Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Circulation 2006;113;2803-2809; originally published online Jun 12, 2006;
DOI: 10.1161/CIRCULATIONAHA.106.618066
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Prevalence, Predictors, and Outcomes of Premature Discontinuation of Thienopyridine Therapy After Drug-Eluting Stent Placement

Results From the PREMIER Registry

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Background—Although drug-eluting stents (DES) significantly reduce restenosis, they require 3 to 6 months of thienopyridine therapy to prevent stent thrombosis. The rate and consequences of prematurely discontinuing thienopyridine therapy after DES placement for acute myocardial infarction (MI) are unknown.

Methods and Results—We used prospectively collected data from a 19-center study of MI patients to examine the prevalence and predictors of thienopyridine discontinuation 30 days after DES treatment. We then compared the mortality and cardiac hospitalization rates for the next 11 months between those who stopped and those who continued thienopyridine therapy. Among 500 DES-treated MI patients who were discharged on thienopyridine therapy, 68 (13.6%) stopped therapy within 30 days. Those who stopped were older, less likely to have completed high school or be married, more likely to avoid health care because of cost, and more likely to have had preexisting cardiovascular disease or anemia at presentation. They were also less likely to have received discharge instructions about their medications or a cardiac rehabilitation referral. Patients who stopped thienopyridine therapy by 30 days were more likely to die during the next 11 months (7.5% versus 0.7%, $P<0.0001$; adjusted hazard ratio=9.0; 95% confidence interval=1.3 to 60.6) and to be rehospitalized (23% versus 14%, $P=0.08$; adjusted hazard ratio=1.5; 95% confidence interval=0.78 to 3.0).

Conclusions—Almost 1 in 7 MI patients who received a DES were no longer taking thienopyridines by 30 days. Prematurely stopping thienopyridine therapy was strongly associated with subsequent mortality. Strategies to improve the use of thienopyridines are needed to optimize the outcomes of MI patients treated with DES. **(*Circulation*. 2006; 113:2803-2809.)**

Key Words: angioplasty ■ anticoagulants ■ mortality ■ revascularization ■ stents

Drug-eluting stents (DES) substantially reduce restenosis compared with bare metal stents and represent a significant advance in percutaneous coronary interventions (PCIs).[1,2] Accordingly, DES have been rapidly adopted into practice and are currently used in the vast majority of PCI procedures. Despite their rapid acceptance, DES are not without limitations. In particular, patients who receive DES (like those who receive conventional bare metal stents) remain at risk of a 1% to 2% incidence of stent thrombosis, which is often associated with devastating consequences.[3,4] Understanding and eliminating mediators of stent thrombosis are thus important goals for optimizing the clinical benefits of DES.

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Two previous studies have examined risk factors for stent thrombosis after DES implantation and have found that premature discontinuation of thienopyridine therapy was the most important risk factor.[5,6] Although the risk of stent thrombosis after bare metal stent implantation decreases rapidly after 2 to 4 weeks,[4,7,8] delayed endothelial coverage

Received February 1, 2006; revision received April 11, 2006; accepted April 20, 2006.

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Guest Editor for this article was David C. Goff, Jr, MD, PhD.

The online-only Data Supplement, which contains a list of participating Cardiovascular Outcomes Research Consortium (CORC) sites and investigators, can be found at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.106.618066/DC1.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.618066**

after DES implantation is thought to prolong the window of vulnerability to stent thrombosis.[3,9] Consequently, recommendations for both the currently approved sirolimus-eluting stent and the paclitaxel-eluting stent include a minimum of 3 to 6 months of thienopyridine therapy, in addition to long-term aspirin use for the patients' underlying coronary disease.

Despite its recognized contribution to stent thrombosis, no previous studies have examined the rates and correlates of thienopyridine discontinuation after DES treatment for a myocardial infarction (MI). Using data from a multicenter, prospective registry of MI patients, we estimated the rate of thienopyridine discontinuation 30 days after DES implantation for acute MI, a time period during which there is universal consensus that thienopyridines ought to be used. We then examined factors associated with discontinuing thienopyridine therapy and determined the association between stopping therapy and adverse clinical outcomes in the next 11 months.

