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J Am Heart Assoc. 2014;3:e000669; originally published May 28, 2014;
doi: 10.1161/JAHA.113.000669
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

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ORIGINAL RESEARCH

Delay in Filling First Clopidogrel Prescription After Coronary Stenting Is Associated With an Increased Risk of Death and Myocardial Infarction

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***Background*—**Patients frequently experience difficulties with medication compliance after hospital discharge. We investigated the effect of a delay in filling a first clopidogrel prescription after hospital discharge on clinical outcomes subsequent to coronary stenting.

***Methods and Results*—**Hospital administrative, community pharmacy, and cardiac revascularization data were determined for all patients receiving a coronary stent in British Columbia 2004–2006 with follow-up out to 2 years. Cox's proportional hazard regression analysis, adjusting for baseline demographics and procedural variables, was performed to examine the effects of delay in filling a clopidogrel prescription after hospital discharge on clinical outcomes.
Of 15 629 patients treated with coronary stents, 3599 received at least 1 drug-eluting stent (DES), whereas 12 030 received bare metal stents (BMS) alone. In total, 1064 (30%) and 3758 (31%) patients in the DES and BMS groups, respectively, failed to fill a prescription within 3 days of discharge (median, 1 day; interquartile range [IQR], 1 to 3). After regression analysis, a delay of >3 days was predictive of mortality and recurrent myocardial infarction (MI) irrespective of stent type (DES: hazard ratio [HR], 2.4; 95% confidence interval [CI], 1.7 to 3.4; and HR, 2.0; 95% CI, 1.5 to 2.7, respectively, and BMS: HR, 2.2; 95% CI, 1.9 to 2.6; and HR, 1.8; 95% CI, 1.5 to 2.1, respectively). This excess hazard was greatest in the 30-day period immediately after hospital discharge (mortality: HR, 5.5; 95% CI, 3.5 to 8.6; and MI: HR, 3.1; 95% CI, 2.4 to 4.0, for all patients).

***Conclusions*—**Delays in patients filling their first prescription for clopidogrel after coronary stenting are common and associated with adverse clinical outcomes, irrespective of stent type. Strategies to reduce delays have the potential to improve clinical outcomes. **(*J Am Heart Assoc*. 2014;3:e000669 doi: 10.1161/JAHA.113.000669)**

Key Words: clopidogrel • death • myocardial infarction • percutaneous coronary intervention

Current guidelines recommend adjuvant treatment with clopidogrel, in combination with aspirin, for 1 month in patients undergoing implantation of a bare metal stent (BMS) and 6 to 12 months in patients treated with drug-eluting coronary artery stents (DES) to reduce the risk of stent thrombosis. Delays in filling a prescription on hospital discharge are common and dependent on a number of factors.[1,2] Whereas premature discontinuation of clopidogrel therapy has emerged as a strong independent risk factor for coronary stent thrombosis,[3] few studies have examined the effects of a delay in filling a first prescription for clopidogrel after hospital discharge on clinical outcomes subsequent to coronary stent implantation.[4,5] To address this issue, we performed a retrospective cohort analysis to examine the frequency of delays in filling a first prescription for clopidogrel on hospital discharge and determine the relationship with clinical outcomes in all patients undergoing coronary artery stent implantation in British Columbia (BC) over a 3-year period.

Methods

Data Sources

The Cardiac Services BC Registry is a prospective clinical registry collecting detailed clinical and procedural data on all percutaneous coronary intervention (PCI) procedures performed in BC. Pharmanet is a province-wide network that

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Received November 19, 2013; accepted April 2, 2014.

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maintains electronic data on every prescription dispensed by a community pharmacy in BC. Patient-level data on mortality as well as International Classification of Diseases (ICD) codes for all hospital admissions in BC are recorded in the Ministry of Health Vital Statistics and Hospitalizations databases, respectively. This study was approved by the University of BC Research Ethics Board.

