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.)

Drug-eluting stents (DES) have been adopted into the routine practice of interventional cardiology worldwide because of their ability to substantially reduce in-stent restenosis and repeated revascularization after percutaneous coronary interventions (PCIs).[1] However, the antirestenosis properties of DES through inhibition of endothelialization also expose patients to a higher long-term risk of stent thrombosis.[2] Clinical studies have consistently shown that premature discontinuation of thienopyridine therapy is the strongest predictor of stent thrombosis after DES implantation.[3-5] Accordingly, recent practice guidelines have been revised to recommend 12 months of uninterrupted thienopyridine therapy after DES implantation to reduce adverse outcomes.[6,7]

Despite the importance of thienopyridine therapy after DES, early data suggest that medication adherence in the short term is suboptimal.[8,9] Spertus et al[9] demonstrated that almost 1 in 7 patients was no longer taking thienopyridine at 30 days after hospital discharge. Whether this was the result of an inability to fill an initial prescription (herein termed *primary nonadherence*) or an inability to continue taking thienopyridine is unknown.[10-12] Furthermore, although several studies found that premature discontinuation of thienopyridine therapy is associated with adverse outcomes after DES implantation,[9,13,14] little is known about the importance of consistent use of thienopyridine. Finally, little data are available regarding the patterns of use of thienopyridine

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at longer term. An improved understanding of these gaps in knowledge may allow us to develop interventions to increase overall adherence with this potentially life-saving medication.

Since the approval of DES in Ontario in 2003, all patients ≥65 years old who were treated with PCI (either with DES or bare-metal stents [BMS]) were recommended to receive 12 months of thienopyridine under the Ontario Drug Benefit plan at minimal cost.[15,16] This policy recommendation afforded a unique opportunity to evaluate 12-month patterns of use of thienopyridine therapy and factors associated with suboptimal medication adherence, and to examine the association of thienopyridine adherence and mortality after PCI at the population level.

Methods

Data sources

The Cardiac Care Network of Ontario (CCNO) collects a prospective clinical registry of all patients undergoing cardiac invasive procedures in Ontario.[15,16] Clinical nurse coordinators at each cardiac center gather information on demographics, clinical characteristics, and relevant comorbid conditions. Details on PCI procedures were added in 2003.[15,16]

The Ontario Drug Benefit prescription claims database was used to determine thienopyridine use (clopidogrel and ticlopidine) after PCI procedures. This database contains information on outpatient prescription drug use and costs for all 1.4 million residents ≥65 years old in Ontario.[17] Residents are subjected to a maximum dispensing fee of $6.11 per prescription after a $100 annual deductible, but this fee is waived for residents whose annual personal income is <$16,018 or when household income is <$24,175.[17]

These databases were linked to the Canadian Institute for Health Information hospital discharge abstract database to identify additional comorbid conditions and to the Ontario Registered Persons Database to ascertain mortality outcomes. Linkages were performed using unique encrypted patient identifiers to protect patient confidentiality, and the need for informed patient consent was waived because participation in the CCNO database is mandatory under Ontario's legislation regarding the privacy of health information. This study was approved by the research ethics board at the Sunnybrook Health Sciences Center.

Study sample

Our study cohort initially consisted of 16,057 patients ≥65 years old who were treated with PCI from December 1, 2003, to March 31, 2006. We excluded patients who had missing information on important prognostic factors (n = 2,131) and patients who had severe comorbidities such as metastatic cancer, dementia, or severe liver disease (n = 116) because of competing risks of death. We also excluded patients who received any thienopyridine prescriptions 90 days before the index PCI (n = 2,899) to limit the influence of prior exposure on postdischarge prescription-filling behaviors. Patients who died during hospitalization (n = 273) were excluded because of the inability to examine long-term medication use. We considered patients who received both DES and BMS in the index PCI as part of the DES 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.[10,18] 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.[12,17,19] Based on cut points used in previous studies,[17] patients were subdivided a priori into 2 groups: *adherent patients* were defined as those with a PDC of ≥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.[11,12] 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.[3,14]

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 interests included demographics, cardiac risk factors and medical comorbidities, prior medications, and procedure characteristics as shown in Table I.

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.[17] 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.

Table I. Baseline characteristics

Characteristic	DES (n = 5263)	BMS (n = 6081)
Demographics		
Age, mean ± SD	73.2 ± 5.8	73.8 ± 6.1
65-74	2915 (55.4)	3172 (52.2)
75-84	2083 (39.6)	2495 (41.0)
≥85	265 (5.0)	414 (6.8)
Male	3249 (61.7)	3785 (62.2)
Low income*	1021 (19.4)	1167 (19.2)
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 before procedure		
I or II	1334 (25.3)	1488 (24.5)
III	1323 (25.1)	1162 (19.1)
IV	2606 (49.5)	3431 (56.4)
Cardiac risk factors and comorbidities		
Hypertension	2381 (45.2)	2750 (45.2)
Diabetes	2076 (39.4)	1672 (27.5)
Prior coronary artery bypass grafting	707 (13.4)	649 (10.7)
Prior PCIs	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)	1585 (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 drugs 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).

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Table II. Time course of first thienopyridine prescription filling after PCI with DES or BMS

Days after hospital discharge	n (%) DES	n (%) BMS
0 (same day)	2941 (55.9)	3526 (58.0)
1	849 (16.1)	940 (15.5)
2-7	621 (11.8)	656 (10.8)
8-14	115 (2.2)	115 (1.9)
15-30	155 (2.9)	173 (2.8)
31-90	137 (2.6)	157 (2.6)
91-120	24 (0.5)	16 (0.3)
121-180	20 (0.4)	26 (0.4)
181-365	38 (0.7)	40 (0.7)
None filled within 365 d	363 (6.9)	432 (7.1)

Thienopyridine therapy included prescriptions for clopidogrel and/or ticlopidine.

