Patterns of use of thienopyridine therapy after percutaneous coronary interventions with drug-eluting stents and bare-metal stents

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Background Twelve months of uninterrupted thienopyridine therapy after drug-eluting stents (DES) implantation was recently recommended, but limited data are available regarding long-term use in clinical practice. The objective of the study was to determine the adherence to thienopyridine therapy after stent implantation, factors associated with suboptimal adherence, and association of suboptimal adherence with mortality.

Methods We evaluated 5,263 older patients (≥65 years) who received DES and 6,081 older patients who received bare-metal stents (BMS) from December 1, 2003, to March 31, 2006, in Ontario, Canada, who were eligible to receive 12 months of thienopyridine at minimal cost.

Results Primary nonadherence was observed among 6.9% in the DES group and 7.1% in the BMS group that did not fill a single prescription of thienopyridine within 1 year of stent implantation. Premature discontinuation occurred in a progressive manner, with 28% in the DES group and 34% in the BMS group discontinuing therapy by 6 months. Low-income patients eligible for a waiver of deductible and dispensing fee were almost 70% more likely to fill their first prescription. For DES patients, primary nonadherence (hazard ratio [HR] 2.68, 95% CI 1.77-4.07), 12-months proportional days covered <80% (HR 2.39, 95% CI 1.67-3.43), and prematurely discontinuing therapy within 6 months (HR 2.64, 95% 1.60-4.35) were associated with an increased risk of death.

Conclusions We found suboptimal patterns of adherence to thienopyridine therapy after DES implantation that was strongly associated with an increased mortality risk. Eliminating any costs for thienopyridine therapy may be an effective strategy to increase medication adherence. (Am Heart J 2009;158:592-598.e1.)
group because the optimal duration of thienopyridine therapy is mainly driven by the use of DES.

Definitions

Primary nonadherence was defined in our study as patients who did not fill any thienopyridine prescriptions after hospital discharge following PCI procedures. We determined the degree of prescription filling in a given interval by evaluating proportion of days covered (PDC). The PDC was calculated by the total number of days supplied divided by the total time for which the patient was at risk and under observation. Based on cut points used in previous studies, patients were subdivided a priori into 2 groups: adherent patients were defined as those with a PDC of $\geq 80\%$ in a given interval, and suboptimal adherent patients were those having a PDC $< 80\%$.

We used the term persistence to represent the continuous use of thienopyridine therapy after PCI. We prespecified discontinuation when a patient failed to refill a prescription within a grace period of 14 days between prescription refills. We chose this relatively stringent definition because several studies have shown that major adverse outcomes may occur at short periods after clopidogrel discontinuation.

Statistical analysis

Because patients were only eligible to receive 12 months of thienopyridine after PCI under the Ontario Drug Benefit program, we assessed primary nonadherence, PDC, and persistence within a year after PCI. The discharge date after the PCI procedure was used as the index date. Multivariable logistic regression models were used to identify predictors of primary nonadherence and suboptimal adherence of thienopyridine therapy, and Cox proportional hazards models were used to identify predictors of thienopyridine persistence with time to discontinuation as the dependent variable of interest. Candidate variables of interest included demographics, cardiac risk factors and medical comorbidities, prior medications, and procedure characteristics as shown in Table 1.

The relationship between different measures of thienopyridine adherence and mortality was assessed using Cox proportional hazards models adjusting for important potential confounders similar to those used to evaluate suboptimal compliance. Time to 1-year mortality after hospital discharge was chosen as the main outcome measure. A series of analyses was undertaken to examine the robustness of our results. In addition to evaluating the relationship between 12-month primary nonadherence and mortality, we also evaluated the relationship at 120 days, consistent with a previous study. For adherence, we first evaluated the relationship between 6- and 12-month PDC for all patients with mortality. We then sequentially excluded (1) patients who never filled a single thienopyridine prescription and (2) patients who died within 6 and 12 months to delineate the influence of deaths within the PDC interval. We also performed a sensitivity analysis using different PDC levels to define adherence (70% and 90%), and our findings were not substantially changed.