Data Analysis Protocol

Using the Cardiac Services BC Registry, we identified all patients undergoing PCI in BC during the period 2004–2006 and linked this data set to Pharmanet and the BC Ministry of Health Vital Statistics and Hospitalizations databases to obtain patient-level information on demographics, index PCI procedure, clopidogrel prescription, and clinical outcomes. Database linkage provided follow-up information on all patients out to 2 years after index PCI. Clinical outcomes were examined according to duration from hospital discharge after index PCI to first clopidogrel prescription being filled for patients treated with BMS alone or at least 1 DES.

Outcomes

The primary outcome was all-cause mortality. Secondary outcomes were readmission for recurrent myocardial infarction (recurrent myocardial infarction; based on primary discharge ICD-10 diagnostic codes I21.0 to I21.4, I21.9 to I22.1, I22.8, and I22.9), the combined endpoint of all-cause mortality and readmission for myocardial infarction (MI), and cancer-related mortality (reported as a marker for overall health behavior unrelated to prescription of clopidogrel).

Statistical Analysis

Means of continuous variables were compared using the independent samples *t* test (with equal and unequal variance determined with Levine's test). Pearson's chi-square test was used to analyze frequencies between groups. In the primary analysis, outcomes for patients filling a first clopidogrel prescription >3 days from discharge were compared with those filling a first prescription for clopidogrel ≤3 days from discharge. Cox's proportional hazard regression was performed step-wise with forward selection complemented with backward elimination under the criterion of maximum likelihood to identify factors independently associated with the primary and secondary outcomes and, in a separate analysis, cancer-related mortality. Variables examined included age, gender, body mass index, procedural indication, previous cardiac history, traditional risk factors for coronary artery disease, history of congestive cardiac failure, baseline renal function, hemodynamic instability or cardiogenic shock during the index procedure, and mean stent diameter. All patients dying within 3 days of hospital discharge were excluded from the primary analysis, irrespective of whether a prescription was filled. To explore the effect of the duration of delay on mortality, Cox's proportional hazard regression analyses were repeated using 1- and 5-day cutoffs, as well as by further stratifying patients into those who delayed filling a community prescription for clopidogrel by >3 days and those who never filled a prescription for clopidogrel after coronary stent implantation.

To differentiate between immediate and long-term risk, Cox's proportional hazard regression modeling was performed for mortality and readmission for MI from 4 to 30 days and from 30 days to end of follow-up, respectively, subsequent to hospital discharge after coronary stent implantation. The mandated use of clopidogrel during the first 30 days, irrespective of the type of stent implanted, permitted analysis of the combined DES and BMS cohorts to ensure a sufficient number of early occurrences and robustness of coefficients.

Finally, Cox's proportional hazard regression modeling was performed to compare outcomes for patients who delayed filling a first community prescription for clopidogrel >3 days with those who obtained and those who never filled a community prescription for clopidogrel after coronary stenting.

Statistical analysis was performed using SPSS software (version 15; SPSS, Inc., Chicago, IL). Data are presented as mean (SD) or median (interquartile range; IQR). In all cases, 2-tailed tests were performed, and statistical significance was taken at the 5% level.

Results

Of 15 629 patients treated with coronary stents, 3599 received at least 1 DES and 12 030 were treated with BMS alone. The median duration from hospital discharge to patients filling a first prescription for clopidogrel in the community was 1 day (IQR, 1 to 3; Figure 1). In total, 1064 (30%) and 3758 (31%) patients in the DES and BMS groups, respectively, failed to fill a community prescription for clopidogrel within 3 days of hospital discharge. Patients who delayed filling their first prescription for clopidogrel by at least 3 days after hospital discharge were older, more likely to have suffered an ST-elevation MI during the index admission, and had more comorbidity than those filling a prescription within 3 days of discharge (Table 1).

At 2 years after the index procedure, 1055 (7%) patients had died (184 [5%] patients in the DES cohort and 871 [7%] in the BMS cohort), whereas 1004 (6%) were readmitted with MI (228 [6%] patients in the DES cohort and 776 [6%] in the BMS cohort). Clinical outcomes at 2 years, according to the delay in filling a first community prescription for clopidogrel, are shown in Table 2.

