Evaluating the Impact of Public Health Notification
Duke Clopidogrel Experience

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Background—Provider and public health interventions in the late 2006 sought to change the duration of clopidogrel use after drug-eluting stent (DES) implantation. We evaluated whether public health interventions were associated with changes in patient-reported clopidogrel use among DES patients.

Methods and Results—We used interrupted time analyses to evaluate trends in duration of patient-reported clopidogrel use before, during, and after public and provider interventions. We included patients with significant coronary artery disease receiving an intracoronary stent between April 2004 and December 2007 at a single tertiary care center. The center supplemented national and regulatory messaging regarding the role of clopidogrel after DES implantation with direct-to-patient and to-their-provider notifications in December 2006. The combination of public and provider direct notification was associated with significant changes in the percent of DES patients reporting clopidogrel use at 6 months (16.55% increase, \( P=0.010 \)) and 12 months (15.33% increase, \( P=0.004 \)), but no change at 24-month follow-up (4.64, \( P=0.295 \)). During the same period, there was no change in the percent of bare-metal stent patients reporting clopidogrel use at 6-month (−3.73%, 0.654), 12-month (−5.98%, \( P=0.389 \)), and 24-month follow-up (−5.16, \( P=0.708 \)). Although mortality rates through 24 months seemed to decrease between the pre- and postintervention periods, these changes were not significant (DES, \( P=0.086 \); bare-metal stent, \( P=0.296 \)).

Conclusions—The combination of national scientific and regulatory messaging supplemented by local, personal communications to DES patients and their primary healthcare providers was associated with a significant increase in patient-reported clopidogrel use. (Circ Cardiovasc Qual Outcomes. 2012;5:767-774.)

Key Words: angioplasty ■ antiplatelet ■ clopidogrel ■ follow-up studies ■ population ■ stents

Although the pace of medical discovery continues to accelerate, there typically remains a long lag between discovery and dissemination. Several works have documented these translational challenges, and the Institute of Medicine has highlighted the intense need for advancements in implementation science. 1, 2 The need for rapid information dissemination and practice change is particularly important in settings where a serious safety concern is identified and may be facilitated through the use of health information technologies. 3

In 2006, a randomized clinical trial raised initial concerns that patients receiving drug-eluting stent (DES) who received clopidogrel for ≤6 months were at elevated risk for subsequent late-stent thrombosis and potentially worse outcomes compared with bare-metal stent (BMS) implantation. 4 This trial was quickly followed by case series and registry studies that similarly identified a risk for stent thrombosis associated with early clopidogrel discontinuation in DES patients. 5, 6 The results prompted the Food and Drug Administration (FDA) to convene a special public hearing in December 2006. 7 Within a month of this meeting, major medical societies jointly issued a Clinical Alert and Science Advisory stressing the importance of a 12-month dual-antiplatelet regimen for all DES patients who were not at high risk of bleeding. 12, 13

Although the speed of inquiry into the clopidogrel-DES safety issue by the medical and regulatory community was remarkable, generic communications to general audiences often are not effective in changing community practice. 14-16 We hypothesize that the likelihood of practice change is diminished when guidance is not provided in the context of real-time clinical decision making and does not directly target patients at risk. To address these gaps, in early December 2006 the Duke University Heart Center undertook the unusual step of sending letters to all patients who had received a DES at its institution as well as to their referring physicians, which outlined the available evidence and suggested that DES patients contact their physicians to determine whether they should consider long-term use of dual-antiplatelet therapy beyond that previously recommended.

The present study seeks to evaluate whether these public health interventions were associated with changes in patient-reported clopidogrel use among Duke Heart Center DES patients, when they occurred, and whether they persisted.
Specifically, this study examines overall use of DES among percutaneous coronary intervention (PCI) patients; trends in use of clopidogrel 6, 12, and 24 months post-PCI (among DES and BMS patients), and the predictors of patient-reported clopidogrel use 12 months post-DES implantation.

