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Hospital Variation in Premature Clopidogrel Discontinuation After Drug-Eluting Stent Placement in the Veterans Affairs (VA) Healthcare System

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Background—Premature clopidogrel discontinuation after drug-eluting stent placement is associated with adverse outcomes. Little is known about patient and hospital factors associated with premature discontinuation or whether less variation in premature discontinuation exists in integrated health care systems such as the Veterans Affairs (VA).

Methods and Results—We evaluated the frequency of premature clopidogrel discontinuation, defined as a gap between clopidogrel refills of ≥90 days during the first 6 months of treatment, among 12,707 patients who received drug-eluting stents in VA hospitals between 2008 and 2010. We evaluated the association between premature discontinuation and all-cause mortality and/or acute myocardial infarction, variation in the proportion of premature discontinuation among hospitals, the patient and hospital characteristics associated with premature discontinuation, and the extent to which unexplained hospital characteristics contribute to premature discontinuation. Of the patients, 963 (7.6%) discontinued clopidogrel prematurely. Premature discontinuation was associated with acute myocardial infarction and all-cause mortality (hazard ratio 1.65, 95% CI 1.37–1.99, P<0.001). The proportion of patients with premature discontinuation varied across hospitals from 0% to 16.5% (P<0.001). We found a median of 24% greater odds of patients with identical covariates with premature discontinuation at one randomly selected hospital compared with another (median odds ratio 1.24, 95% CI 1.17–1.44). Patient factors associated with premature discontinuation included lack of cardiology follow-up within 30 days of discharge and smaller initial clopidogrel fill.

Conclusion—One in 13 patients prematurely discontinued clopidogrel, and variation in discontinuation across hospitals was observed. Patient factors were associated with premature discontinuation that may represent targets for quality improvement. (J Am Heart Assoc. 2016;5:e001376 doi: 10.1161/JAHA.114.001376)

Key Words: adherence • clopidogrel • drug-eluting stents

Clopidogrel is recommended as adjuvant medical therapy for 1 year after drug-eluting stent (DES) placement based on clinical practice guidelines. Prior studies have reported that ≈9% to 14% of patients discontinue clopidogrel prematurely after DES placement, and premature discontinuation has been associated with stent thrombosis, cardiac rehospitalization, cardiovascular death, and all-cause mortality. However, the prevalence of premature clopidogrel discontinuation has not been studied within an integrated health care delivery system in which cost barriers to medications are less of an issue. Moreover, little is known about patient and hospital factors associated with premature clopidogrel discontinuation. Regional variation is common in terms of health care use and outcomes. Variability in prescription drug spending, cardiac procedures such as implantable cardioverter-defibrillator implantation, and provider adherence to established practice guidelines have been demonstrated. A prior study from our group showed significant national hospital-level variation ranging from 22% to 97% in clopidogrel use for medically managed non–ST-segment elevation myocardial infarction (NSTEMI) patients at hospital discharge. It is unknown whether similar variations occur in premature clopidogrel discontinuation in an
integrated health care system such as the Veterans Affairs (VA) where all patients have prescription drug coverage and where copayments are low.

Accordingly, we evaluated the frequency of premature clopidogrel discontinuation among all veterans receiving percutaneous coronary intervention (PCI) with DES in VA cardiac catheterization laboratories between 2008 and 2010. Next, we assessed the association between premature discontinuation and all-cause mortality and/or MI. Finally, we evaluated the degree of variation in premature clopidogrel discontinuation across VA hospitals and assessed the patient and hospital characteristics associated with premature discontinuation.

Methods

The VA Clinical Assessment, Reporting, and Tracking system for Catheterization Laboratories (CART-CL) is a customized software application that collects patient and procedural data at the point-of-care for all cardiac catheterizations and PCIs performed in the 76 VA cardiac catheterization laboratories nationwide. It is designed to simultaneously allow for data entry by clinicians during routine clinical workflow, integrate into the VA’s electronic medical record system, and collect individual and aggregate data to support quality management and improvement initiatives for cardiovascular procedures. CART-CL was initially implemented in 2005 and was in active use in all VA catheterization laboratories by 2009. The methods of its implementation have been previously described.