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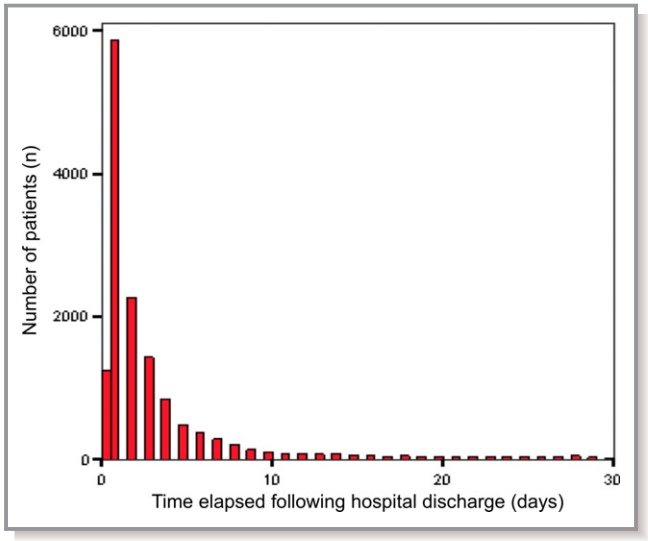

Figure 1. Frequency of delay in filling a first community prescription for clopidogrel in the 30 days after hospital discharge.

Overall Risk

A delay of >3 days in filling a first prescription for clopidogrel after hospital discharge was associated with an increased risk of death, readmission with MI, and the combined endpoint of death and readmission for MI during long-term follow-up, irrespective of the type of stent used (hazard ratio [HR], 2.4; 95% confidence interval [CI], 1.7 to 3.4; HR, 2.0; 95% CI, 1.5 to 2.7; and HR, 2.0; 95% CI, 1.6 to 2.6, respectively, for DES; HR, 2.2; 95% CI, 1.9 to 2.6; HR, 1.8; 95% CI, 1.5 to 2.1; and HR, 2.0; 95% CI, 1.8 to 2.3, respectively, for BMS; Table 3; Figure 2).

When the definition of delay was redefined as >1 day, or >5 days after hospital discharge, patients delaying filling a first prescription for clopidogrel remained at increased risk for both the primary and secondary endpoints, irrespective of the stent type used (Table 3). Patients who never filled a prescription for clopidogrel were at greatest risk of death (HR, 12.0; 95% CI, 7.2 to 19.9; for DES and HR, 5.1; 95% CI, 4.0 to 6.6; for BMS), compared with patients who delayed by more than 3 days (HR, 1.7; 95% CI, 1.2 to 2.5; for DES and HR, 1.8; 95% CI, 1.5 to 2.1; for BMS).

Immediate Versus Long-Term Risk

The excess hazard associated with a delay in filling a first community prescription for clopidogrel was greatest in the immediate period (up to 30 days) after hospital discharge for both mortality (HR, 5.5; 95% CI, 3.5 to 8.6) and recurrent admission for MI (HR, 3.1; 95% CI, 2.4 to 4.0) for all patients undergoing coronary stent implantation (Figure 3). Stent type did not modify this early excess hazard (HR, 6.1; 95% CI, 2.2 to 17.0; and HR 2.6; 95% CI, 1.5 to 4.5, respectively, for DES and HR, 5.3; 95% CI, 3.2 to 8.7; and HR, 3.4; 95% CI, 2.6 to 4.5, respectively, for BMS).