WHAT IS KNOWN

- The Institute of Medicine has highlighted the need for advancements in implementation science to address the lag between medical discovery and dissemination. The need for rapid information dissemination and practice change is particularly important when serious safety concerns are identified.
- In late 2006, concerns were raised that drug-eluting stent (DES) patients who received clopidogrel for ≤6 months were at elevated risk for late-stent thrombosis and worse outcomes compared with bare-metal stent patients. These concerns prompted major medical societies to jointly issue a Clinical Alert and Science Advisory stressing the importance of a 12-month dual-antiplatelet regimen for DES patients not at high risk of bleeding.

WHAT THE STUDY ADDS

- The Duke Heart Center decided to supplement national messaging by sending letters to all of their DES patients and their referring physicians. The letters outlined the available evidence and suggested that the patients contact their physicians to evaluate their use of dual-antiplatelet therapy.
- The combination of public and patient-provider direct communication was associated with an immediate increase in the percent of DES patients reporting clopidogrel use at 6- and 12-month follow-up, with no reported change in clopidogrel use for bare-metal stent patients.
- Local messages directed to DES patients and their referring physicians served to amplify and focus public health messaging from external sources.

Methods

Study Population

The study population includes all patients with significant coronary artery disease (CAD) (≥75% stenosis in ≥1 epicardial segments) undergoing PCI with ≥1 intracoronary stents at Duke University Medical Center between April 2004 and December 2007. If patients had ≥1 PCI during the study period, the first was selected as their index procedure. Patients <18 years of age, with congenital heart disease, moderate/severe valvular disease, or ≥75% left main disease, as well as those receiving coumadin at the time of stent implantation, were excluded. Patients receiving ≥1 DES during their index procedure were assigned to the DES analysis group; whereas, those who received only BMS were assigned to the BMS group.

Data Collection

All study information, baseline, and follow-up, were maintained in the Duke Databank for Cardiovascular Disease and collected prospectively using methods previously described by our group.20–22

Baseline Data

Baseline demographic data were obtained from Duke University Medical Center’s administrative systems and clinical data were collected by the Duke Heart Center. Study demographic data included subject age, sex, and race (collapsed into the categories of white, black, American Indian, and other). Study clinical data were collected by the Duke Heart Center at the time of interventional catheterization and included the following medical history: diagnoses of hypertension, diabetes mellitus, chronic obstructive pulmonary disease; family history of CAD; history of congestive heart failure, chest pain, cerebrovascular disease, and peripheral vascular disease; CAD history (prior coronary artery bypass graft surgery, PCI, myocardial infarction [MI], and multivessel CAD [≥2 vessels]); and acute coronary syndrome (ACS) admission (ST-segment elevation myocardial infarction [STEMI], non-STEMI, unstable angina, or unspecified ACS).

Follow-Up Data

Patients were contacted via mail or, secondarily, by telephone at 6 and 12 months after their interventional catheterization procedure and annually thereafter. At this contact, patients were asked about various medication uses. Patient-reported medication use was not verified, nor was there an assessment of the daily compliance with the medications. Patient follow-up is considered complete if the patient was contacted during a Duke Databank for Cardiovascular Disease protocol-mandated follow-up interval, or if his or her death was confirmed by the mortality committee. We included patient-reported clopidogrel use information for the period January 2006 through December 2008. All patients included in this study gave informed consent for follow-up contact at the time of their PCI procedure. The Duke University Medical Center Institutional Review Board approved the study protocol with a waiver of informed consent on May 8, 2009 (Protocol ID: Pro00016342).

Baseline Characteristics

Intracoronary stent assignment for the patient index procedure is reported as percent DES and BMS use by quarter. Patients are grouped according to whether 6-month follow-up contact after their index PCI procedure would have been scheduled before or after receipt of the Duke Heart Center letter in December 2006. Baseline characteristics for each group are summarized as mean (SD) for continuous variables and as counts (percentages) for categorical variables.