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).

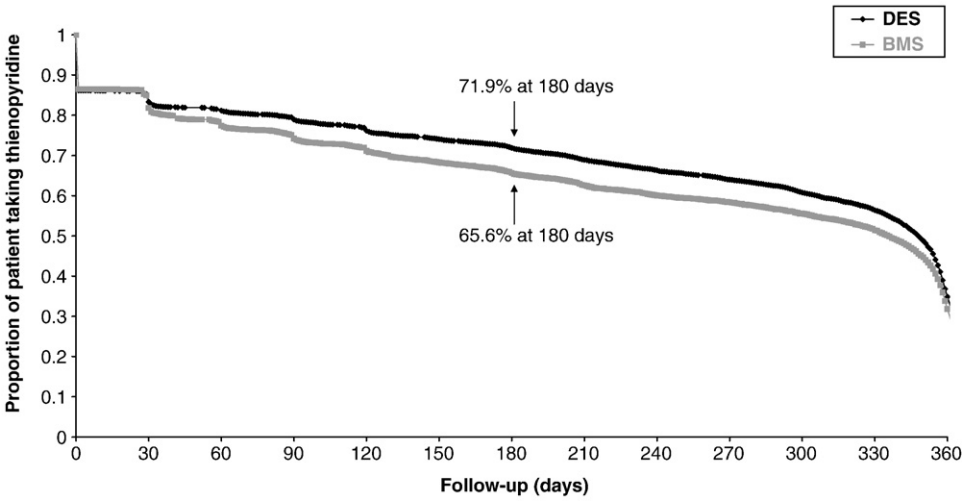
Many demographic and clinical characteristics were observed at similar proportions among patients who received DES and BMS. However, a higher prevalence of diabetes, multivessel stenting, and stenting in the left main artery or left anterior descending artery was observed in the DES group; and a higher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

Figure 1



Pattern of use of thienopyridine after DES or BMS implantation.

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

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

	OR (95% CI)		HR (95% CI)
Characteristic	**Primary nonadherence**	**Low PDC (<80%)**	**Premature discontinuation**
Age	0.99 (0.97-1.01)	1.01 (1.00-1.02)	1.00 (1.00-1.01)
Low income	0.32 (0.21-0.48)	0.75 (0.63-0.90)	0.88 (0.81-0.96)
Prior PCIs	1.67 (1.18-2.37)	1.69 (1.33-2.14)	NS
Chronic obstructive pulmonary disease	1.35 (0.90-2.02)	1.47 (1.14-1.89)	1.16 (1.02-1.32)
Heart failure	1.62 (1.13-2.32)	1.56 (1.25-1.97)	1.23 (1.09-1.38)
Hemodialysis	2.78 (1.41-5.47)	1.73 (1.01-2.95)	NS
Cancer	NS	NS	1.34 (1.03-1.76)

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

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

*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.

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 polices can have deleterious impact on medication adherence.[22,23] Accordingly, our cohort might be expected to have better medication adherence

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.[9] 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.[17] 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.[13,14] For example, Eisenstein et al[13] 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 at 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.[10-12,24] 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,[15,16] concerns about stent thrombosis associated with DES and consensus statements recommending long-term thienopyridine therapy did not emerge until later in the study period.[6,7] 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.[17] 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.

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Appendix A

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

Different measures of thienopyridine compliance	DES			BMS		
	No. of patients	Crude 1-y mortality rate (%)	HR (95% CI)*	No. of patients	Crude 1-y mortality rate (%)	HR (95% CI)*
Primary nonadherence: no thienopyridine prescription within 12 m						
No	4900	2.86	1 [reference]	5649	4.00	1 [reference]
Yes	363	7.99	2.68 (1.77-4.07)	432	12.50	2.83 (2.08-3.85)
6-m PDC (no exclusion)						
≥80%	4425	2.37	1 [reference]	4760	3.42	1 [reference]
<80%	838	7.64	2.88 (2.09-3.96)	1321	8.86	2.09 (1.64-2.67)
6-m PDC excluding patients who did not fill any thienopyridine						
≥80%	4425	2.37	1 [reference]	4669	3.42	1 [reference]
<80%	475	7.37	2.67 (1.81-3.95)	889	7.09	1.58 (1.17-2.12)
6-m PDC excluding patients who did not fill any thienopyridine or who died within 6 m						
≥80%	4373	1.21	1 [reference]	4669	1.54	1 [reference]
<80%	452	2.65	1.89 (1.00-3.58)	852	3.05	1.42 (0.89-2.24)
12-m PDC (no exclusion)						
≥80%	4146	2.27	1 [reference]	4404	3.36	1 [reference]
<80%	1117	6.71	2.69 (1.97-3.67)	1677	7.87	1.90 (1.49-2.42)
12-m PDC excluding patients who did not fill any thienopyridine						
≥80%	4146	2.27	1 [reference]	4404	3.36	1 [reference]
<80%	754	6.10	2.39 (1.67-3.43)	1245	6.27	1.46 (1.10-1.93)
Premature discontinuation of thienopyridine therapy within 6 m						
No	3760	2.34	1 [reference]	3960	2.98	1 [reference]
Yes	1140	4.56	2.64 (1.60-4.35)	1689	6.39	2.96 (2.05-4.27)
Thienopyridine therapy as a time-varying covariate within 6 m†						
	5263	3.21	3.10 (2.07-4.66)	6081	4.60	3.55 (2.61-4.83)
Thienopyridine therapy as a time-varying covariate within 12 m†						
	5263	3.21	3.26 (2.39-4.44)	6081	4.60	3.29 (2.58-4.19)

*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.