Beyond 30 days after hospital discharge, a delay of >3 days in filling a first clopidogrel prescription remained an independent predictor of death and MI (HR, 2.1; 95% CI, 1.4 to 3.1; and

Table 1. Baseline Demographics According to Delay in Filling First Prescription for Clopidogrel After Hospital Discharge

	DES				BMS			
	All N=3599	≤3 Days (n=2535)	>3 Days (n=1064)	*P* Value*	All (N=12 030)	≤3 days (n=8272)	>3 days (n=3758)	*P* Value*
Age, y	64±11	63±11	65±12	<0.001	65±12	64±12	67±12	<0.001
Male	2591 (72%)	1869 (74%)	722 (68%)	<0.001	8797 (73%)	6152 (74%)	2645 (70%)	<0.001
Acute coronary syndrome	2153 (60%)	1542 (61%)	611 (57%)	0.057	8823 (73%)	5993 (72%)	2830 (75%)	0.001
ST elevation MI	542 (15%)	329 (13%)	213 (20%)	<0.001	3371 (28%)	1911 (23%)	1460 (39%)	<0.001
Previous MI	887 (25%)	561 (23%)	326 (32%)	<0.001	2812 (24%)	1828 (23%)	984 (28%)	<0.001
Hypertension	2271 (65%)	1576 (64%)	695 (68%)	0.035	7070 (61%)	4928 (62%)	2142 (61%)	0.289
Hyperlipidemia	2250 (65%)	1590 (65%)	660 (65%)	0.966	6534 (58%)	4719 (60%)	1815 (53%)	<0.001
Diabetes mellitus	1038 (29%)	674 (27%)	364 (34%)	<0.001	2504 (21%)	1632 (20%)	872 (23%)	<0.001
Cerebrovascular disease	243 (7%)	137 (6%)	106 (10%)	<0.001	911 (8%)	512 (6%)	399 (11%)	<0.001
Previous PCI	383 (11%)	243 (10%)	140 (14%)	0.001	962 (8%)	651 (8%)	311 (9%)	0.222
Previous CABG	400 (11%)	257 (10%)	143 (14%)	0.003	915 (8%)	606 (8%)	309 (9%)	0.029
History of cigarette smoking	2266 (63%)	1581 (62%)	685 (64%)	0.254	8214 (68%)	5639 (68%)	2575 (69%)	0.702
Serum creatinine, μmol/L	99±58	96±47	107±78	<0.001	100±63	95±50	110±85	<0.001

BMS indicates bare metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*Pearson's chi-square or independent samples *t* test, with equal or unequal variance determined by Levine's test (≤3 days versus >3 days).

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Table 2. Delay in Filling a First Clopidogrel Prescription and Unadjusted Clinical Outcomes at 2 Years

	Duration of Delay	
	≤3 Days	>3 Days
Drug-eluting stent cohort (n=3599)	(n=2535)	(n=1064)
Died	73 (3%)	111 (10%)
Readmitted with recurrent myocardial infarction	128 (5%)	100 (9%)
Combined endpoint	192 (8%)	191 (18%)
Bare metal stent cohort (n=12 030)	(n=8272)	(n=3758)
Died	324 (4%)	547 (15%)
Readmitted with recurrent myocardial infarction	394 (7%)	382 (10%)
Combined endpoint	675 (8%)	841 (22%)

HR, 2.0; 95% CI, 1.5 to 2.6, respectively, for DES and HR, 2.0; 95% CI, 1.7 to 2.4; and HR, 1.8; 95% CI, 1.5 to 2.1, respectively, for BMS). We found no effect of a delay in filling a first clopidogrel prescription on deaths resulting from cancer during early (4 to 30 days) or late (>30 days) follow-up.

Discussion

In this province-wide study of real-world clinical practice in Canada, almost 1 in 3 patients undergoing coronary stent implantation experienced a delay in filling their first community prescription for clopidogrel. Consistent with previous work,[4,5] this delay was associated with an increase in mortality and recurrent hospital admission for MI over the study period. Importantly, this delay was associated with a ~3-fold greater excess hazard in the 30 days immediately after hospital discharge than during long-term follow-up out to 2 years.