The analytic cohort consisted of all patients who received a DES and were prescribed clopidogrel at hospital discharge. We restricted our analysis to patients who received DES because practice guidelines recommend 1 year of clopidogrel after DES placement. For this analysis, we selected all patients who underwent PCI with DES placement between 2008 and 2010 from the 56 VA catheterization laboratories that performed ≥20 annual PCIs with DES during this time period. Patient characteristics were obtained via CART-CL and VA national databases. Pharmacy data were obtained through VA national databases for medications dispensed. To be included in the cohort, patients had to fill at least 1 prescription for clopidogrel within 30 days of hospital discharge after PCI, to exclude patients who may have filled clopidogrel at pharmacies outside the VA system.

Exposure Variable

Premature discontinuation of clopidogrel was defined as a gap between clopidogrel prescription refills of ≥90 days during the first 6 months (180 days) of treatment. We chose this definition to exclude patients who may have small gaps in refills of clopidogrel and only temporarily discontinued clopidogrel as opposed to patients who permanently stopped the medication prematurely. Of the patients who discontinued prematurely, only 0.9% reinitiated clopidogrel within the year after their initial prescription.

Outcome Variable

The primary end point was a combined end point of all-cause mortality or rehospitalization for acute MI (AMI). Follow-up for adverse outcomes began after determination of premature clopidogrel discontinuation status (ie, 6 months after hospital discharge) and continued for 1 year. All-cause mortality was assessed via the VA vital status file. The file has 98.3% sensitivity and 97.6% exact agreement with the National Death Index. AMI was assessed via International Classification of Diseases, Ninth Revision (ICD-9) codes (410.xx) from VA inpatient treatment files. Additionally, if patients were hospitalized at non-VA hospitals for AMI in which the VA paid for the care, we were able to include these events as outcomes through the use of fee basis files.

Statistical Methods

Baseline characteristics including variables from the previously validated National Cardiovascular Data Registry (NCDR) risk model for in-hospital mortality after PCI were compared between patients with and without premature clopidogrel discontinuation by using χ² tests for dichotomous variables and Ix tests for continuous variables. These variables included in the NCDR risk score were used for risk adjustment. Differences in all-cause mortality and rehospitalization for AMI among those who did and did not discontinue clopidogrel prematurely were compared by using Kaplan–Meier survival curves and log rank tests. A Cox proportional hazards model with a random effect for hospital clustering was constructed to obtain adjusted risk estimates for all-cause mortality and/or MI for premature clopidogrel discontinuation. The NCDR risk score was entered into the linear predictor of our model in the form of a spline with 3 degrees of freedom, to allow for possible differences in calibration between our population and the NCDR population. This assumes the NCDR score is associated with the hazard of outcome while allowing for differences in the exact form of the association and outcome definition between NCDR and CART, and relaxes the assumption of the Cox model so that a 1-unit increase in the NCDR score corresponds to the same increase in the hazard of outcome (on the log scale) across all values of NCDR score. Variables included in the NCDR risk point score include the presence of cardiogenic shock, peripheral vascular disease, chronic lung disease, glomerular filtration rate, New York Heart Association functional class, and PCI status (STEMI or NSTEMI).

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ORIGINAL RESEARCH
Next, differences in rates of premature clopidogrel discontinuation across VA hospitals were assessed and compared by using proportions and \( \chi^2 \) tests. We then assessed whether patient-level characteristics including baseline comorbidities, cardiology clinic follow-up within 30 days of hospital discharge, and the prescription size (based on the number of days supplied) of the initial clopidogrel fill were associated with premature clopidogrel discontinuation by using a logistic regression risk model with a random effect for hospital. The number of days supplied in initial clopidogrel fill was categorized as initial clopidogrel prescription for <30, 30, 60, or 90 days. We also evaluated whether hospital-level characteristics including number of beds, PCI volume, teaching versus nonteaching status, and presence of on-site versus off-site cardiothoracic surgery program were associated with premature clopidogrel discontinuation among hospitals with use of a similar model.

Finally, we calculated the median odds ratio (MOR) for discontinuation among hospitals. The MOR is a measure of the heterogeneity across hospitals, with a value always \( \geq 1 \). Conceptually, if 2 patients with identical covariate values were selected from any 2 randomly drawn hospitals and an odds ratio (OR) was obtained for the likelihood of discontinuation between the patient from the hospital with a higher propensity for discontinuation to the patient from the hospital with the lower propensity for discontinuation, then the MOR is the median of all such theoretically derived ORs. Because it is on the same scale as the ORs obtained for patient-level covariates, it can be used to compare the effect of hospital heterogeneity on discontinuation to that of the patient-level factors. An MOR of 1 would indicate no difference in the likelihood of discontinuation between 2 patients with identical covariates at different hospitals. Higher MOR values indicate a higher likelihood of discontinuation at one hospital compared with another.

