Delays in Filling Clopidogrel Prescription After Hospital Discharge and Adverse Outcomes After Drug-Eluting Stent Implantation

Implications for Transitions of Care

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Background—Adjuvant clopidogrel therapy is essential after drug-eluting stent (DES) implantation. The frequency with which patients delay filling a clopidogrel prescription after DES implantation and the association of this delay with adverse outcomes is unknown.

Methods and Results—This was a retrospective cohort study of patients discharged after DES implantation from 3 large integrated health care systems. Filling a clopidogrel prescription was based on pharmacy dispensing data. The primary end point was all-cause mortality or myocardial infarction (MI). Of 7402 patients discharged after DES implantation, 16% (n=1210) did not fill a clopidogrel prescription on day of discharge and the median time delay was 3 days (interquartile range, 1 to 23 days). Compared with patients filling clopidogrel on day of discharge, patients with any delay in filling clopidogrel had higher death/MI rates during follow-up (14.2% versus 7.9%; P<0.001). In multivariable analysis, patients with any delay had increased risk of death/MI (hazard ratio, 1.53; 95% confidence interval, 1.25 to 1.87). Patients with any delay remained at increased risk of adverse outcomes when the delay cutoff was changed to >1, >3, or >5 days after discharge. Factors associated with delay included older age, prior MI, diabetes, renal failure, prior revascularization, cardiogenic shock, in-hospital bleeding, and clopidogrel use within 24 hours of admission.

Conclusions—One in 6 patients delay filling their index clopidogrel prescription after hospital discharge after DES implantation. This delay was associated with increased risk of adverse outcomes and highlights the importance of the transition period from hospital discharge to outpatient setting as a potential opportunity to improve care delivery and patient outcomes.

Key Words: stents | drugs | epidemiology

The transition period from hospital discharge to the outpatient setting is a critical period in which medication problems often arise.1-4 Few studies have evaluated the frequency with which patients delay filling their initial prescriptions after hospital discharge.1,2 Although small gaps in therapy may not have immediate consequences for many cardiovascular medications, filling a prescription for clopidogrel and taking the medication without gaps is particularly important after drug-eluting stent (DES) implantation. Prior studies suggest that stent thrombosis can occur early after the procedure, and lack of adjuvant thienopyridine therapy is one of the major risk factors for this complication.5-7

Little is known about when patients fill their clopidogrel prescription after hospital discharge for DES implantation and whether a delay in filling a prescription is associated with adverse outcomes. Accordingly, we assessed the length of time between hospital discharge and when a clopidogrel prescription was filled after DES implantation in a large cohort from 3 integrated health care systems. Next, we compared the risk of death or myocardial infarction (MI) between patients who had a delay in filling their initial clopidogrel prescription and those who filled their clopidogrel on the day of hospital discharge. Finally, we identified factors associated with delay in filling the initial clopidogrel prescription.

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WHAT IS KNOWN

- The transition period from hospital discharge to the outpatient setting is an important period in which medication problems can arise.
- A few studies have found that patients delay filling their initial prescriptions after hospital discharge for cardiovascular conditions.

WHAT THE STUDY ADDS

- This study found that in 1 in 6 patients delay filling their initial clopidogrel prescription after drug-eluting stent implantation, highlighting the importance of the transition period from inpatient to outpatient care.
- This delay in filling a clopidogrel prescription was associated with an increased risk of death or myocardial infarction particularly within the initial 30 days after hospital discharge.
- These findings highlight an opportunity to improve the care of patients receiving drug-eluting stents by ensuring that patients fill their clopidogrel prescription in a timely manner after hospital discharge.

Methods

This was a retrospective cohort study using linked clinical registry and administrative data from three integrated health care delivery systems, Kaiser Permanente of Northern California, Kaiser Permanente of Colorado, and Health Partners in Minneapolis. The dataset contained longitudinal patient information on demographic characteristics, coexisting illness, outpatient pharmacy prescriptions, and the occurrence of hospitalizations and death. Baseline demographic, clinical, and procedural characteristics were derived from the National Cardiovascular Data (NCDR) CathPCI Registry versions 2.0 and 3.0.

Patients were included if they had a pharmacy benefit plan which allowed them to obtain medications within their respective health care system at reduced costs, were discharged alive after receiving a DES in ≥1 coronary arteries between January 1, 2004, and December 20, 2007, and did not have a clopidogrel prescription in the 3 months before the index procedure. The average copay during this study period for clopidogrel ranged from $20 to $35 across the 3 systems. During this period, 8045 patients were discharged alive after DES implantation. Of these patients, 643 patients (8.0%) had a clopidogrel prescription in the 3 months before the procedure and were excluded, resulting in 7402 patients for the analytic cohort.