Premature interruption of clopidogrel has emerged as a major predictor of serious adverse outcomes after coronary stent implantation, including stent thrombosis and death.[3,6,7] The risk of coronary stent thrombosis appears highest in the early period after stent implantation and reduces in the subsequent weeks to months.[8,9] This coincides with a period immediately after hospital discharge when patients often experience difficulties with medication compliance, the most common issue being failure or a delay to fill a discharge prescription.[1] Consistent with these observations, we have demonstrated that a delay in obtaining a first community prescription for clopidogrel is associated with an increased risk of death and recurrent myocardial infarction that is greatest in the period immediately after stent implantation, irrespective of the type of stent implanted.

Our findings complement and extend the results of earlier work, addressing a number of key limitations with previous study design.[4,5] Sheehy et al. reported a significant association between both failure to fill, and a delay in filling, a first community prescription for clopidogrel and mortality after hospital discharge in patients undergoing coronary stent implantation in Quebec, Canada, between 2000 and 2004.[5] The study was limited predominantly to patients treated with BMS because DES were only commercially available in Canada from 2004 onward, follow-up was limited to 12 months, and rates of recurrent myocardial infarction were not examined.[5] Ho et al. demonstrated an association between delay in filling a first clopidogrel prescription and the combined endpoint of death or recurrent myocardial

Table 3. Duration of Delay in Obtaining a First Clopidogrel Prescription and Risk-Adjusted Hazard Ratios (95% confidence interval) for Clinical Outcomes

	Duration of Delay		
	>1 Day*	>3 Days*	>5 Days*
DES			
Death	2.3 (1.6 to 3.4)	2.4 (1.7 to 3.4)	3.0 (2.0 to 4.3)
Readmission with MI	1.7 (1.2 to 2.3)	2.0 (1.5 to 2.7)	1.7 (1.2 to 2.4)
Death/MI	1.8 (1.4 to 2.3)	2.0 (1.6 to 2.6)	1.9 (1.5 to 2.5)
BMS			
Death	2.1 (1.7 to 2.6)	2.2 (1.9 to 2.6)	2.1 (1.7 to 2.5)
Readmission with MI	1.7 (1.4 to 2.1)	1.8 (1.5 to 2.1)	1.7 (1.4 to 2.0)
Death/MI	2.0 (1.7 to 2.3)	2.0 (1.8 to 2.3)	1.9 (1.7 to 2.2)

BMS indicates bare metal stent; DES, drug-eluting stent; MI, myocardial infarction.

*Three separate statistical models using different definitions for duration of delay. The variables examined in the statistical models were age, gender, history of MI, congestive cardiac failure, hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking and cerebrovascular disease, previous percutaneous coronary intervention and coronary artery bypass surgery, serum creatinine, body mass index, urgency of index procedure (acute coronary syndrome and ST segment elevation), hemodynamic instability, cardiogenic shock, and mean stent diameter during index stent implantation.