Methods

Patient Population

Between January 1, 2003, and June 28, 2004, 2498 MI patients were prospectively screened and enrolled into the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) study from 19 US centers (see online-only Data Supplement). A detailed description of the PREMIER study has been previously reported.[10] In brief, patients aged ≥18 years who were admitted with prolonged (>20 minutes) signs or symptoms of myocardial ischemia or ischemic ECG changes and biochemical evidence of myocardial necrosis were eligible for participation. Patients who did not present to the enrolling institution were eligible only if they were transferred within 24 hours of symptom onset. Patients who were incarcerated and those who developed elevated cardiac enzymes as a complication of elective coronary revascularization were not eligible. For the purposes of the present study, we restricted our analysis to those patients who underwent PCI, received at least 1 DES during the initial hospitalization, and were discharged on thienopyridine therapy. This population was selected because although there is some debate about the optimal duration of thienopyridine therapy after bare metal stent placement,[7] there is currently universal agreement that DES recipients require >1 month of thienopyridine therapy in addition to the routine use of aspirin. Furthermore, the DES package inserts of the 2 currently approved devices recommend either 3 or 6 months of thienopyridine therapy. Institutional review board approval was obtained at each participating center, and patients gave their signed, informed consent for baseline and follow-up interviews.

Classification of Thienopyridine Use

Although long-term aspirin use is recommended in all post-MI patients[11–13] and has been designated as both an inpatient and an outpatient performance measure of quality,[14] sustained thienopyridine use is not. Given the unique importance of thienopyridines in preventing stent thrombosis, however, we focused on the sustained use of thienopyridines after discharge. Patients were contacted by telephone 1 month (±1 week) after their initial procedure to determine their current medical regimen. At the 30-day interview, patients were asked to collect all of their current medications and to read each medicine to the interviewer. Both ticlopidine and clopidogrel were considered to be thienopyridines for the purpose of these analyses.

Follow-Up

In addition to the 1-month interview, patients were contacted at 6 and 12 months. At each of these interviews, detailed questions about interval hospitalizations since the last contact were administered. Cardiac rehospitalizations were defined as those admissions for MI, heart failure, a cardiac test, or coronary revascularization. A final query of the Social Security Administration Death Master File was conducted in September 2005 to determine vital status through 1 year.

Statistical Analysis

We compared the baseline sociodemographic, clinical, and treatment characteristics of patients who continued to use thienopyridines and those who were no longer taking thienopyridines at 30 days. Between-group differences were assessed with χ^2 tests for categorical variables and t tests for continuous variables.

We used multivariable logistic-regression models to identify predictors of discontinuing thienopyridine therapy. Because the number of events was small for prediction purposes (68 individuals were not taking thienopyridines at 1 month), we sought to minimize overfitting of the model by restricting the selection of variables to those that were a priori identified as relevant based on clinical experience and the previous literature. Candidate variables for the model included sociodemographic factors (age, sex, race, marital status, education level, and avoidance of health care because of cost); a depression screen score (Patient Health Questionnaire-9[15] administered at the baseline interview); preexisting cardiovascular disease (defined as any prior MI, revascularization procedure, stroke, or documented peripheral arterial disease); anemia; use of warfarin; receipt of instructions on taking discharge medications; and referral to cardiac rehabilitation. Past medical history, treatments, and the latter 2 variables were abstracted from patients' charts and discharge summaries. Continuous variables (age and Patient Health Questionnaire-9 score) were modeled as linear terms.

Because there were <10 events per candidate variable, we fitted a penalized logistic-regression model to increase the likelihood that the model would have good predictive accuracy with future data.[16] Odds ratios (ORs), 95% confidence intervals (95% CIs), and probability values are reported for the penalized models. Bootstrap validation of model calibration and c statistics was performed.

