Increased Risk of Bleeding in Patients on Clopidogrel Therapy After Drug-Eluting Stents Implantation
Insights From the HMO Research Network-Stent Registry (HMORN-Stent)
association between clopidogrel use and risk of major bleeding in 6-month intervals after DES implantation. In addition, we evaluated the association between clopidogrel use and risk of MI or death in 6-month intervals after DES implantation.

Methods
The HMO Research Network-Stent Registry is a registry of all patients who underwent percutaneous coronary intervention (PCI) with a DES between January 2004 and December 2007 at 3 large integrated healthcare delivery systems, Kaiser Permanente of Northern California, Kaiser Permanente of Colorado, and Health Partners in Minneapolis. Each of these sites participates in the National Cardiovascular Data CathPCI registry, which contains detailed information from the PCI inpatient admission on patient demographics, cardiac risk factors, cardiac history, comorbid conditions, admission symptoms/presentation, noninvasive test results, diagnostic catheterization indications and findings, PCI procedural details, complications, discharge status, and admission, and discharge medications. The complete definitions of all variables were prospectively defined by a committee of the American College of Cardiology and are available at the American College of Cardiology Web site (http://www.acc.org/ncdr/cathlab.htm). Each health plan maintains detailed follow-up data including the medication use through pharmacy dispensing data and hospitalizations and vital status. Institutional review board approval was obtained at each of the 3 sites.

Study Population
All patients in the HMO Research Network-Stent Registry who were discharged alive after receiving a DES in ≥1 coronary arteries were enrolled in the National Cardiovascular Data CathPCI registry and filled a clopidogrel prescription at least once were considered for the study. Of these patients, 202 (2.6%) had a clopidogrel prescription before the procedure and were excluded to avoid competing indications for clopidogrel use. Our final cohort included 7689 patients.

Data Collection
Clopidogrel Use
All patients included in this study had a health plan pharmacy benefit, which allowed them to fill clopidogrel prescriptions at a modest cost (~ $20 to 25 for a 60-day supply). Patients with a pharmacy benefit have been shown to fill nearly all prescriptions (>98%) at their health plan pharmacies. Each site has detailed pharmacy data, including the dispense date and the number of days supplied for each dispensed medication. Clopidogrel use started on the day the prescription was filled and was considered available and taken based on the dispense date and number of days supplied (Figure 1). If there was a prescription refill gap of ≤7 days, patients were considered to have continuous clopidogrel therapy. The last day of clopidogrel use was based on the date of the last prescription refill plus the number of days supplied for that refill (see Figure 1 for patient scenarios and calculated clopidogrel exposure).

Outcomes
The primary outcomes were hospitalization for major bleeding, MI, or death in 3 discrete time intervals (0 to 6 months, 7 to 12 months, and 13 to 18 months) after DES implantation. The time intervals were chosen a priori to reflect the historical guideline recommendations of clopidogrel use after DES implantation. The 0- to 6-month interval includes the manufacturer recommended duration of clopidogrel therapy for the first-generation DES. The 7- to 12-month interval represents the recommendation of clopidogrel therapy for 1 year as
outlined by the American College of Cardiology/American Heart Association PCI guidelines released in December 2005, and the 13- to 18-month interval reflects the period of prolonged clopidogrel therapy proposed to decrease the risk of very late stent thrombosis.10

Major bleeding was defined by a primary hospital discharge diagnosis based on International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9) for intracerebral hemorrhage (ICD-9 codes 430 to 432), gastrointestinal tract hemorrhage (455 to 578), hemarthrosis (719.2 to 719.2), hemopericardium (423), hematuria (599.7), vaginal bleeding (623.8 to 626.2), hemoptysis (786.3), epistaxis (784.7) or hemorrhage not otherwise specified (459) or a secondary diagnosis for bleeding with associated blood transfusion during hospitalization. Mortality was derived from multiple health plan data sources and state death certificates. Vital status information was available after hospital discharge on all patients through December 31, 2007. Hospitalizations for MI were based on inpatient primary ICD-9 diagnosis codes 410.XX for events occurring ≥2 weeks after the index hospitalization because troponin levels may remain increased for a period of time after the index MI event. Hospitalizations outside the HMO were also captured through administrative claims data.

Statistical Analysis
Baseline characteristics were summarized for patient groups as numbers (percentages) for categorical variables and as means (±SD) and median (interquartile range) for continuous variables.