Follow-up Patient-Reported Clopidogrel Use

Clopidogrel use is summarized as the percent of patients reporting clopidogrel use at follow-up intervals (6, 12, or 24 months). These results are reported by stent type (DES or BMS), as well as for the periods before and after the public health interventions ending in December 2006. Because patient follow-up reporting varied, we defined the 6-, 12-, and 24-month interval as including months 3 to 9, 9 to 15, and 21 to 27, respectively. Patients were considered on clopidogrel for a follow-up interval if they had 1 self-report of clopidogrel use during that interval. Multiple imputation methods were used to impute clopidogrel use for patients who did not report this information in a follow-up interval.

Adjusted patient-reported clopidogrel use analyses are conceived as interrupted time series characterized by a series of percent use measurements occurring over time that were interrupted by the public health interventions ending in December 2006. Segmented linear regression analysis methods are used to perform these analyses with the following results reported: (1) a baseline trend occurring before the intervention (interpreted as a percent change in use per quarter in the preintervention period), (2) a level change in December 2006 (interpreted as the percent change in use attributable to the intervention after accounting for trends in use occurring before the intervention), and (3) a trend change after the intervention (interpreted as a percent change in use per quarter after December 2006).23 Separate analyses are conducted by stent type (DES or BMS) and time since implantation (6-, 12-, and 24-month follow-up). We conducted a subgroup analyses for ACS and non-ACS patients to determine whether clopidogrel use differed depending upon ACS status. We also conducted a sensitivity analysis in which patients were censored at the time of their first repeat revascularization procedure to determine whether these events altered patient-reported clopidogrel use results for DES and BMS patients.
Patient-Reported Clopidogrel Use Descriptors

A logistic regression model was derived on DES patients to determine baseline characteristics that were associated with patient-reported clopidogrel use at 12-month follow-up. Candidate variables in this model included baseline patient characteristics and an indicator of whether the patient’s 12-month follow-up occurred before or after the end of this study’s public health interventions in December 2006.

Patient Mortality

Cox proportional hazards methods were used to estimate mortality rates for DES and BMS patients at 6-, 12-, 18-, and 24-months follow-up. Comparisons were made between patients whose 6-month follow-up occurred before versus after December 2006 and were tested using the log rank test.

Results

Study Population and Baseline Characteristics

Beginning with the second quarter of 2006, the percent of stent patients receiving DES declined rapidly and was less than the percent receiving BMS through 2007 (Figure 1). Baseline characteristics were largely similar for DES and BMS patients reaching their 6-month follow-up before and after December 2006 (Table 1). Patients with 6-month follow-up intervals after December 2006 had less history of coronary artery bypass graft surgery and PCI procedures, and the percent of DES patients with ACS (STEMI, non-STEMI, and unstable angina) declined between the pre- and postintervention periods.

Patient-Reported Clopidogrel Data

The reporting of clopidogorel use (yes or no) was ≥90% for DES and BMS patients in all follow-up intervals before and after December 2006 (Table 2). Generally, reporting of these data were greater at 12 and 24 months than at 6-months follow-up. The percent of DES versus BMS patients reporting clopidogrel use in a time interval typically differed by <2%.

Adjusted Patient-Reported Clopidogrel Use

Among DES patients, the prevalence of patient-reported clopidogrel use at 6 and 12 months increased between the fourth quarter of 2006 and the first quarter of 2007, whereas the increase in use at 24 months was less pronounced (Figure 2A–2C). In contrast, there were no such trend in patient-reported clopidogrel use among BMS patients (Figure 2D–2F). Segmented regression analyses for DES patients at 6-month follow-up showed no change in patient-reported clopidogrel use in the period just before the intervention, a 16% increase with the intervention, and slightly decreased use in the period after the intervention. Similar analyses for DES patients at 12-month follow-up showed a 15% increase in use with the intervention and no change (increase or decrease) in use at 24 months (Table 3). Analyses for BMS patients at 6-, 12-, and 24-month follow-up demonstrated no change in
patient-reported clopidogrel use attributable to the intervention itself. Both ACS and non-ACS DES patients showed increased patient-reported clopidogrel use with the intervention at 6-month follow-up. However, only ACS patients showed an increased use with the intervention at 12 months. ACS and non-ACS estimates for BMS patients were unstable because of the small number of patients. Patient-reported clopidogrel use results for DES and BMS patients changed little when follow-up was censored at the occurrence of a repeat revascularization procedure. With censoring, the level change at intervention for DES patients at 6-month follow-up increased from 16.55 ($P=0.010$) to 18.55 ($P=0.003$), whereas the change at 12-month follow-up decreased from 15.33 ($P=0.004$) to 14.55 ($P=0.004$).