We also examined the association of 30-day thienopyridine discontinuation with subsequent clinical outcomes. Crude event rates were estimated by Kaplan-Meier methods, and hazard ratios (HRs) were calculated from Cox proportional-hazards models. Proportional-hazards assumptions were evaluated with the use of Schoenfeld residuals. In addition, because patients were not randomized to thienopyridine discontinuation, we used propensity scores to adjust for differences between those who were and were not taking thienopyridines at 30 days. Propensity scores (ie, the probability of not taking thienopyridines) were estimated from a logistic-regression model predicting the likelihood of discontinuing thienopyridine therapy 30 days after admission, including all variables listed in the Table. The c statistic for the propensity model was 0.78. Propensity scores were calculated for each patient and included in the outcome models as covariates (with the use of restricted cubic splines) to adjust for differences in patient characteristics between those who continued and those who discontinued thienopyridine therapy. Previous studies have used this approach to isolate the effect of a process of care that could not be randomized between groups.[17] To exclude the possibility that discontinuation of thienopyridine therapy was merely a marker for discontinuing other important medications for secondary prevention, we conducted a series of secondary analyses that included variables indicating whether patients had discontinued β-blockers, statins, or angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) that had been prescribed at discharge. With the inclusion of this variable, the effect size of prematurely discontinuing thienopyridine therapy, independent of stopping other important medications, could be defined.

Missing values were present in <1% of the data; these were imputed from expectation maximization methods (which estimate conditional means for missing values, given the observed values of the other covariates) to allow all patients to be retained in the analysis. Probability values <0.05 were considered statistically significant. All analyses were performed with SAS version 9.1 (SAS Institute, Inc, Cary, NC), R version 2.1.0[18], and the R Design library.[19]

Characteristics of Patients Taking and Not Taking Thienopyridines at 30 Days After MI*

Characteristic	Taking Thienopyridines at 30 Days (n=432)	Not Taking Thienopyridines at 30 Days (n=68)	*P*
Demographics			
Age, y	60±12	64±13	0.03
Male	291 (67)	48 (71)	0.60
White	371 (86)	56 (82)	0.44
Latino/Hispanic ethnicity	12 (3)	3 (4)	0.46
Socioeconomic status			
Married	304 (71)	38 (56)	0.01
High school education	378 (89)	48 (73)	<0.001
No healthcare insurance/self-pay	36 (9)	6 (9)	0.92
Avoided health care because of cost	55 (13)	16 (24)	0.02
Depression			
PHQ score	4.9±4.9	5.1±4.0	0.79
Depression screen (PHQ ≥10)	79 (19)	8 (12)	0.16
Medical history			
Preexisting cardiovascular disease	130 (30)	33 (49)	0.003
Chronic heart failure	21 (5)	5 (7)	0.38
Diabetes	96 (22)	18 (27)	0.44
Hypertension	265 (61)	41 (60)	0.87
Hypercholesterolemia	225 (52)	36 (53)	0.90
Chronic renal failure	8 (2)	3 (4)	0.18
Body mass index, kg/m^2	29.9±5.9	29.3±6.1	0.48
Smoked within 30 days of admission	147 (34)	27 (40)	0.69
MI severity			
STEMI	233 (54)	33 (49)	0.41
TIMI risk score, STEMI	3.2±2.1	3.6±2.6	0.28
TIMI risk score, NSTEMI	3.1±1.4	3.4±1.4	0.27
Left ventricular ejection fraction <50%	179 (42)	32 (47)	0.31
Anemia (hematocrit <36% for males, <33% for females)	31 (7)	13 (19)	0.001
Treatments			
Aspirin within 24 hours of arrival	420 (97)	68 (100)	0.39
β-Blocker within 24 hours of arrival	392 (91)	58 (85)	0.16
Aspirin at discharge	415 (96)	65 (96)	0.74
β-Blocker at discharge	399 (92)	64 (94)	0.61
ACEI or ARB for left ventricular dysfunction at discharge	154/179 (86)	29/32 (91)	0.48
Statin therapy at discharge	390 (90)	64 (94)	0.31
Coumadin therapy at discharge	32 (7.4)	5 (7.4)	0.99
Discharge instructions for medication use	410 (95)	60 (88)	0.05
Referral for cardiac rehabilitation	275 (64)	34 (50)	0.03
Baseline health status			
Angina frequency at baseline			0.43
Daily/weekly	60 (14)	11 (16)	
Monthly	155 (36)	19 (28)	
None	216 (50)	38 (56)	

Values are mean±SD or n (%). PHQ indicates Patient Health Questionnaire; STEMI, ST-segment elevation MI; TIMI, Thrombolysis In Myocardial Infarction; and NSTEMI, non-STEMI.