Propensity Score Weighting
Because clopidogrel use in our cohort was not random, we used inverse propensity score weighted estimators to obtain relative risks (RRs) of bleeding, MI, and death, adjusting for known confounders, to control for selection bias.13-15 Because a patient can discontinue and then resume the use of clopidogrel during our study period, we measured clopidogrel use as time-varying variable in creating propensity scores (Figure 1). We calculated the daily propensity to receive clopidogrel therapy using ordinal logistic regressions adjusting for a set of known covariates including indicators for prior bleeding and MI, age, prior MI, gender, body mass index, previous valve surgery, diabetes, renal insufficiency, cerebrovascular disease, peripheral vascular disease, chronic lung disease, hypertension, current tobacco use, hypercholesterolemia, previous revascularization, history of congestive heart failure, cardiogenic shock, use of glycoprotein IIb/IIIa inhibitor, left ventricular function assessment, length of stay, discharge status, periprocedural MI, multivessel intervention, postprocedure thrombolysis in myocardial infarction (TIMI) flow and off-label status. Stabilized weights were then calculated and used in calculation of adjusted RRs.16,17 The stabilized weight is superior to the inverse of propensity weights were then calculated and used in calculation of adjusted RRs.16,17

Analysis of the Outcomes
Separate Poisson regression models using stabilized weights were used to estimate the RRs of bleeding, MI, and death in patients on clopidogrel compared to “off” clopidogrel.

Sensitivity Analysis
Although propensity score-based methods can adjust for confounding by indication, they are unable to account for unmeasured confounders. Thus, significant associations may only represent residual confounding rather than a true relationship. To evaluate this quantitatively, we performed a sensitivity analysis to estimate what magnitude of association between an unmeasured confounder and our exposure variable would be needed to alter our conclusions.18 These sensitivity analyses estimated the magnitude of odds ratios between an unmeasured confounder and exposure that would invalidate our results. We varied the prevalence of a potential confounder between 0.2 and 0.4. We assumed a strong association of the confounder to the outcome (RR=13) because weaker associations would require stronger associations between the unmeasured confounder and the exposure so that the reported magnitudes are conservative. In a randomized trial, the randomization step usually results in no association between unmeasured confounders and the exposure of interest (ie, odds ratio=1).

Results
Baseline characteristics of the study population are presented in Table. The average age was 64.1 years (SD, ±11.5 years). Patients in the cohort had multiple comorbidities including diabetes (31%), prior MI (26%), hypertension (77%), and dyslipidemia (81%). Almost one-fifth of the patients were active smokers and 11% had peripheral vascular disease. The mean number of clopidogrel-covered days was 257 days (SD, ±159 days) with a median of 215 days (25th to 75th percentile) (104.0 to 391.0). A total of 3603 patients (49.1%) received clopidogrel for >6 months. The mean duration of each refill was 72.4 days (SD, ±27.5 days) with 86% of patients filling their initial prescription on the day of discharge and 94% within 7 days.

Unadjusted Clinical Outcomes
During a mean follow-up ±SD of 418±168 days, 271 (3.6%) patients had a major bleeding event, 279 (3.7%) had a MI, and

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ACS indicates acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction.

Data are presented as n (%) or mean±SD.
217 (2.9%) died. Incidence rates for events were calculated for bleeding complication, MI, and death. Overall, the rate of events per 100 000 person days was 10.2 major bleeds, 10.2 MIs, and 7.3 deaths. During the 18-month follow-up period, 497 patients (6.5%) of the initial cohort were censored because of loss to follow-up, primarily from disenrollment from the health plan.

### Propensity Score–Adjusted Clinical Outcomes

After multivariable adjustment, there was a significant association between patients on clopidogrel therapy and increased major bleeding in all time interval (0 to 6 months: RR = 2.70, 95% CI = 1.41 to 5.19; 7 to 12 months: RR = 1.71, 95% CI = 1.05 to 2.79; 13 to 18 months: RR = 2.34, 95% CI = 1.26 to 4.34) compared with patients off clopidogrel (Figure 2). Major bleeding events per 100 000 days were also higher in the on versus off clopidogrel groups during the 0- to 6-month (16.5 versus 6.1 bleeds, \( P = 0.003 \)), 7- to 12-month (10.1 versus 5.9 bleeds, \( P = 0.031 \)), and 13- to 18-month (9.2 versus 3.9 bleeds, \( P = 0.007 \)) intervals (Figure 3).