Clopidogrel Prescription

Filling a clopidogrel (or ticlopidine) prescription was based on pharmacy data that record the date dispensed for the medication. In the primary analysis, we dichotomized patients based on whether they filled clopidogrel on the day of hospital discharge versus any time after discharge which was categorized as a delay. In secondary analyses, we changed the dichotomization of the delay in filling clopidogrel to >1 day, >3 days, or >5 days after hospital discharge.

Outcome

The primary outcome was all-cause mortality or MI. Hospitalizations for MI were based on primary discharge ICD-9 diagnosis codes 410.XX. Hospitalizations outside the health care delivery system were also captured through administrative claims data for non-network care. Data on mortality were derived from multiple internal network care. Data on mortality were derived from multiple internal sources within each health care system. Vital status information was available through April 29, 2008.

Statistical Methods

We compared baseline characteristics and outcomes (all-cause mortality and MI) between patients with any delay in filling clopidogrel versus patients filling clopidogrel on the day of hospital discharge. Survival was measured beginning at hospital discharge and censored at the end of follow-up. Multivariable Cox proportional hazards regression, adjusting for all variables in Table 1, assessed the independent association between any delay in filling clopidogrel and the primary outcome of death/MI. Multivariable logistic regression models also identified factors associated with any delay in filling the initial clopidogrel prescription.

Next, we performed a series of additional analyses to confirm our primary findings. First, we repeated the analyses for the mortality outcome alone. Second, we changed the dichotomization of the delay to ≤1 day or >1 day, ≤3 days or >3 days, and ≤5 days or >5 days after hospital discharge for DES implantation. Third, we assessed whether patients with any delay were more likely to have long gaps (>7 days) between subsequent clopidogrel prescription refills because this initial delay may be a marker of less adherent patients. Fourth, we excluded patients with any in-hospital (major or minor) bleeding (n=138) because these patients may have contraindications to long-term clopidogrel therapy. Fifth, we adjusted for delays in filling statin, β-blocker, and/or angiotensin-converting enzyme inhibitors.
(ACE) inhibitor/angiotensin receptor blocker (ARB) medications among patients prescribed the medication and adherence to each of these cardiovascular medications at discharge (Table 1).

The median duration of follow-up was 664 days. During follow-up, patients with any delay in filling clopidogrel had a higher risk of death/MI (14.3% versus 7.9%; \( P<0.001 \)) (Figure 1). Of these death/MI events, a large proportion occurred in the first 30 days after hospital discharge for patients with any delay in clopidogrel filling (28.5% (49 of 172 events) versus 12.2% (60 of 490 events) \( P<0.001 \)) (Figure 2). In multivariable analysis, patients with any delay in filling clopidogrel had significantly increased risk of death/MI (hazard ratio [HR], 1.54; 95% confidence interval [CI], 1.24 to 1.91) as well as death alone (HR, 1.45; 95% CI, 1.06 to 1.97) (Table 2). Furthermore, patients with any delay in filling clopidogrel remained at increased risk of adverse outcomes when the delay cutoff was changed to ≥1 day (HR, 1.53; 95% CI, 1.19 to 1.96), ≥3 days (HR, 1.56; 95% CI, 1.19 to 2.06), and ≥5 days (HR, 1.55; 95% CI, 1.16 to 2.07) after hospital discharge. Finally, patients who had any delay were significantly more likely to have gaps of >7 days between subsequent clopidogrel prescription refills (odds ratio, 1.51; 95% CI, 1.31 to 1.75) compared with patients without any delay.

Next, the findings remained consistent when adjusting for delays in filling concomitant cardiovascular medications, statin, \( \beta \)-blocker, and/or ACE inhibitor/ARB medications (HR, 1.47; 95% CI, 1.16 to 1.86) or adherence to these cardiovascular medications after hospital discharge (HR, 1.36; 95% CI, 1.09 to 1.70) and excluding patients with any bleeding during the hospitalization (HR, 1.50; 95% CI, 1.20 to 1.88). Among patients filling clopidogrel on the day of discharge, filling a new statin prescription late (>1 day after discharge) was not associated with adverse outcomes (HR, 1.14; 95% CI, 0.78 to 1.67).

**Results**

Among 7402 patients receiving a DES, 83.7% (n=6192) of patients filled a clopidogrel prescription on the day of hospital discharge and 16.3% (n=1210) had a delay of at least 1 day in filling clopidogrel with a median delay of 3 days (interquartile range, 1 to 23 days). Among patients with a delay, 165 (13.6%) patients never filled a clopidogrel prescription. On average, patients with delay in filling clopidogrel were older, had more comorbid conditions, and were prescribed more concomitant cardiovascular medications at discharge (Table 1).