*Some percentages differ from reported frequencies owing to missing data (<1% of data).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Of the 2498 MI patients enrolled in PREMIER, 572 received a DES (DES became available approximately halfway through enrollment). Four patients died in the hospital, and 563 (99.1%) of the remaining survivors were discharged on thienopyridine therapy. By the 30-day assessment, an additional 4 patients had died, 52 (9.3%) were lost to follow-up, 6 were too ill, and 1 refused to be interviewed. Thus, 1-month follow-up data were available for 500 DES patients discharged on thienopyridine therapy, and these patients form the primary cohort for analysis. One month after discharge, 432 patients (86.4%) reported that they were still taking a thienopyridine, whereas 68 (13.6%) were not. Baseline characteristics of the 2 groups are summarized in the Table. Patients no longer taking thienopyridines at 1 month were older (64 versus 60 years, $P=0.03$), less likely to have completed high school (73% versus 89%, $P<0.001$), and less likely to be married (56% versus 71%, $P=0.01$). They were more likely to avoid health care because of cost (24% versus 13%, $P=0.02$), to have had preexisting cardiovascular disease (49% versus 30%, $P=0.003$), and to have had anemia at presentation (19% versus 7%, $P=0.001$).

In addition to patient factors, several institutional processes of care differed between those who continued and those who discontinued thienopyridine therapy. Patients who were not taking a thienopyridine at 30 days were less likely to have been given discharge instructions about their medications (88% versus 95%, $P=0.05$) and were less likely to have been referred to cardiac rehabilitation (50% versus 64%, $P=0.03$).

Figure 1 shows adjusted ORs for discontinuing thienopyridine therapy by 1 month. Not completing high school was the only factor that was independently associated with premature discontinuation of thienopyridine therapy (OR=1.79, 95% CI=1.01 to 3.1). None of the other factors that were associated with thienopyridine discontinuation in the bivariate analyses remained significant in our fully adjusted and penalized model. The bootstrap-validated calibration slope was 0.95, suggesting minimal overfitting, and the model *c* statistic was 0.71, indicating modest discriminatory capacity.

Association Between Discontinuing Thienopyridine Therapy and 1-Year Outcomes

Patients who discontinued thienopyridine therapy within 30 days of their MI had a significantly higher likelihood of dying in the year after their MI. By 12 months after MI, all-cause mortality was 7.5% for patients who discontinued thienopyridine therapy within 30 days compared with 0.7% for those who continued taking thienopyridines (Figure 2, $P<0.0001$). After adjusting for the propensity to discontinue thienopyridine therapy, the mortality HR was 9.02 (95% CI=1.3 to 60.6, $P=0.02$).

The rate of cardiac rehospitalization between 30 days and 1 year also tended to be greater in those who discontinued their thienopyridine therapy. Among those patients who continued taking thienopyridines at 30 days, 14% experienced 1 or more cardiac hospitalizations during follow-up. In contrast, the rate of rehospitalization for a cardiac condition was 23% among those patients who discontinued thienopyridines therapy within 30 days (Figure 3, $P=0.08$). The propensity-adjusted HR for cardiac rehospitalization was 1.5 (95% CI=0.8 to 3.0, $P=0.21$).

To explore whether it was the actual use of thienopyridines or the patient characteristics of those who stopped taking them that was associated with outcome, we compared the outcomes of