For premature discontinuation, we assessed the relationship of thienopyridine discontinuation within 6 months and within 9 months with mortality. We repeated the analysis using thienopyridine therapy as a time-varying exposure that allowed patients to start and stop thienopyridine therapy.
Admission characteristics
Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DES (n = 5263)</th>
<th>BMS (n = 6081)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>73.2 ± 5.8</td>
<td>73.8 ± 6.1</td>
</tr>
<tr>
<td>65-74</td>
<td>2915 (55.4)</td>
<td>3172 (52.2)</td>
</tr>
<tr>
<td>75-84</td>
<td>2083 (39.6)</td>
<td>2495 (41.0)</td>
</tr>
<tr>
<td>≥85</td>
<td>265 (5.0)</td>
<td>414 (6.8)</td>
</tr>
<tr>
<td>Male</td>
<td>3249 (61.7)</td>
<td>3785 (62.2)</td>
</tr>
<tr>
<td>Low income*</td>
<td>1021 (19.4)</td>
<td>1167 (19.2)</td>
</tr>
</tbody>
</table>

Admission characteristics
Recent AMI (same day as procedure) | 336 (6.4) | 885 (14.6) |
Recent AMI (day 1-7) | 1079 (20.5) | 1321 (21.7) |
Recent AMI (day 7-30) | 459 (8.7) | 488 (8.0) |
No prior AMI | 3389 (64.4) | 3387 (55.7) |
CCS angina classification
I or II | 1334 (25.3) | 1488 (24.5) |
III | 1323 (25.3) | 1366 (22.5) |
IV | 2606 (49.5) | 3431 (56.4) |

Cardiac risk factors and comorbidities
Hypertension | 2381 (44.9) | 2750 (45.2) |
Diabetes | 2076 (39.4) | 1672 (27.5) |
Prior coronary artery bypass grafting | 707 (13.4) | 649 (10.7) |
Prior PCs | 389 (7.4) | 293 (4.8) |
Prior stroke or transient ischemic attacks | 215 (4.1) | 276 (4.5) |
Chronic obstructive pulmonary disease | 334 (6.3) | 449 (7.4) |
Heart failure | 441 (8.4) | 428 (7.0) |
Peripheral vascular disease | 483 (9.2) | 507 (8.3) |
Cancer | 66 (1.3) | 94 (1.5) |
Hemodialysis | 65 (1.2) | 45 (0.7) |

Medical therapy before PCI
ACE inhibitor | 2362 (44.9) | 2392 (39.3) |
β-Blocker | 2658 (50.5) | 2645 (43.5) |
Statin | 2859 (54.3) | 2837 (46.7) |

Location of stent implantation
Left main | 143 (2.7) | 56 (0.9) |
Left anterior descending | 2856 (54.3) | 2159 (35.5) |
Left circumflex | 1524 (29.0) | 1583 (26.1) |
Right coronary | 1785 (33.9) | 2639 (43.4) |
Bypass graft (vein or arterial graft) | 267 (5.1) | 332 (5.5) |

Stent characteristics
Multivessel stenting | 1225 (23.3) | 674 (11.1) |
No. of stented vessel, mean ± SD | 1.25 ± 0.48 | 1.12 ± 0.34 |
No. of stents, mean ± SD | 1.81 ± 1.07 | 1.52 ± 0.85 |
Stent size in diameter, mean ± SD | 2.83 ± 0.36 | 3.09 ± 0.48 |
Stent length, mean ± SD | 33.3 ± 20.3 | 24.8 ± 14.9 |

All values presented as number (percentages) unless otherwise specified. AMI, Acute myocardial infarction; CCS, Canadian Cardiovascular Society; ACE, angiotensin-converting enzyme.

*Low-income individuals had annual personal income <$16018 or household income <$24175 and were eligible to have annual deductibles and prescription drug dispensing fees waived.

Thus, this analysis compared the effect of current exposure on the instantaneous hazard of death within 12 months of the index PCI. In all of these analyses, our overall results did not materially change (Appendix A).