Patient-Reported Clopidogrel Use Descriptors
Several factors were associated with a patient’s use of clopidogrel at 12-month follow-up (Table 4). The most important of these was whether their 12-month follow-up date occurred before or after the public health interventions ending in December 2006. Prior MI was associated with increased patient-reported clopidogrel use, whereas history of diabetes mellitus was associated with decreased use. Importantly, there were no associations between patient-reported clopidogrel use and a patient’s age, race, sex, and ACS status at admission and its components of STEMI, non-STEMI, and unstable angina.

Patient Mortality
Among patients who received DES and BMS, mortality rates at 6, 12, 18, and 24 months seemed to decline after the public health interventions (Table 5). However, these differences were not statistically significant.

Discussion
Our study results suggest that public health interventions in late 2006 were associated with significant increases in the percent of Duke Heart Center DES patients with recent procedures ($\leq$12 months) reporting clopidogrel use, with the magnitude of improvement being similar in both the 6- and 12-month follow-up groups. However, there were no patient-reported increases in patient-reported clopidogrel use for DES patients who were further out from their procedures (at 24-month follow-up) or for BMS patients at 6-, 12-, and 24-month follow-up. Thus, the combination of national scientific and regulatory messaging supplemented by local, personal communications to patients and their primary healthcare providers was associated with changes in the standard of care related to post-PCI patient-reported clopidogrel use during just a few months.

<table>
<thead>
<tr>
<th>Table 2. Patient Visits and Patient-Reported Clopidogrel Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients With Visits at 6 Mo</td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Implant before July 1, 2006</td>
</tr>
<tr>
<td>DES</td>
</tr>
<tr>
<td>BMS</td>
</tr>
<tr>
<td>Implant after July 1, 2006</td>
</tr>
<tr>
<td>DES</td>
</tr>
<tr>
<td>BMS</td>
</tr>
<tr>
<td>Implant before January 1, 2006</td>
</tr>
<tr>
<td>DES</td>
</tr>
<tr>
<td>BMS</td>
</tr>
<tr>
<td>Implant after January 1, 2006</td>
</tr>
<tr>
<td>DES</td>
</tr>
<tr>
<td>BMS</td>
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<tr>
<td>Implant before January 1, 2005</td>
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<tr>
<td>DES</td>
</tr>
<tr>
<td>BMS</td>
</tr>
<tr>
<td>Implant after January 1, 2005</td>
</tr>
<tr>
<td>DES</td>
</tr>
<tr>
<td>BMS</td>
</tr>
</tbody>
</table>

DES indicates drug-eluting stent; BMS, bare-metal stent.
likely that this change was related to growing concern about the safety of DES. Along with changes in stent type, there were increases in the percent of all stent patients (both DES and BMS) reporting they were taking clopidogrel at 6- and 12-month follow-up during the postintervention period. Despite these trends, our adjusted analyses also detected additional, significant increases in patient-reported clopidogrel use at 6- and 12-month follow-up for DES patients that coincided with the public health interventions ending in December 2006. Patient results for 12-month patient-reported clopidogrel use among DES patients were confirmed by the logistic regression analysis, in which timing of 12-month follow-up (before or after December 2006) was identified as the most important factor associated with patient-reported clopidogrel use.