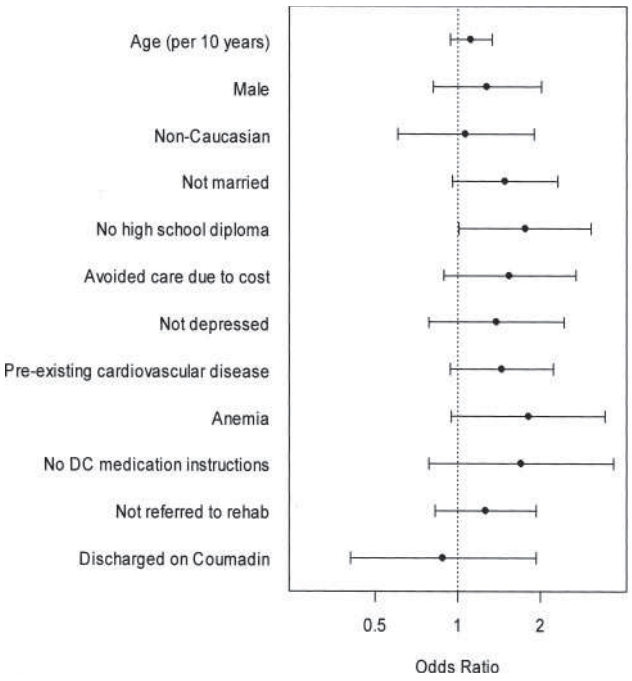

Figure 1. Factors associated with discontinuing thienopyridine therapy at 30 days. The figure shows the fully adjusted, multivariable, logistic-regression model for discontinuing thienopyridine therapy within 30 days of discharge (DC) for an MI treated with a DES. Point estimates are represented by points, and the 95% CIs are shown as bars.

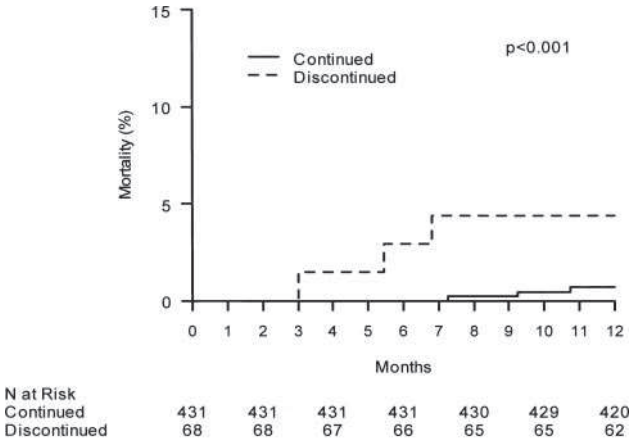

Figure 2. Kaplan-Meier curves of mortality from 1 to 12 months after MI among those who continued and those who discontinued thienopyridine therapy at 1 month after MI. The Kaplan-Meier mortality plots show the rate of death for those who continued thienopyridine therapy (solid line) and those who did not (dashed line). The origin is at the time of the patient's MI, but the lines begin at the 1-month assessment point.

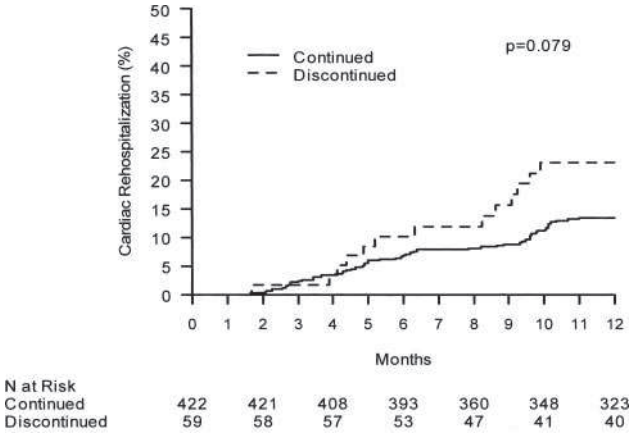

Figure 3. Kaplan-Meier curves of cardiac rehospitalization from 1 to 12 months after their MI among those who continued and those who discontinued thienopyridine therapy at 1 month. The Kaplan-Meier plots show the rates of cardiac hospitalization for those who continued thienopyridine therapy (solid line) and those who did not (dashed line). The origin is at the time of the patients' MI, but the lines begin at the 1-month assessment point.

thienopyridine-using patients in the lowest quintile of propensity to be taking thienopyridines (ie, those most likely to have characteristics similar to those who stopped taking thienopyridines) with those in the highest quintile. No difference in survival was observed ($P=0.67$), but the low number of deaths precluded a definitive conclusion.

Because patients who discontinue taking thienopyridines may also prematurely stop taking other important medications, we sought to define the hazard associated with stopping thienopyridine therapy independent of the effect of stopping β-blockers, statins, or ACEIs/ARBs. Compared with the propensity-adjusted hazard for mortality of 9.0, the hazards after adjusting for prematurely stopping β-blockers, statins, or ACEIs/ARBs were 8.4, 6.6, and 7.8, respectively. Compared with the propensity-adjusted hazard for the combined end point of mortality/rehospitalization of 1.75, the hazards after adjusting for prematurely stopping β-blockers, statins, or ACEIs/ARBs were 2.1, 2.6, and 1.63, respectively.