SAS 9.2 (SAS Institute Inc) and R version 2.11.1 (R Foundation for Statistical Computing) were used to perform statistical analyses. This study was approved by the Colorado Multiple Institutional Review Board, and informed consent was waived.

**Results**

Of the 12,707 patients in our cohort who underwent PCI, 963 (7.6%) patients discontinued clopidogrel prematurely by 6 months. The majority of baseline characteristics of patients who did and did not discontinue clopidogrel prematurely at 6 months were similar (Table 1) aside from sex and prior MI. Patients who discontinued clopidogrel prematurely had lower event-free survival compared with those patients who continued clopidogrel at 6 months (84.5% versus 90.6%, log rank test \( P<0.001 \), Figure 1). In multivariable analysis, premature discontinuation remained associated with increased risk of all-cause mortality or AMI (hazard ratio 1.69, 95% CI 1.40–2.04, \( P<0.001 \)). Of the 963 patients who discontinued prematurely, 7 underwent coronary artery bypass graft surgery, and 37 patients had bleeding events. When these individuals were censored at the time of their bypass or bleeding event, the findings were consistent with the primary analysis (hazard ratio 1.65, 95% CI 1.36–1.99).

Of the 56 VA catheterization laboratories that performed >20 annual PCIs with DES, the mean number of beds was 174 (IQR 25–75% 119–215). A total of 48 (86%) of the 56 hospitals were teaching facilities and 40 (71%) had on-site cardiothoracic surgery. The proportion of patients who prematurely discontinued clopidogrel at 6 months varied significantly among PCI hospitals, ranging from 0% to 16.5% (\( P<0.001 \), Figure 2). The mean proportion of patients who discontinued prematurely across hospitals was 7.6%, and the median was 7.2% (IQR 5.9–9.1%).

The MOR for discontinuation was 1.24 (95% CI 1.17–1.44), indicating a substantial hospital contribution to the probability of premature discontinuation after accounting for patient factors. This suggests that there was a median of 24% greater odds of patients with identical covariates with premature discontinuation at one randomly selected hospital compared with another. However, the hospital-level characteristics that we measured, such as number of beds, PCI volume, teaching versus nonteaching status, and presence of on-site versus off-site CT surgery program, were not associated with premature clopidogrel discontinuation (Table 2). Patient-level factors associated with premature clopidogrel discontinuation included lack of cardiology clinic follow-up within 30 days of hospital discharge (OR 1.39, 95% CI 1.20–1.61) and smaller index clopidogrel prescription size (OR 1.004, 95% CI 1.001–1.007). Additionally, 432 (44.9%) of 963 patients who were not persistent had primary care physician follow-up within 30 days of discharge compared with 6179 (52.6%) of 11,744 patients who were persistent (\( P=0.01 \)). In addition, 56 (5.8%) of 963 patients who were not persistent had surgery within 180 days of discharge compared with 479 (4.1%) of 11,744 patients who were persistent (\( P=0.010 \)).

**Discussion**

Approximately 7% of DES patients prematurely discontinued clopidogrel at 6 months, and premature discontinuation was associated with increased all-cause mortality and AMI. Additionally, significant hospital variation in premature discontinuation was seen across the VA system. Patients who did not have cardiology follow-up within 30 days of hospital discharge and those who received smaller clopidogrel
Prescription sizes were more likely to prematurely discontinue clopidogrel. The likelihood of premature discontinuation was substantially different among hospitals independent of patient-level covariates and the hospital characteristics we evaluated. Future qualitative studies designed to elucidate the potential hospital-level variables associated with premature discontinuation are needed.