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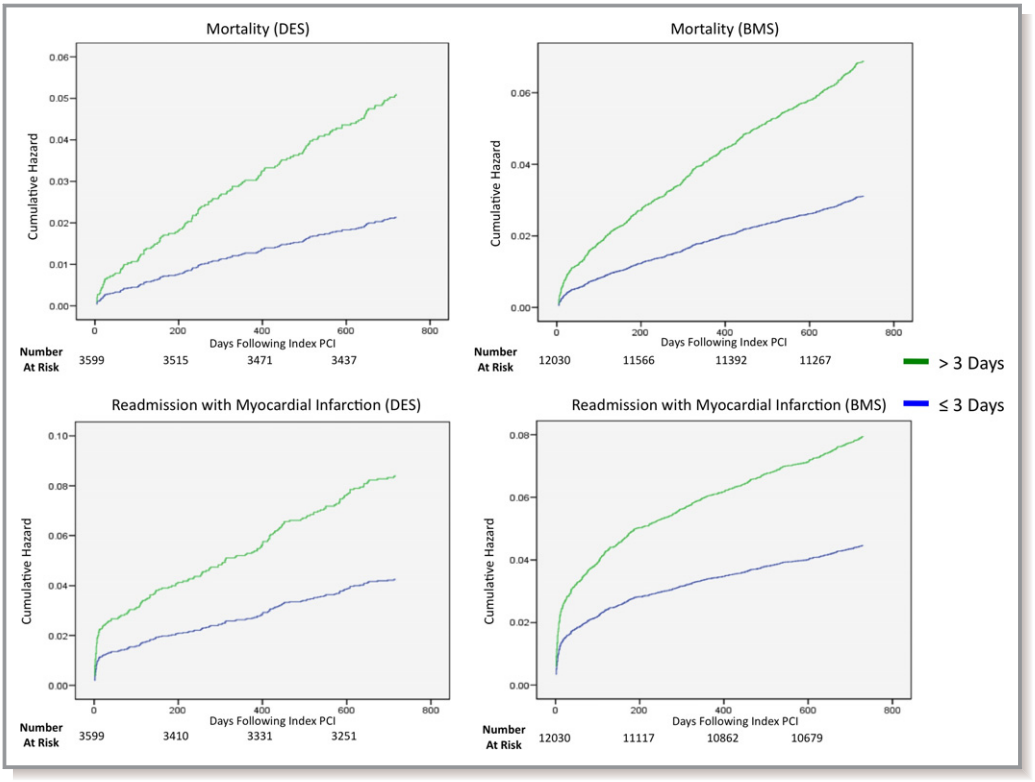

Figure 2. Risk-adjusted mortality (upper panels) and readmission for myocardial infarction (lower panels) for patients treated with drug-eluting (DES) or bare metal (BMS) coronary stents stratified by time to fill a first community prescription for clopidogrel after coronary stent implantation (≤3 days [solid blue line] versus >3 days [solid green line]). BMS indicates bare metal stent; DES, drug-eluting stent; PCI, percutaneous coronary intervention.

infarction (14.2% versus 7.9%; $P<0.001$) in patients treated with DES in 3 North American centers.[4] In contrast to the current study, the population studied was limited to patients on a pharmacy benefit plan, excluded patients treated with BMS, and data on the individual components of the composite endpoint were not presented.[4] In the largest study to date to

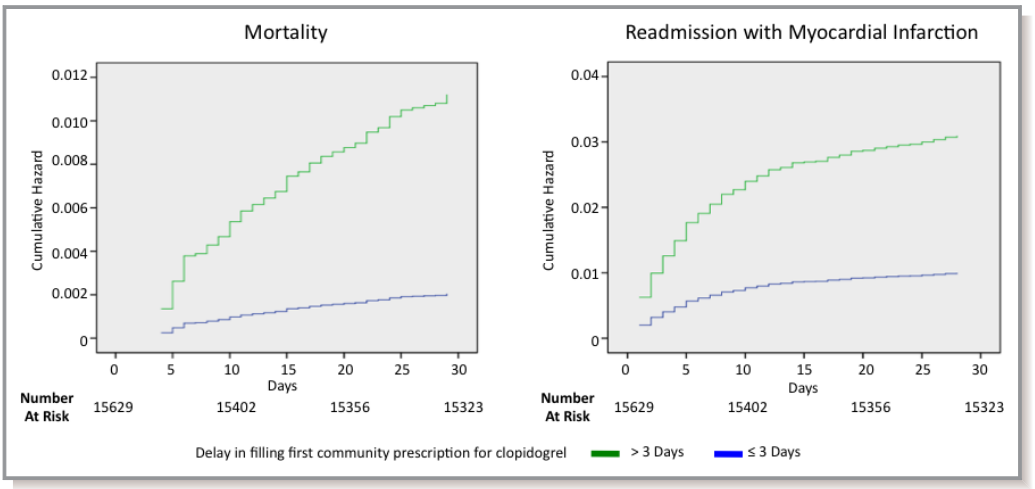

Figure 3. Risk-adjusted mortality (left panel) and readmission for myocardial infarction (right panel) in the immediate period after hospital discharge (4 to 30 days) for patients treated with any coronary stent stratified by time to fill a first community prescription for clopidogrel (≤3 days [solid blue line] versus >3 days [solid green line]).