Discussion

Despite the well-established importance of thienopyridine therapy after DES implantation, we found that nearly 1 in 7 DES-treated patients were not taking this medication 30 days after their MI. Patient education level was the only factor independently associated with thienopyridine discontinuation, but marital status, avoidance of health care because of cost, preexisting cardiovascular disease, and anemia tended to be associated with discontinuation, whereas receipt of discharge instructions and the use of cardiac rehabilitation tended to reduce the likelihood of prematurely discontinuing thienopyridine therapy. Importantly, the rate of death was significantly higher and the frequency of cardiac hospitalizations was almost twice as great in the next 11 months among those who stopped taking thienopyridines compared with those who continued them—findings that were unaltered in risk-adjusted analyses.

These findings extend our current knowledge about the use of DES in contemporary clinical practice. Although case reports,[9,20] registries,[5,6,21–23] and meta-analyses[4,24,25] have all confirmed the benefits of thienopyridines in preventing stent thrombosis after DES implantation, no study has prospectively defined the prevalence and outcomes of discontinuing thienopyridine therapy after DES treatment. Furthermore, most prior studies excluded MI patients—a setting in which the use of DES remains controversial and in which rapid treatment may limit a physician's ability to assess the patient's capacity to adhere to thienopyridine therapy. Although a small randomized trial (STRATEGY)[26] and a recent single-center Dutch registry[23] have demonstrated no excess mortality after DES implantation for an MI, it is not clear whether these findings apply to unselected patients in the US healthcare system. In particular, it is possible that patient selection as well as close follow-up mandated by the study itself may have favorably influenced medication compliance in the STRATEGY trial. Similarly, in the RESEARCH registry, universal access to prescribed medication and follow-up care may have obscured the relationship between DES placement, medication compliance, and outcomes that occurred in the United States. In contrast, our study demonstrates that in contemporary US practice, discontinuation of thienopyridine therapy after DES treatment for an MI is relatively common and is associated with substantial risk of a major cardiovascular event in the next 11 months.

Examining the factors associated with stopping thienopyridines can identify opportunities to improve adherence. In this study, lack of a high school education was associated with a 79% higher risk of stopping treatment. This suggests that additional patient education about the rationale for and importance of continuing thienopyridine treatment may be needed—particularly for patients with less formal education. Supporting the idea that physicians need to be vigilant in explaining the importance of sustained thienopyridine use, previous investigators have found that a strong belief on the part of patients in the necessity of their medications can predict long-term adherence.[27] In fact, the World Health Organization has recently created a manual to assist physicians in educating patients about medication adherence, which may be a useful tool in addressing this need.[28]

Interestingly, patients with preexisting cardiovascular disease were also less likely to be adherent, despite increasing evidence suggesting the benefits of prolonged thienopyridine treatment in this population.[29,30] Whether this reflects patients who, by virtue of being admitted for a new MI, identified themselves as being less compliant with secondary coronary prevention, or another clinical phenomenon will require further study. Nonetheless, patients with established cardiovascular disease before their MI represent a high-risk group for whom additional efforts to ensure adherence appear warranted.

Our study also provides important insight into the role of processes of care in optimizing outcomes for DES recipients. Though not significant in the multivariable models, both documentation of discharge medication instructions and referral to cardiac rehabilitation were associated with a trend toward a reduced likelihood of stopping thienopyridine therapy within 30 days of discharge. If larger studies can confirm the importance of these steps in supporting medication persistence, then these may be important, modifiable targets for future quality improvement efforts.

Despite our efforts to identify factors associated with thienopyridine discontinuation, our regression models could

explain only a modest amount of the observed variability. Thus, it appears that there are not sufficiently strong predictors for discontinuing thienopyridine therapy to allow interventions targeted at specific, high-risk patient subgroups. Rather, the relatively high prevalence of thienopyridine discontinuation suggests that all DES recipients should be targeted for aggressive education to ensure high compliance with adjunctive dual-antiplatelet therapy.