**Figure 1.** Cumulative incidence of death/MI between patients with delay in filling clopidogrel versus patients without delay in filling clopidogrel after hospital discharge.

**Figure 2.** Percent of death/MI events occurring in each 30-day interval after hospital discharge. *\( P<0.05 \). Only the 1 to 30, 151 to 180, and 211 to 240-day intervals were significantly different between patients who filled clopidogrel on day of discharge versus after discharge. For the rest of the time intervals, there was no difference in event rates between the 2 groups.
Factors associated with delayed clopidogrel filling included older age, prior MI, diabetes, renal dysfunction, prior revascularization, cardiogenic shock, in-hospital bleeding, and admission clopidogrel use (Table 3). In contrast, male sex, history of dyslipidemia, and emergent status were associated with filling clopidogrel on the day of hospital discharge.

Discussion

We found that 1 in 6 patients delayed filling their initial clopidogrel prescription and this delay was associated with an increased risk of death/MI. The findings were consistent when alternative definitions for delay in filling clopidogrel were used and adjusting for delays in filling other cardiovascular medications or adherence to these medications. In addition, filling a new statin prescription late was not associated with adverse outcomes suggesting that the association between the delay in filling a prescription and adverse outcomes was specific to clopidogrel. These findings suggest the need for quality improvement efforts to ensure that patients fill their clopidogrel prescription in a timely manner after DES implantation.

This study highlights the importance of the transition period from inpatient to outpatient care, particularly for patients receiving DES. Prior studies demonstrated that medication discrepancies occur frequently after hospital discharge; however, these studies did not focus on clopidogrel among patients receiving DES for which the consequences of not taking the medication can be fatal.1,2 Our results expand on prior studies from Canada, which showed higher mortality among patients who delayed filling a clopidogrel prescription after hospital discharge due to restrictive administrative processes requiring an authorization form for clopidogrel.3,4 We included a contemporary cohort receiving DES, used clinical data to adjust for baseline patient differences, and enrolled patients from 3 large integrated health care systems where a preauthorization was not required for clopidogrel.

The finding that 1 in 6 patients have a delay in filling clopidogrel after hospital discharge and the association of this delay with adverse outcomes stresses the need to improve the transition process for patients from the inpatient setting to outpatient care.

There are many potential reasons for delays in filling clopidogrel after hospital discharge including cost of the medication, logistics of obtaining the medication at discharge, and lack of understanding of the intended medication regimen.11,12 A prior study found that <50% of patients were able to state their diagnosis, recall the purpose of their medications, or list their medications at hospital discharge.11 In addition, a qualitative study of patients after DES implantation found that the most common reasons for early discontinuation of clopidogrel therapy were that patients were unaware that they should be taking the medication and the intended duration of the therapy.13 In our study, older patients and those with comorbid conditions were more likely to have a delay in filling clopidogrel. These patients may potentially benefit from a pharmacist or a “transition coach” to review their medications at the time of discharge or shortly thereafter as studies involving these intervention components have reduced adverse drug events and rehospitalizations, respectively.14,15 These findings suggest that interventions must be tested to assess whether a systematic process that includes patient education, timely filling, and adherence to clopidogrel therapy can have the potential to improve patient outcomes.

There was an increased death/MI risk among patients with any delay in filling clopidogrel after hospital discharge. A large proportion of these adverse events occurred within the first 30 days of hospital discharge particularly for patients with any delay in filling clopidogrel. The occurrence of these adverse events early coincides with the timing of early stent thrombosis seen in various stent registries.5,6,16 These studies have demonstrated that a large proportion of stent thrombosis cases occur early with a median of 2 to 11 days but can occur up to 30 days after the procedure. There is often local inflammation after stent implantation due to balloon dilation and/or the stent itself, which can lead to increased thrombotic activity around the stented lesion or there could be lack of

### Table 2. Association Between Delay in Filling Clopidogrel and Adverse Outcomes

<table>
<thead>
<tr>
<th>Factors</th>
<th>Adjusted HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any delay vs no delay</td>
<td>1.54</td>
<td>1.24–1.91</td>
</tr>
<tr>
<td>Death outcome only</td>
<td>1.45</td>
<td>1.06–1.97</td>
</tr>
<tr>
<td>Adjust for delays in filling concomitant cardiovascular medications</td>
<td>1.47</td>
<td>1.16–1.86</td>
</tr>
<tr>
<td>Adjust for adherence to concomitant cardiovascular medications after hospital discharge</td>
<td>1.36</td>
<td>1.09–1.70</td>
</tr>
<tr>
<td>Excluding patients with any in-hospital bleeding event</td>
<td>1.50</td>
<td>1.20–1.88</td>
</tr>
<tr>
<td>Change delay to &gt;1 day vs ≤1 day</td>
<td>1.53</td>
<td>1.19–1.96</td>
</tr>
<tr>
<td>Change delay to &gt;3 day vs ≤3 days</td>
<td>1.56</td>
<td>1.19–2.06</td>
</tr>
<tr>
<td>Change delay to &gt;5 day vs ≤5 days</td>
<td>1.55</td>
<td>1.16–2.07</td>
</tr>
</tbody>
</table>