This analysis of the study was funded by operating grants by the Canadian Institutes of Health Research (CIHR) (MOP 82747) and a CIHR Team Grant in Cardiovascular Outcomes Research. The authors are solely responsible for the design and conduct of this study; all study analyses, the drafting and editing of the paper, and its final contents.

All analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC). Statistical significance was defined as a 2-tailed P < .05.

Results
Baseline characteristics
After exclusion criteria were applied, our cohort included 5,263 patients who received DES and 6,081 patients who received BMS. Among patients who received DES, the mean age was 73 years, 61.7% were male, and 35.6% had an acute myocardial infarction within the past month (Table I). Annual deductible and dispensing fees were waived for 19.4% of patients who had a low personal or household income (Table I).

Many demographic and clinical characteristics were observed at similar proportions among patients who received DES and BMS. However, a higher prevalence of diabetes, multivessel stenting, and stenting in the left main artery or left anterior descending artery was observed in the DES group; and a higher prevalence of recent acute myocardial infarction in the BMS group was observed (Table I).

Primary nonadherence, adherence, and persistence of thienopyridine therapy
The time course of first thienopyridine prescription filling after DES and BMS is shown in Table II. Most patients in both the DES group (83.8%) and the BMS group (84.3%) filled their first thienopyridine prescription within a week of hospital discharge. However, primary nonadherence was observed in 6.9% of patients who never filled a single prescription of thienopyridine within a year of DES implantation. Similarly, primary nonadherence was observed in 7.1% of patients within a year of BMS implantation.

In the DES group, the mean PDC was 84% within a year of stent implantation; and the proportion of patients who were adherent to thienopyridine (PDC ≥ 80%) was 84.0%
after 6 months and 78.8% after 12 months. In the BMS group, the mean PDC was 79%; and the proportion of patients who were adherent to thienopyridine was 72% after 12 months.

**Figure 1** shows persistence of thienopyridine therapy after DES and BMS implantations. The mean duration of thienopyridine use was 8.4 months in the DES group and 7.8 months in the BMS group. The proportion of patients in the DES group who continued to refill thienopyridine prescriptions was 79.0% at 3 months, 71.9% at 6 months, and 64% at 9 months. In the BMS group, 74.2%, 65.6%, and 58.4% were still receiving thienopyridine therapy at 3, 6, and 9 months, respectively.

**Factors associated with thienopyridine adherence after DES implantation**

Table III details significant factors associated with nonadherence, PDC <80%, and early discontinuation of medications after DES implantation. Age, gender, recent acute myocardial infarction, and location of DES implantation were not significantly associated with medication adherence. Patients with low income status were 68% (odds ratio [OR] 0.32, 95% CI 0.21-0.48) more likely to fill their first thienopyridine prescription. In addition, they were also 25% (OR 0.75, 95% CI 0.63-0.90) more likely to be adherent with a PDC ≥80%. Chronic obstructive pulmonary disease, heart failure, hemodialysis, and a history of cancer were significantly associated with worse medication adherence. The ability to predict compliance was low to modest as shown by the C statistics of 0.664 for predicting primary nonadherence and 0.587 for predicting suboptimal adherence.

**Association of primary nonadherence, adherence, and persistence of thienopyridine with mortality**

The relationship between thienopyridine adherence and mortality after PCI procedures is shown in Table IV. For patients who did not refill any thienopyridine therapy after PCI, a significantly increased hazard of death was observed at 1 year (hazard ratio [HR] 2.68, 95% CI 1.77-4.07) in the DES group and in the BMS group (HR 2.83, 95% CI 2.08-3.85).

We also found that patients who had suboptimal adherence (PDC <80%) have higher hazards of death in the DES and the BMS group. In addition, the hazards of death among the DES group trended higher than the BMS group. For example, PDC <80% at 6 months was associated with an increased hazard of death of 2.67 (95% CI 1.81-3.95) in the DES group compared with the hazard in the BMS group of 1.58 (95% CI 1.17-2.12) (Table IV).

Similarly, premature discontinuation of therapy within 6 months was associated with an increased hazard of death in both the DES (HR 2.64, 95% CI 1.60-4.35) and the BMS groups (HR 2.96, 95% CI 2.05-4.27). We were unable to examine the hazards of death among patients who discontinued therapy at 12 months because of the sharp discontinuation pattern we observed around that time. Increased hazards of death were also observed if thienopyridine was analyzed as a time-varying variable within a year of the index PCI (Table IV).