Our study has several important limitations. First, patients had to have survived 30 days after their MI to be included. Accordingly, we cannot comment on the association of persistent thienopyridine use and deaths occurring before 30 days (n=8). A second concern is that some patients who reported taking a thienopyridine may not have been fully compliant with the medication. Nonetheless, self-reported adherence is commonly used because it is simple and inexpensive and does not typically inflate the rate of adherence.[31,32] Moreover, to the extent that such misclassification may have existed, the differences in outcomes that we observed may have underestimated the true magnitude of the effect of noncompliance, because random misclassification of some patients would tend to bias our results toward the null hypothesis.

An additional concern is that ≈9% of patients were lost to follow-up at 30 days, and their use of thienopyridines could not be assessed. These patients were more likely to be younger and depressed and to report that they avoided seeking medical care because of cost. Thus, we may have underestimated the true rates of discontinuing thienopyridine therapy. Furthermore, it should be noted that the adverse prognosis associated with discontinuing thienopyridines may not be explained solely by stent thrombosis. Indeed, it is likely that failure to adhere to prescribed thienopyridines is a marker for overall medical noncompliance, which may have accounted for some of the excess mortality and rehospitalization that we observed. Previous studies[33–35] have suggested that poorer adherence is independently associated with increased mortality and hospitalization in cardiac patients. When we adjusted for the discontinuation of other important post-MI medications, however, only modest changes in the HRs on outcomes for discontinuing thienopyridines were observed. Finally, although we adjusted for numerous characteristics in our propensity model, residual confounding cannot be excluded.

In summary, treatment decisions made at a moment of clinical urgency can impart long-lasting consequences on the long-term care that patients require to optimize their outcomes. In the case of DES implantation for acute MI treatment, it is clear that sustained use of thienopyridines after implantation is required so that the benefits of reduced restenosis are not offset by the catastrophic complication of stent thrombosis. Although previous studies have clarified the importance of continued thienopyridine therapy after DES implantation, this is the first study to define the frequency, predictors, and consequences of discontinuing therapy after an MI. If the benefits of DES with respect to lower rates of restenosis are to be fully realized, physicians will need to identify novel approaches to ensure compliance with this important therapy. Although many strategies exist to support compliance,[32] explicit investigations into the best mechanisms to improve adherence after an MI are urgently needed. One potential approach might be to develop the sustained use of thienopyridines after DES implantation as a performance measure of cardiovascular quality.[36] This could stimulate substantial innovation at the level of individual hospitals to improve patient adherence to care recommendations and allow both patients and payors to realize the full benefits of this promising technology.

Sources of Funding

This work was supported in large part by CV Therapeutics, Palo Alto, Calif. Dr Rumsfeld has received research support and honoraria from Pfizer and is supported by a VA Health Services Advanced Research Career Development Award (ARCD-98-341-2). Dr Cohen has received research grant support from Cordis, Inc; Boston Scientific, Inc; Bristol Myers Squibb; and CV Therapeutics. Drs Decker and Spertus have a research grant from Sanofi-Aventis.

Disclosures

Drs Spertus, Rumsfeld, Krumholz, and Cohen are consultants for CV Therapeutics and United Healthcare. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Although drug-eluting stents (DES) represent a major advance in the field of percutaneous coronary revascularization, their use mandates prolonged dual-antiplatelet therapy with aspirin and thienopyridines. This 19-center study of 500 myocardial infarction patients treated with a DES found that almost 1 in 7 patients stopped taking thienopyridines within 30 days of discharge. Moreover, the rates of death (7.5% versus 0.7%; adjusted hazard ratio=9.0; 95% confidence interval=1.3 to 60.6) and of hospitalization (23% versus 14%, $P=0.08$; adjusted hazard ratio=1.5; 95% confidence interval=0.78 to 3.0) during the next 11 months were significantly higher for patients who discontinued taking thienopyridines compared with those who continued their therapy. Few patient characteristics were independently associated with thienopyridine discontinuation, suggesting that high-risk patients cannot readily be identified and that all patients are at risk of prematurely stopping their dual-antiplatelet therapy. These results highlight the immense challenge in transitioning care from the hospital to the outpatient setting. Although an interventional cardiologist may have the best of intentions in placing a DES to prevent restenosis, new strategies to minimize the risk of patients' stopping their thienopyridine therapy prematurely are needed to optimize the potential benefits of this new technology.