Of note, the choice of December 2006, although coinciding with the Duke Heart Center’s letters to DES patients and their primary physicians, occurred at the end of a brief series of events that undoubtedly contributed to the trends observed in patient-reported clopidogrel use. Although one could make the case that the public health intervention evolved over the
last half of 2006 and culminated around the time of the Duke Heart Center letters, we believe that the choice of an analysis date at the end of this period is conservative and reflects the greatest concentration of events (beginning with the Food and Drug Administration (FDA) special public hearing and ending with FDA and medical society reports and advisories). Despite the significance of these findings, 3 issues remain to be addressed. These include the following: (1) whether changing DES selection criteria influenced our results; (2) how the results of this public health intervention compare with similar interventions; (3) why our use of letters differed from previous attempts; and (4) implications of our findings for quality improvement initiatives.

**DES Selection Criteria**

Physician concerns regarding late-stent thrombosis likely influenced DES versus BMS selection criteria during the course of this study and may have impacted clopidogrel adherence. These changes in DES selection criteria are evidenced in the dramatic reduction in DES use that began in the second quarter of 2006 and in the percent of STEMI and non-STEMI patients receiving DES before and after the December 2006 public health intervention. Clearly, the intent of these changes was to minimize patient risk.

However, the DES cohort that exhibited an increase in 12-month clopidogrel adherence immediately after the December 2006 public health notifications received their coronary interventions in early 2006, well before concerns arose regarding DES use. Thus, changes in DES selection criteria do not explain the initial increase in 12-month clopidogrel adherence observed in the first quarter of 2007. However, these changes may have played an important role in supplementing the December 2006 messages to patients and their providers and in sustaining their effect.

**Previous Public Health Interventions**

The off-label use of atypical antipsychotics has been an area of heightened public health concern. In 2003, the FDA issued a requirement that atypical antipsychotics contain warnings about the risks of hyperglycemia and diabetes mellitus (including death). In 2005, the FDA issued a second warning that the use of atypical antipsychotics for behavioral problems in the elderly increased the risk of mortality. One study of nursing home residents reported continued high rates of antipsychotic prescribing after the 2005 warning with large variations by facility. However, another study conducted using methods similar to ours found that before the warning prescribing of this medication class was increasing at 16% per year in patients with dementia and that after the advisory there was a 19% reduction. The literature on public health interventions is inconsistent, and is not uncommon to find 2 analyses of the same intervention reaching opposing conclusions. Differing methods may be one factor contributing to this situation. An interrupted time series design, such as was used in the present study, is one of the stronger research designs because it separates the effect of the intervention from trends occurring before and after the intervention period. Had we conducted a before versus after analysis in the present study, we may have reported an effect at 24-month follow-up for DES patients that did not exist. Another methodological issue is the reporting of changes. Our study reported change as an absolute value. Had we reported change in relative terms as commonly occurs, our reported 6- and 12-month increases in patient-reported clopidogrel use for DES patients would have been much larger.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>χ²</th>
<th>P</th>
<th>Odds Ratio</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.2622</td>
<td>0.0889</td>
<td>8.7049</td>
<td>0.0032</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent implantation &lt;1 y since December 2006</td>
<td>1.1124</td>
<td>0.1083</td>
<td>105.4531</td>
<td>&lt;0.0001</td>
<td>3.042</td>
<td>2.460</td>
<td>3.761</td>
</tr>
<tr>
<td>Hx of diabetes mellitus</td>
<td>−0.2616</td>
<td>0.1197</td>
<td>4.7730</td>
<td>0.0289</td>
<td>0.770</td>
<td>0.609</td>
<td>0.973</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>0.2812</td>
<td>0.1075</td>
<td>6.8444</td>
<td>0.0089</td>
<td>1.325</td>
<td>1.073</td>
<td>1.635</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
Table 5. Mortality Rates

<table>
<thead>
<tr>
<th>Time Since Implantation, mo</th>
<th>Drug-Eluting Stent</th>
<th>Bare-Metal Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Intervention*</td>
<td>After Intervention†</td>
</tr>
<tr>
<td></td>
<td>Events</td>
<td>At Risk</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>105</td>
<td>2850</td>
</tr>
<tr>
<td>12</td>
<td>155</td>
<td>2778</td>
</tr>
<tr>
<td>18</td>
<td>207</td>
<td>2701</td>
</tr>
<tr>
<td>24</td>
<td>260</td>
<td>2601</td>
</tr>
</tbody>
</table>

*Patients with stent implantation before July 1, 2006.
†Patients with stent implantation on or after July 1, 2006.