**Discussion**

The availability of a population-based PCI cohort with complete prescription medication data afforded an
opportunity to gain new insights into the pattern of use of thienopyridine after PCI. Despite strong recommendation from practice guidelines to take thienopyridine therapy in an uninterrupted fashion for 12 months, we found that 6.9% of patients never filled a single prescription after hospital discharge, 1 in 5 patients had suboptimal adherence, and 1 in 4 patients discontinued thienopyridine within 6 months after DES implantation. Importantly, primary nonadherence, suboptimal adherence, and early discontinuation of thienopyridine therapy were all associated with increased mortality after DES implantation.

Our compliance data should be interpreted in the context of an Ontario Drug Benefit program where older patients are subjected to a relatively low annual copayment and dispensing fees. In contrast, the standard Medicare Part D has a much higher initial copayment and a coverage gap commonly described as a "doughnut hole."20,21 It is estimated that an elderly patient is required to pay $3,850 plus premiums for the first $5,451 in drug costs.21 Even under the fairly generous Ontario Drug Benefit program with small copayments, we found that older patients with low incomes and who had complete waivers on copayment deductibles and dispensing fees were 70% more likely to fill the initial thienopyridine prescription. Our data are in accordance with other investigations suggesting that fixed copayment and coinsurance policies can have deleterious impact on medication adherence.22,23 Accordingly, our cohort might be expected to have better medication adherence.

### Table III. Factors associated with primary nonadherence, low PDC, and premature discontinuation of thienopyridine therapy after DES implantation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary nonadherence</th>
<th>Low PDC (≤80%)</th>
<th>Premature discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99 (0.97-1.01)</td>
<td>1.01 (1.00-1.02)</td>
<td>1.00 (1.00-1.01)</td>
</tr>
<tr>
<td>Low income</td>
<td>0.32 (0.21-0.48)</td>
<td>0.75 (0.63-0.90)</td>
<td>0.88 (0.81-0.96)</td>
</tr>
<tr>
<td>Prior PCIs</td>
<td>1.67 (1.18-2.37)</td>
<td>1.69 (1.33-2.14)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1.35 (0.90-2.02)</td>
<td>1.47 (1.14-1.89)</td>
<td>1.16 (1.02-1.32)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.62 (1.13-2.32)</td>
<td>1.56 (1.25-1.97)</td>
<td>1.23 (1.09-1.38)</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>2.78 (1.41-5.47)</td>
<td>1.73 (1.01-2.95)</td>
<td>NS</td>
</tr>
<tr>
<td>Cancer</td>
<td>NS</td>
<td>NS</td>
<td>1.34 (1.03-1.76)</td>
</tr>
</tbody>
</table>

Candidate variables entered into prediction models included demographics, cardiac risk factors and medical comorbidities, prior medications, and procedure characteristics as shown in Table I. Only statistically significant factors are shown. Higher ORs or HRs indicate that a factor was more likely to be associated with worse medication adherence. See text for definitions of primary nonadherence, PDC, and premature discontinuation. NS, Not significant (P > .05).

### Table IV. Relationship between different measures of thienopyridine adherence and mortality after DES and BMS implantation

