There is a vast difference between venting discomfort among colleagues and providing suboptimal care or potential harm to those we "took an oath to heal." I believe I became more humane from the experience. This was an era before advance directives, and during one particularly painful rotation I had the misfortune of working with an attending whose sole goal seemed to be extending life at all costs. There was no such thing as a "no code," and patients who were terminally ill and suffering were routinely resuscitated if they experienced a cardiopulmonary arrest. After my first week on the service, my goal was to meet with family members to help them understand that they did have a say in the care their loved one received.

I appreciate Markel's concerns but apparently do not feel as guilty as he.

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1. Markel H. The House of God: 30 years later. *JAMA*. 2008;299(2):227-229.

In Reply: I appreciate Dr Katz reflecting on his own responses to this book.

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CORRECTION

Incorrect Data: In the Original Contribution entitled "Incidence of Death and Acute Myocardial Infarction Associated With Stopping Clopidogrel After Acute Coronary Syndrome" published in the February 6, 2008, issue of *JAMA* (2008;299[5]:532-539), some numbers were incorrectly reported. On page 532, in the fourth line of Results section in the abstract, the mean (SD) duration of clopidogrel treatment among medically treated patients should be "278 (169) days." Also in the Results section in the abstract, line 12, the mean (SD) duration of clopidogrel treatment among patients treated with percutaneous coronary intervention should be "302 (151) days." On page 535, column 1, second full paragraph under the heading "Medically Treated Patients With ACS," line 3, the mean (SD) age should be "68.5 (11.7) years." Also in that paragraph, line 10, the mean (SD) duration of clopidogrel therapy following hospital discharge among medically treated patients should be "278 (169) days" and the median should be "281 days." On page 536, column 1, line 12, the mean (SD) duration of clopidogrel therapy following hospital discharge should be "302 (151) days" and the median should be "310 days." On page 537, Table 3, in the eighth row in the table, "Acute myocardial infarction outcome only," the value in the second column under "No. of Patients" should be changed from "158" to "1568." The next row in the table, "Treated with percutaneous coronary intervention," the value in the second column under "No. of Patients" should be changed from "1568" to "1569."