Physician Letters

Labeling changes for pharmaceuticals may be accompanied by direct mailings to targeted health care professionals. The effectiveness of these Dear Doctor letters has long been a subject of investigation. An example involves the FDA’s 1995 and 1998 black box warnings regarding cisapride and their associated Dear Doctor letters. In analyses of different populations, Smalley et al concluded that the FDA’s 1998 actions had no effect on contraindicated cisapride use, whereas a second study by Weatherby et al found a significant decline in same-day codispensing of cisapride and contraindication medications and a smaller decline using wider time windows. Although both studies noted that unlike the 1995 intervention, the 1998 intervention also included substantial media and internet coverage, only the Weatherby study mentioned efforts to inform large pharmacy dispensing organizations of the warning and cited this effort as being a primary contributor to the reduction in codispensing.

Previous research has cited the poor dissemination of drug knowledge to physicians as the most common system failure associated with medical errors. However, it is difficult for practitioners to remain current on all drugs relevant to their patients; black box warnings cannot provide the context they require to individualize risks and benefits to their patients, and Dear Doctor letters often do not clearly and effectively communicate labeling changes suggesting their effectiveness may be limited. Further, none of this information is provided to physicians at the time of medical decision making. The Duke Heart Center letter to patients and their physicians did not attempt to fully explain the rationale for this warning to patients. Rather, it directed patients to contact their physicians so that an assessment could be made. Unlike black box warnings and Dear Doctor letters, the Duke Heart Center letters simplified the message and focused patient and primary physician attention upon the medical problem.

Quality Improvement Implications

The public health intervention described in this study was made possible because the Duke Heart Center maintains a longitudinal database of patients with significant CAD that includes information on dual-antiplatelet therapy use. Nonetheless, our public health intervention was distinguished because physicians within the Duke Heart Center took the unusual step of using information in this database to communicate important safety information directly to patients and their physicians. Without this decision, the mere existence of a longitudinal patient database was not sufficient of itself to change practice.

Limitations

Our study has several limitations. First, it represents the results of patients who consented to participate in a registry study at a single site, and it cannot provide evidence that the Duke Heart Center’s experience is transferable to other locations. Second, clopidogrel use data were patient-reported without verification or assessment of compliance. Thus, there is a significant possibility for under and over reporting of patient-reported clopidogrel use that may affect our results. Third, patients were not randomized to this study’s public health intervention and it is possible that other, unmeasured factors may have contributed to this study’s results. Fourth, had our study included data from other sites, we might have been able to separate the effects of national scientific and regulatory communications from those of the Duke Heart Center’s personal communications to patients and their primary physicians. Fifth, our methods did not account for patients having >1 PCI procedure that would have extended their initial clopidogrel duration. Nonetheless, we do not believe that any of these limitations, individually or collectively, are of sufficient magnitude to nullify the results of this study.

Conclusions

Gaps between medical discovery and practice change are well known and their effects become amplified when there are safety concerns regarding a drug or device. Our study demonstrated that the combination of national scientific and regulatory messaging supplemented by local, personal communications to patients and their primary health care providers was associated with change in the standard of care related to post-PCI patient-reported clopidogrel use during just a few months. Although these results serve to highlight the benefits that may be achieved by directly involving patients and their primary physicians in quality management initiatives, patient-reported clopidogrel use at 6 and 12 months remained below target levels suggesting that more focused methods may be required to solicit more adherence beyond these thresholds.

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Eric Eisenstein, DBA (corresponding author), had full access to all data in the study, and takes responsibility for the integrity of data and the accuracy of the data analysis.

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References

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