Rates of premature clopidogrel discontinuation in this VA cohort are lower than those observed in previous studies. In an Italian cohort from 2 hospitals in northern Italy, 8.8% of

| Table 1. Baseline Patient Characteristics | No Premature Discontinuation | Premature Discontinuation |
|------------------------------------------|-----------------------------|---------------------------|
|                                          | n=11 744                    | n=963                     |
|                                          | No. or Mean | Percent | No. or Mean | Percent | P Value |
| Age, y (mean)                            | 64.3 | 63.9 | 0.16 |
| Male sex                                 | 11 572 | 98.5 | 943 | 97.9 | 0.13 |
| Tobacco use                              | 6889 | 58.7 | 579 | 60.1 | 0.39 |
| Hypertension                             | 10 821 | 92.1 | 878 | 91.2 | 0.29 |
| Diabetes                                 | 5423 | 46.1 | 453 | 47.0 | 0.61 |
| Coronary heart disease                   | 1913 | 16.3 | 179 | 18.6 | 0.07 |
| Prior myocardial infarction              | 3488 | 29.7 | 353 | 36.7 | <0.001 |
| NCDR points, mean                       | 15.33 | 16.16 | 0.11 |
| Cardiogenic shock                        | 2531 | 21.6 | 229 | 23.8 | 0.11 |
| Congestive heart failure                 | 2346 | 20.0 | 209 | 21.7 | 0.21 |
| Peripheral vascular disease              | 2313 | 19.7 | 202 | 21.0 | 0.33 |
| Chronic obstructive pulmonary disease    | 2481 | 21.1 | 180 | 18.7 | 0.08 |
| eGFR, mL/min per 1.73 m²                 |      |      |      |      |      |
| ≥90                                      | 3363 | 28.6 | 282 | 30.0 | 0.68 |
| 60–89                                    | 6140 | 52.3 | 474 | 49.2 | 0.07 |
| 30–59                                    | 1839 | 15.7 | 156 | 16.2 | 0.64 |
| 15–29                                    | 106 | 0.9 | 20 | 2.1 | 0.002 |
| <15                                      | 296 | 2.5 | 31 | 3.2 | 0.20 |
| NYHA functional class                    |      |      |      |      |      |
| I–III                                    | 9112 | 77.6 | 719 | 74.7 | 0.04 |
| IV                                       | 2632 | 22.4 | 244 | 25.3 | 0.04 |
| Status at admission                      |      |      |      |      |      |
| Elective                                 | 8376 | 71.3 | 657 | 68.2 | 0.04 |
| Urgent                                   | 2639 | 22.5 | 243 | 25.2 | 0.05 |
| Emergent                                 | 374 | 3.2 | 47 | 4.9 | 0.01 |
| Salvage                                  | 10 | 0.1 | 0 | 0 | 1.00 |
| Indication                               |      |      |      |      |      |
| STEMI                                    | 426 | 3.6 | 48 | 5.0 | 0.04 |
| Other indications                        | 11 318 | 96.4 | 915 | 95.0 | 0.04 |
| Completed 30-day cardiology follow-up visit | 8406 | 71.6 | 616 | 64 | <0.01 |
| Completed 30-day PCP follow-up visit     | 6179 | 52.6 | 432 | 44.9 | <0.01 |
| 30-Day clopidogrel prescription          | 4985 | 42.4 | 411 | 42.7 | 0.89 |
| 60-Day clopidogrel prescription          | 224 | 1.9 | 22 | 2.3 | 0.41 |
| 90-Day clopidogrel prescription          | 6458 | 55 | 424 | 44 | <0.01 |

eGFR indicates estimated glomerular filtration rate; NCDR, National Cardiovascular Data Registry; NYHA, New York Heart Association; PCP, primary care physician; STEMI, ST-segment elevation myocardial infarction.

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patients had discontinued clopidogrel by 12 months.\(^3\) In a study of AMI patients from the Prospective Registry Evaluating Outcomes After Myocardial Infarctions: Events and Recovery registry, 13.6% of patients were not taking clopidogrel at 30 days after hospitalization for AMI and DES placement.\(^5\) There are several potential explanations for the lower rates of premature discontinuation in the VA health care system compared with prior studies. These include reduced costs to filling a clopidogrel prescription in the VA and the integration of VA services (ie, pharmacy and medical services) as well as treatment settings (inpatient and outpatient settings).

The hospital characteristics that we evaluated were not associated with premature clopidogrel discontinuation in this study. However, understanding that this variation in premature discontinuation exists is an important initial step to further evaluate the causes of the variation in subsequent research. This finding differs from previous studies that demonstrated associations between hospital characteristics and guideline-recommended implantable cardioverter-defibrillator utilization\(^14\) and clopidogrel prescription at discharge for medically managed NSTEMI patients.\(^9\) These outcomes are largely dictated by provider behaviour, while premature clopidogrel discontinuation is influenced by both patients and providers. This key difference may explain the lack of association between premature discontinuation and hospital characteristics in our study. It is likely that VA hospital-level characteristics that were not evaluated in our study may be associated with premature clopidogrel discontinuation. For instance, facility-level care processes such as the wait times encountered by patients when refilling medication, the use of pharmacy reminders when prescriptions expire, or whether patients can easily access their provider for prescription renewals may be associated with site-level rates of premature discontinuation. Future qualitative research will identify the processes of care at high-performing hospitals that account for low rates of premature discontinuation. These processes of care can then be implemented at low-performing hospitals to decrease rates of premature discontinuation.