<table>
<thead>
<tr>
<th>Measures of thienopyridine adherence</th>
<th>DES No. of patients</th>
<th>Crude 1-y mortality rate (%)</th>
<th>HR (95% CI)*</th>
<th>BMS No. of patients</th>
<th>Crude 1-y mortality rate (%)</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary nonadherence: no thienopyridine prescription within 12 m</td>
<td>No 4900</td>
<td>2.9</td>
<td>1 [reference]</td>
<td>5649</td>
<td>4.0</td>
<td>1 [reference]</td>
</tr>
<tr>
<td></td>
<td>Yes 363</td>
<td>8.0</td>
<td>2.68 (1.77-4.07)</td>
<td>432</td>
<td>12.5</td>
<td>2.83 (2.08-3.85)</td>
</tr>
<tr>
<td>6-m PDC‡</td>
<td>≥80% 4425</td>
<td>2.4</td>
<td>1 [reference]</td>
<td>4760</td>
<td>3.4</td>
<td>1 [reference]</td>
</tr>
<tr>
<td></td>
<td>&lt;80% 475</td>
<td>7.4</td>
<td>2.67 (1.81-3.95)</td>
<td>889</td>
<td>7.1</td>
<td>1.58 (1.17-2.12)</td>
</tr>
<tr>
<td>6-m PDC excluding patients who died within 6</td>
<td>≥80% 4373</td>
<td>1.2</td>
<td>1 [reference]</td>
<td>4669</td>
<td>1.5</td>
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<tr>
<td></td>
<td>&lt;80% 452</td>
<td>2.7</td>
<td>1.89 (1.00-3.58)</td>
<td>852</td>
<td>3.1</td>
<td>1.42 (0.89-2.24)</td>
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<tr>
<td>12-m PDC†</td>
<td>≥80% 4146</td>
<td>2.3</td>
<td>1 [reference]</td>
<td>4404</td>
<td>3.4</td>
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<tr>
<td></td>
<td>&lt;80% 754</td>
<td>6.1</td>
<td>2.39 (1.67-3.43)</td>
<td>1245</td>
<td>6.3</td>
<td>1.46 (1.10-1.93)</td>
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<tr>
<td>Premature discontinuation of thienopyridine therapy within 6 m</td>
<td>No 3760</td>
<td>2.3</td>
<td>1 [reference]</td>
<td>3960</td>
<td>3.0</td>
<td>1 [reference]</td>
</tr>
<tr>
<td></td>
<td>Yes 1140</td>
<td>4.6</td>
<td>2.64 (1.60-4.35)</td>
<td>1689</td>
<td>6.4</td>
<td>2.96 (2.05-4.27)</td>
</tr>
<tr>
<td>Thienopyridine therapy as a time-varying covariate within 12 m‡</td>
<td>5263</td>
<td>3.2</td>
<td>3.26 (2.39-4.44)</td>
<td>6081</td>
<td>4.6</td>
<td>3.29 (2.58-4.19)</td>
</tr>
</tbody>
</table>

*Hazard models adjusted for demographics, cardiac risk factors and medical comorbidities, prior medications, and procedure characteristics as shown in Table I. ‡ Excluded patients who did not fill any prescriptions within 12 months of DES or BMS. † Time-varying covariate allowed patients to start and stop thienopyridine therapy. Hazard ratios compared the effect of current exposure on the instantaneous hazard of death within 12 months of the index PCI.
compared with other jurisdictions with limited medication coverage and higher copayments. Policy makers should consider eliminating added costs for thienopyridine therapy as a potential strategy to increase compliance that can possibly lead to improved clinical outcomes after PCI procedures.

Our findings extend current knowledge about the patterns of use of thienopyridine after PCI. The Prospective Registry Evaluating Myocardial Infarction: Events and Recovery study showed that almost 1 in 7 acute myocardial infarction patients was no longer taking thienopyridine therapy at a month. However, this estimate was based on patient self-report and might have been subjected to recall bias. Our findings show that a significant proportion of these patients never filled a single prescription of thienopyridine after hospital discharge with DES, leading to substantially worse long-term mortality outcomes. Even among those who initiated thienopyridine therapy, we found that 1 in 4 patients discontinued thienopyridine within 6 months after DES implantation. The limited ability to predict thienopyridine adherence accurately and the high proportion of patients discontinuing thienopyridine within a year of PCI pose a challenge to physicians on how to ensure medication adherence and safety after DES implantation.

The decision whether to use a DES or BMS may have been made during a moment of clinical urgency. Therefore, we aimed to identify factors associated with medication compliance using characteristics available at the time of the PCI procedures. We found that patients with chronic obstructive pulmonary disease, heart failure, hemodialysis, and a history of cancer were more likely to have worse thienopyridine adherence after DES implantation. This may be explained in part by the fact that patients with these conditions received more concurrent medications and clinicians may be less attentive when managing the necessities of other concurrent conditions because of constraints in time, expertise, and preferences. However, these factors only account for a small to modest amount of the observed variability in medication compliance; and it is unlikely that physicians can definitely select patients at high risk for therapy discontinuation based on these factors above.