The crude rates of death/MI were 14.3% in patients with any delay in filling clopidogrel and 7.9% in patients without a delay in filling clopidogrel (HR, 2.05; 95% CI, 1.72 to 2.43).

### Table 3. Factors Associated With Delay in Filling Clopidogrel

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt;65</td>
<td></td>
</tr>
<tr>
<td>65 to ≤75</td>
<td>1.31 (1.11–1.56)</td>
</tr>
<tr>
<td>≥75</td>
<td>1.61 (1.34–1.92)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.22 (1.01–1.48)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.55 (1.18–2.03)</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>1.40 (1.17–1.68)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>2.55 (1.60–4.07)</td>
</tr>
<tr>
<td>Any bleeding complication during hospitalization</td>
<td>1.94 (1.26–2.96)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.32 (1.12–1.53)</td>
</tr>
<tr>
<td>Clopidogrel prescribed within 24 hours of admission</td>
<td>1.41 (1.14–1.75)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.60 (0.51–0.72)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.72 (0.62–0.84)</td>
</tr>
<tr>
<td>Emergent status</td>
<td>0.77 (0.60–0.99)</td>
</tr>
</tbody>
</table>

*Odds ratio >1 indicates factor associated with delay in filling clopidogrel.
endothelialization within the stent which may make the stent struts more vulnerable to thrombosis. Patients with a delay in filling clopidogrel may not have adequate antiplatelet activity to counter this prothrombotic state, and this can potentially lead to stent thrombosis. Furthermore, there was a strong association between a delay in filling the initial clopidogrel prescription and long gaps between subsequent clopidogrel refills, suggesting that the initial delay may be a marker of patients who are less adherent to clopidogrel therapy longer term. Poor adherence to clopidogrel therapy may be a potential explanation for the late adverse events observed in the study.

Some potential limitations should be addressed. First, filling a clopidogrel prescription was based on pharmacy records and we could not exclude the possibility that patients may have received a clopidogrel supply at discharge or obtained the medication outside the health care system. However, this would most likely occur among patients who delayed filling clopidogrel and bias our results toward the null. Second, our study did not include patients who received a bare-metal stent, but we do not have an a priori reason to believe that the patterns of delay or its association with outcomes would be different based on the type of stent received. Third, we could not assess for delays in filling aspirin because most patients get it over the counter without a prescription. Fourth, delays in filling clopidogrel may be a marker of more severe cardiac, noncardiac conditions, lower socioeconomic status, or poor adherence in general or specifically to clopidogrel, and we cannot conclude causality nor exclude unmeasured confounding as a contributor to the observed association. However, we adjusted for known confounders and our findings remained consistent with various sensitivity analyses. In addition, whereas patients filling clopidogrel late may be sicker, they may also derive more benefit from filling a clopidogrel prescription and taking the medication as prescribed to prevent adverse events due to gaps in therapy. Even if delayed filling is a risk marker, this has important implications for targeting such patients for postdischarge interventions. Fifth, there were no significant differences in the risk of adverse outcomes associated with shorter versus longer delays to filling a clopidogrel prescription. This may be related to differences in clopidogrel loading dose, which affects subsequent antiplatelet activity, heterogeneity in patient metabolism of clopidogrel, or patients may not take the medication on the day of filling their prescription, all of which would bias toward not finding a significant difference in the risk of adverse outcomes based on the cutoffs used in the analysis. Finally, this study was conducted within integrated health care systems which could limit generalizability. However, we anticipate that the number of patients with delays in filling clopidogrel may be greater in other outpatient health care settings, given that all patients in the current study had a prescription drug benefit and can obtain clopidogrel at reduced costs. Therefore, our results may be conservative in the estimate of the prevalence of delays in filling clopidogrel after DES implantation.

In conclusion, we found that 1 in 6 patients delayed filling their initial clopidogrel prescription after hospital discharge and this delay was associated with increased risk of adverse events. These findings highlight potential opportunities to improve the care of patients after stent implantation in the transition from hospital discharge to the outpatient setting to avoid gaps in clopidogrel therapy.

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Disclosures
The funders did not have involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of this manuscript. Drs Ho and Magid 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.

References
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