This study is the first to evaluate variability in premature clopidogrel discontinuation across a national integrated health care system in which the cost of medications is less of a barrier. The associations that we observed between index

### Table 2. Association Between Patient- and Hospital-Level Factors and Premature Clopidogrel Discontinuation

|                        | Odds Ratio | 95% CI     | P Value |
|------------------------|------------|------------|---------|
| **Patient factors**    |            |            |         |
| No cardiology follow-up at 30 days | 1.39       | 1.20–1.61  | <0.001  |
| Days supplied          | 1.004      | 1.001–1.007| 0.03    |
| **Hospital factors**   |            |            |         |
| No. of beds            | 1.00       | 0.99–1.00  | 0.32    |
| PCI volume             | 1.00       | 0.99–1.00  | 0.34    |
| Teaching vs nonteaching| 1.02       | 0.76–1.36  | 0.89    |
| Presence of CT surgery program | 1.01     | 0.80–1.26  | 0.95    |

CT indicates cardiothoracic; PCI, percutaneous coronary intervention.
prescription size and follow-up after discharge and premature clopidogrel discontinuation are potential targets for VA quality improvement initiatives. For instance, given that short initial prescription size for clopidogrel after DES placement was associated with premature discontinuation, an intervention that standardizes clopidogrel prescription to at least 90 days could be tested to determine whether this practice would decrease rates of premature clopidogrel discontinuation. It is possible that the associations we observed are not causal; therefore, it is important to test whether such interventions would be efficacious before implementation.

Several potential limitations of this study should be noted. First, we used VA pharmacy records to determine whether patients prematurely discontinued clopidogrel. It is possible that patients could obtain their prescription through a non-VA pharmacy and therefore be incorrectly categorized to have prematurely discontinued therapy. However, this misclassification would have biased our results toward the null. Additionally, given the medication cost savings available by obtaining medications through the VA for a medication such as clopidogrel, veterans are less likely to obtain their prescriptions elsewhere. Second, because the follow-up period in this study started at 6 months after DES placement, it is possible that the analysis may underestimate early events associated with premature discontinuation. Third, it is unknown whether the associations we observed in this study are causal. They may reflect unmeasured differences in the patient populations. For instance, patients who have cardiology follow-up after hospital discharge are likely different than those who fail to have follow-up. Fourth, there are hospital characteristics or process measures that are likely influencing premature clopidogrel discontinuation among patients that cannot be studied using retrospective data. Therefore, qualitative analyses of hospital processes are needed. Fifth, it is possible that emergent surgery may have been the cause of premature discontinuation and we were unable to differentiate emergent versus nonemergent surgery in this cohort. Finally, the results of this study may not be generalizable to other patient populations as the VA represents a unique patient population and health care delivery system.

In conclusion, we found that premature discontinuation of clopidogrel after DES placement occurs in 1 in 13 patients in the VA health care system and is associated with adverse outcomes. Significant variability in premature discontinuation across VA hospitals exists, and patients with smaller index prescriptions and those who fail to have cardiology follow-up within 30 days of discharge are more likely to discontinue prematurely. These observations can inform quality improvement initiatives aimed at decreasing rates of premature clopidogrel discontinuation after DES placement among veterans.

Disclosures
Dr Bhatt discloses the following relationships—advisory board: Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; board of directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; chair: American Heart Association Get With The Guidelines Steering Committee; data monitoring committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; honorary: American College of Cardiology (editor, Clinical Trials, Cardiosource), Belvoir Publications (editor in chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor in chief, Journal of Invasive Cardiology), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, Cardiology Today’s Intervention), WebMD (CME steering committees); other: Clinical Cardiology (deputy editor), Journal of American College of Cardiology (section editor, Pharmacology); research grants: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Roche, Sanofi Aventis, The Medicines Company; Unfunded Research: FlowCo, PLx Pharma, Takeda.

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