Regardless of the measure chosen to evaluate medication compliance, we found almost a 2- to 3-fold increased risk of mortality associated with patients who had suboptimal thienopyridine compliance after DES implantation. Although we did not have information on bleeding, noncardiac surgery, or causes of death, our results were robust under many different sensitivity analyses. In addition, adjustment for major confounding variables did not alter our results. We believe that increased hazards of death are likely mediated through increased cardiovascular risk from inadequate thienopyridine and not merely explained by a “healthy adherer effect”—generally described as the adoption of healthier lifestyles that often accompanies adherence behaviors for several reasons. First, we found a graded response in the association with thienopyridine use and outcomes. Patients who never received a prescription had the worst outcome compared with patients with suboptimal adherence and persistence. Second, our estimates were in line with estimates in other studies. For example, Eisenstein et al reported a doubling of the adjusted rates of myocardial infarction (1.3% vs 2.6%) and death (2.0% vs 5.3%) among patients who withdrew clopidogrel after 6 months in the DES group. Third, the associated increased hazards of poor persistence were slightly higher among the DES group than the BMS group, consistent with the biological plausibility that thienopyridine withdrawal is more important in DES because of delayed endothelialization leading to stent thrombosis at longer term.

Several limitations of our study merit discussion. First, we used prescription for thienopyridine to ascertain medication adherence but were unable to determine whether patients actually took their medication once it was dispensed. Nonetheless, measures of assessing adherence and compliance used in our study were consistent with earlier studies and have been shown to correlate with pill counts. In addition, misclassification bias (ie, classifying nonusers as users) would tend to diminish the association between adherence and outcomes.

Second, although Ontario has recommended 12 months of thienopyridine therapy after PCI since 2003, concerns about stent thrombosis associated with DES and consensus statements recommending long-term thienopyridine therapy did not emerge until later in the study period. Therefore, we may have overestimated the proportion of patients with suboptimal adherence. Accordingly, we performed a sensitivity analysis comparing thienopyridine adherence among patients who received PCI in 2003 to 2004 versus 2005 to 2006. We found increases in PDC (from 82% to 86%) and 9-month persistence (62.2% to 65.8%) but believe that it is unlikely that suboptimal thienopyridine therapy has ceased to exist.

Third, our study was limited to an older cohort >65 years of age because we did not have information on prescription utilization for younger patients. However, the elderly population represents a vulnerable group with high baseline cardiovascular risk and a propensity for premature drug discontinuation. Finally, we were unable to assess factors such as marital status, education, or depression as predictors of thienopyridine adherence or compliance because these data were not included in our data set.

In summary, we found suboptimal thienopyridine compliance after DES implantation, with most patients failing to complete a 12-month course of therapy. Suboptimal medication compliance was associated with substantially greater risk of death after DES placement.
Eliminating any cost for thienopyridine therapy can be considered as a potential strategy to increase medication compliance, which may lead to improved clinical outcomes after DES.

Acknowledgements

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Disclosures

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References

Appendix A

Sensitivity analyses of the relationship between thienopyridine adherence and mortality after DES and BMS implantation