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address this issue, we included all patients undergoing PCI in BC during the study period, irrespective of stent type, and report on both mortality and readmission for recurrent myocardial infarction, as well as their composite. Moreover, the very large sample size permitted a detailed examination of clinical outcomes based on the period of risk (immediate and long term) and stent type.

In the current study, almost 1 in 3 patients failed to fill a community prescription for clopidogrel within 3 days of hospital discharge. This concerning figure is consistent with previous work.[10,11] In a study of patients discharged from hospital in Ontario, 28% of patients failed to fill a community prescription within 7 days of discharge.[10] Similarly, Kripalani et al. reported that 22% of inner-city patients discharged from hospital after admission with an acute coronary syndrome failed to fill a community prescription within 12 days of hospital discharge.[10]

The factors determining compliance with medication after discharge are complex and were not examined in this study.[12] Previous work has highlighted physician-related prescription discrepancies, including incomplete prescription and omission,[13] older age,[12] income and insurance coverage,[1] number of medications,[1,11,13] and ease of regulatory access to medication.[12] Interventions to enhance discharge planning, educate patients, simplify regulatory hurdles, and ensure early community pharmacy involvement all have the potential to improve early compliance with medications after hospital discharge and, ultimately, clinical outcomes.[11–14] In a recent study of 300 patients treated with DES, planned telephone follow-up at 4 time points after coronary intervention improved patient adherence to oral antiplatelet therapy at 1 year, when compared to standard care.[15] Though encouraging, the effect of this strategy on clinical outcomes remains to be determined.

Limitations

It is important to highlight a number of potential limitations with the current study. This is a retrospective, nonrandomized study with the data and endpoints obtained from provincial pharmacy, hospital, and mortality records. Although the Pharmanet registry collects data on all community pharmacy prescriptions in BC, we cannot exclude the possibility that some patients may have been discharged with a short-term supply of some medication or to a facility where clopidogrel was available without the community pharmacy network (e.g., long-term care). However, both these scenarios would be expected to bias our results toward no difference in clinical outcomes with a delay in obtaining a first clopidogrel prescription.

Although it is possible that the associations between delay in filling a first community prescription for clopidogrel and subsequent clinical outcomes simply reflect differences in other associated health-related factors or behaviors, such as long-term compliance, we do not believe this to be the case. We adjusted for known confounders using multivariate statistical modeling, most of the excess hazard occurred in the period immediately after discharge, and we found no association between a delay in filling a first clopidogrel prescription and cancer-related mortality, suggesting that a delay to obtaining a prescription for clopidogrel was not simply a surrogate for adverse health behavior.

To avoid potential treatment timeline bias, we excluded all patients dying in the early period immediately after hospital discharge. During the study period, all PCIs in BC were performed within 4 high-volume, urban hospitals with similar PCI mortality outcomes. Thus, we do not believe that interhospital bias may have influenced outcomes.

We acknowledge that the data presented relate to patients undergoing coronary stent implantation in the period 2004–2006. Clopidogrel remains a very widely used adjunct after coronary stent implantation and, as such, we believe that our results are relevant to contemporary practice. Whereas it is interesting to note that outcomes during long-term follow-up were similar for patients treated with DES or BMS, the current study was not designed to address this issue. Finally, we do not have data on the concomitant prescription of other cardiovascular medications, such as beta-blockers, and aspirin use was not examined because it was readily available during the study period without prescription.

In summary, we have demonstrated that a delay in filling a first community prescription for clopidogrel after hospital discharge after PCI is common and associated with an increased risk of death and recurrent myocardial infarction, particularly during the period immediately after hospital discharge. Identifying strategies to avoid delays in obtaining a first community prescription for clopidogrel may lead to improved clinical outcomes in this population.

Sources of Funding

This work was supported by the Victoria Heart Institute Foundation (Victoria, British Columbia, Canada).

Disclosures

None.

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