In addition, there was a significant association between patients on clopidogrel and decreased risk of MI in the 0- to 6-month (RR = 0.52, 95% CI = 0.36 to 0.77), 7- to 12-month (RR = 0.46, 95% CI = 0.30 to 0.70), and 13- to 18-month (RR = 0.53, 95% CI = 0.29 to 0.99) intervals. Major MI events per 100 000 days were also lower in the on versus off clopidogrel groups during the 0- to 6-month (11.6 versus 22.1 MIs, \( P < 0.001 \)), 7- to 12-month (6.3 versus 15.7 bleeds, \( P < 0.001 \)), and 13- to 18-month (4.7 versus 10.8 bleeds, \( P = 0.0018 \)) intervals (Figure 4).

A significant association between patients on clopidogrel and decreased death was observed in the 7- to 12-month interval (RR = 0.50, 95% CI = 0.30 to 0.83) but was not seen in the 0- to 6-month (RR = 0.93, 95% CI = 0.53 to 1.65) and 13- to 18-month intervals (RR = 0.54, 95% CI = 0.25 to 1.17). Death events per 100 000 days were similar in the on versus off clopidogrel groups during the 0- to 6-month (8.4 versus 9.0 deaths, \( P = 0.814 \)) and 13- to 18-month (3.5 versus 6.5, \( P = 0.117 \)) intervals and lower in the 7- to 12-month (4.9 versus 9.8) interval (Figure 5).

### Sensitivity Analysis

Sensitivity analysis on residual confounding indicated that an unmeasured confounder would need to be associated with a 3.2- to 6.8-fold increase in the odds of being on clopidogrel therapy with a near-perfect predictor of MI and bleeding to eliminate the significant associations of our findings.

### Discussion

In our observational study comprised 3 large integrated healthcare delivery systems, clopidogrel therapy was associated with a significantly increased risk of major bleeding after PCI with DES over a broad range of time intervals extending through 18 months of follow-up. In addition, extended clopidogrel therapy was associated with a lower risk of MI across all time intervals and mortality in the 7- to 12-month interval. These observations highlight the risks and benefits associated with clopidogrel use in routine clinical practice.

The risk of bleeding associated with clopidogrel use in routine clinical practice is underrecognized. In the 0- to 6-month interval, patients were at significantly greater risk of...
bleeding if they were on clopidogrel therapy. The event rates were highest during this interval, which is consistent with the recent high-risk Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study that showed an increase in the rate of moderate bleeding in the first 2 months after initiation of clopidogrel and aspirin therapy (2.0% versus 1.3%, \( P=0.004 \)). However, unlike the findings of the CHARISMA study, we noted persistently increased major bleeding events in patients treated with clopidogrel in the 7- to 12-month and 13- to 18-month intervals. These findings suggest that the risk of bleeding associated with clopidogrel use persists while patients are taking the therapy and persists for at least 18 months of follow-up. These findings go against the suggestion from the CHARISMA study that patients who bleed, bleed early and those who do not are good candidates for prolonged dual antiplatelet therapy.

Observational studies have shown a potential benefit of >6, 9, and 12 months of clopidogrel in patients with DES.6-8 Eisenstein et al6 performed a landmark analysis of patients with bare metal stent and DES showing extended use of clopidogrel, up to 12 months in patients with DES may be associated with a reduced risk of death and death and MI. However, bleeding was not assessed in their or any of the previously published observational data.6,7 Furthermore, determination of clopidogrel use in their analysis was based on patient report at 2 discrete time points, 6 and 12 months, which is subject to patient recall bias and does not consider interim changes in clopidogrel exposure. Finally, their analysis did not specifically adjust for confounding by clopidogrel treatment duration. Physicians may prescribe different durations of clopidogrel therapy based on angiographic or patient characteristics that may impact follow-up outcomes and thus result in selection bias.

Our study adds significantly to the existing literature. First, to determine the exposure to clopidogrel, we used pharmacy dispensing data that have been shown to be more accurate than patient self-report of medication use, and medication use based on pharmacy data has been associated with a broad range of patient outcomes.19,20 Second, we used propensity adjustment to address potential bias in the selection of patients to different durations of clopidogrel therapy. This propensity adjustment maximizes the similarity of patients compared at different time points. Third, we structured our analysis around clinically relevant intervals. The 0- to 6-month interval represents the original recommendations from the clinical trials that secured DES approval. The 7- to 12-month interval represents the update to the PCI guidelines recommending 12 months of clopidogrel therapy to all patients receiving PCI who are not at high risk of bleeding, and the 13- to 18-month interval represents the period of extended clopidogrel therapy thought to mitigate the increased risk of late stent thrombosis (>1 year).