<table>
<thead>
<tr>
<th>Different measures of thienopyridine compliance</th>
<th>DES</th>
<th></th>
<th></th>
<th></th>
<th>BMS</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Crude 1-y mortality rate (%)</td>
<td>HR (95% CI)*</td>
<td></td>
<td>No. of patients</td>
<td>Crude 1-y mortality rate (%)</td>
<td>HR (95% CI)*</td>
<td></td>
</tr>
<tr>
<td>Primary nonadherence: no thienopyridine prescription within 12 m</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>5649</td>
<td>4.00</td>
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<tr>
<td>Yes</td>
<td>363</td>
<td>7.99</td>
<td>2.68 (1.77-4.07)</td>
<td></td>
<td>432</td>
<td>12.50</td>
<td>2.83 (2.08-3.85)</td>
<td></td>
</tr>
<tr>
<td>6-m PDC (no exclusion) ≥80%</td>
<td>4425</td>
<td>2.37</td>
<td>1 [reference]</td>
<td></td>
<td>4760</td>
<td>3.42</td>
<td>1 [reference]</td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>838</td>
<td>7.64</td>
<td>2.88 (2.09-3.96)</td>
<td></td>
<td>1321</td>
<td>8.86</td>
<td>2.09 (1.64-2.67)</td>
<td></td>
</tr>
<tr>
<td>6-m PDC excluding patients who did not fill any thienopyridine ≥80%</td>
<td>4425</td>
<td>2.37</td>
<td>1 [reference]</td>
<td></td>
<td>4669</td>
<td>3.42</td>
<td>1 [reference]</td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>475</td>
<td>7.37</td>
<td>2.67 (1.81-3.95)</td>
<td></td>
<td>889</td>
<td>7.09</td>
<td>1.58 (1.17-2.12)</td>
<td></td>
</tr>
<tr>
<td>6-m PDC excluding patients who did not fill any thienopyridine or who died within 6 m ≥80%</td>
<td>4373</td>
<td>1.21</td>
<td>1 [reference]</td>
<td></td>
<td>4669</td>
<td>1.54</td>
<td>1 [reference]</td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>452</td>
<td>2.65</td>
<td>1.89 (1.00-3.58)</td>
<td></td>
<td>852</td>
<td>3.05</td>
<td>1.42 (0.89-2.44)</td>
<td></td>
</tr>
<tr>
<td>12-m PDC (no exclusion) ≥80%</td>
<td>4146</td>
<td>2.27</td>
<td>1 [reference]</td>
<td></td>
<td>4404</td>
<td>3.36</td>
<td>1 [reference]</td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>1117</td>
<td>6.71</td>
<td>2.69 (1.97-3.67)</td>
<td></td>
<td>1677</td>
<td>7.87</td>
<td>1.90 (1.49-2.42)</td>
<td></td>
</tr>
<tr>
<td>12-m PDC excluding patients who did not fill any thienopyridine ≥80%</td>
<td>4146</td>
<td>2.27</td>
<td>1 [reference]</td>
<td></td>
<td>4404</td>
<td>3.36</td>
<td>1 [reference]</td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>754</td>
<td>6.10</td>
<td>2.39 (1.67-3.43)</td>
<td></td>
<td>1245</td>
<td>6.27</td>
<td>1.46 (1.10-1.93)</td>
<td></td>
</tr>
<tr>
<td>Premature discontinuation of thienopyridine therapy within 6 m No</td>
<td>3760</td>
<td>2.34</td>
<td>1 [reference]</td>
<td></td>
<td>3960</td>
<td>2.98</td>
<td>1 [reference]</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1140</td>
<td>4.56</td>
<td>2.64 (1.60-4.35)</td>
<td></td>
<td>1689</td>
<td>6.39</td>
<td>2.96 (2.05-4.27)</td>
<td></td>
</tr>
<tr>
<td>Thienopyridine therapy as a time-varying covariate within 6 m†</td>
<td>5263</td>
<td>3.21</td>
<td>3.10 (2.07-4.66)</td>
<td></td>
<td>6081</td>
<td>4.60</td>
<td>3.55 (2.61-4.83)</td>
<td></td>
</tr>
<tr>
<td>Thienopyridine therapy as a time-varying covariate within 12 m†</td>
<td>5263</td>
<td>3.21</td>
<td>3.26 (2.39-4.44)</td>
<td></td>
<td>6081</td>
<td>4.60</td>
<td>3.29 (2.58-4.19)</td>
<td></td>
</tr>
</tbody>
</table>

*Hazard models adjusted for demographics, cardiac risk factors and medical comorbidities, prior medications, and procedure characteristics as shown in Table I.
†Time-varying covariate allowed patients to start and stop thienopyridine therapy. Hazard ratios compared the effect of current exposure on the instantaneous hazard of death within 12 months of the index PCI.