Our findings support an association between the early discontinuation of clopidogrel and increased MI in the 0- to 6-month and 7- to 12-month interval and extended clopidogrel use and its association with decreased risk of MI post-DES placement. However, this association must be considered in the context of an association between clopidogrel use and increased major bleeding across all intervals. These competing events highlight the complex decision making involved in managing patients who require a DES. As with other anticoagulation medications in which there is a fine line between potential therapeutic benefit and harm, further research is necessary to determine which patient subgroups are most likely to benefit from extended clopidogrel therapy and which are most likely to be harmed. Risk models that provide guidance to clinicians on which patients are most likely to receive net benefit from extended clopidogrel (decreased risk of MI or death without an increased risk of bleeding) therapy are needed and may inform clinical practice. Furthermore, the decision making at the point of diagnostic catheterization should be highly scrutinized to determine the necessity of stent placement over medical therapy and DES versus bare metal stents.

**Limitations**

There are several limitations of our study that should be acknowledged. First, the total number of clopidogrel covered days was calculated from the day of discharge to the last clopidogrel refill. All gaps in therapy were assumed to be at the end of the calculated interval and do not take into considerations gaps in the beginning or middle of the prescription period. Furthermore, we did not consider gaps in therapy as a function of patient compliance or adherence. However, the medication use as assessed by pharmacy dispense data has been strongly correlated with medication event monitoring systems and adverse clinical outcomes, which is considered a robust and highly accurate method of medication use.21 Second, because most patients received an initial 60-day supply of clopidogrel, most early events and nonevents would be classified as occurring on clopidogrel thereby underestimating the benefit or harm of clopidogrel therapy in the 0- to 6-month interval. Third, propensity adjustment only balances measured covariates in the treatment groups. Therefore, unmeasured confounders with an association with the outcomes and changes in baseline comorbidities over time could change the results. However, our sensitivity analysis on residual confounding indicated that the unmeasured confounder would have to be associated with a 3.2- to 6.8-fold increase in the odds of being on clopidogrel therapy and a strong relationship with MI and bleeding to eliminate the significance of our findings. It is unlikely that an unmeasured confounder of that magnitude exists and strengthens the validity of our findings. Fourth, we did not have longitudinal data on aspirin use after hospital discharge because most patients receive their aspirin over the counter. Therefore, the use of the term dual antiplatelet therapy presupposes compliance with aspirin.

**Conclusions**

In conclusion, we found that among patients receiving DES, clopidogrel use was associated with an increased risk of major bleeding over a broad range of time intervals out to 18 months. In contrast, clopidogrel use was associated with decreased risk of MI in all time intervals and death in the 7- to 12-month interval. These findings highlight a competing safety end point that must be considered when establishing the optimal clopidogrel duration in patients who receive DES. Randomized clinical trials are urgently needed to definitively establish optimal clopidogrel duration in the face of potential risks (eg, bleeding) and benefits (eg, death and MI).
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References

CLINICAL PERSPECTIVE
Recent studies have suggested that prolonged dual antiplatelet therapy (>6 months) after drug eluting stent placement may be associated with reduced risk of myocardial infarction and death. As a result, many clinicians have extended treatment with clopidogrel to exceed 12 months and even 18 months. However, clopidogrel use has also been associated with treatment related risks such as bleeding complications. Therefore, to consider the appropriate length of clopidogrel therapy, the risks and benefits must be weighed within a patient population. According to the HMO Research Network-Stent Registry, we assessed the association between clopidogrel use and risks of major bleeding to the benefit of decreased myocardial infarction or death in 6-month intervals after discharge. Clopidogrel use was determined by pharmacy dispensing data. After adjustment, patients on clopidogrel therapy was associated with increased major bleeding in all time intervals (0 to 6 months, 7 to 12 months, and 13 to 18 months) compared with patients off clopidogrel. In contrast, clopidogrel use was also associated with a decreased risk of myocardial infarction for all time intervals and decreased death in the 7- to 12-month interval. These results illustrate the risks and benefits associated with clopidogrel use in routine clinical practice and highlight the importance of identifying which patient subgroups are most likely to benefit from extended clopidogrel therapy and which are most likely to be harmed.
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