

Use of and inhospital outcomes after early clopidogrel therapy in patients not undergoing an early invasive strategy for treatment of non-ST-segment elevation myocardial infarction: Results from Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines (CRUSADE)

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Background Although current guidelines recommend early initiation of clopidogrel in patients with non-ST-segment elevation myocardial infarction (NSTEMI), the degree to which it has been adopted in clinical practice remains unclear. We sought to determine patterns of early (<24 hours of arrival) clopidogrel use and its association with clinical outcomes in patients with NSTEMI not undergoing early percutaneous intervention (PCI).

Methods Using data from the CRUSADE initiative, after the exclusion of patients who underwent PCI within 24 hours of arrival, we studied trends in early clopidogrel use among 93,045 patients with NSTEMI. Multivariable logistic regression models were used to determine the association between early clopidogrel treatment and inhospital outcomes.

Results A total of 38.6% of the NSTEMI patients not undergoing PCI within 24 hours of arrival received early clopidogrel. Adjusted inhospital mortality rate was lower in the early clopidogrel group compared to the group that did not receive it on admission (odds ratio 0.68, 95% CI 0.61-0.77). The rate of major bleeding in patients not undergoing coronary artery bypass surgery was similar among the groups treated with and without early clopidogrel (9.5% vs 9.5%, $P = .90$).

Conclusions Until recently, up to 50% of NSTEMI patients in contemporary practice in the United States not undergoing PCI within 24 hours of arrival in the United States are not treated according to guideline recommendations. Among a high-risk NSTEMI population not undergoing PCI within 24 hours of arrival, the nonrandomized short-term use of clopidogrel is associated with a lower risk of inhospital mortality without an increased risk of major bleeding. (*Am Heart J* 2008;156:606-12.)

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CRUSADE is funded by Schering-Plough Corporation (Kenilworth, NJ). Bristol-Myers Squibb (New York, NY)/Sanofi-Aventis Pharmaceuticals (Bridgewater, NJ) Partnership

provides additional funding support. Millennium Pharmaceuticals Inc (Boston, MA) also provided funding for this work.

Submitted November 28, 2007; accepted May 14, 2008.

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0002-8703/\$ - see front matter

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doi:10.1016/j.ahj.2008.05.012

Definitive treatment of a ruptured, thrombotic plaque is the hallmark of therapy for non-ST-elevation myocardial infarction (NSTEMI).^{1,2} Although an early invasive management approach results in an improvement in long-term survival and reduction in late myocardial infarction (MI), many NSTEMI patients still do not undergo early percutaneous coronary intervention (PCI).^{3,4} In such patients, pharmacologic therapy, including antithrombotic agents, are used to arrest and limit the thrombotic process.⁵⁻⁷ Benefit of the addition of clopidogrel to standard therapy for NSTEMI was first demonstrated by the CURE trial, but only a small portion of the patients were enrolled in the United States where early invasive management is more commonly used.⁸ Nevertheless, on the basis of the findings from CURE, the 2002 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommended the immediate initiation of clopidogrel for patients with NSTEMI.⁹ However, the degree to which early clopidogrel therapy has been incorporated into clinical practice and its association with clinical outcomes in the United States remain unclear.

The Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) National Quality Improvement Initiative was designed to promote evidence-based treatment of hospitalized patients with NSTEMI and unstable angina.¹⁰ We used the CRUSADE database to examine temporal patterns, factors associated with early clopidogrel therapy and its impact on in-hospital outcomes of patients admitted with NSTEMI not undergoing PCI within 24 hours of arrival.

Methods

Data collection

Data were collected retrospectively from hospitals participating in the CRUSADE initiative using standardized data collection forms and definitions. The institutional review board of each institution approved participation in the CRUSADE initiative. Data collected included demographics, medical history, presentation, medications at home, and within 24 hours, interventional procedures, in-hospital procedures, and events.

Definitions

Early clopidogrel use was defined as clopidogrel administration within the first 24 hours of hospitalization. *Cardiogenic shock* was defined as systolic blood pressure <90 mm Hg for >1 hour believed to be secondary to cardiac dysfunction. *Heart failure* (HF) was defined as exertional dyspnea, orthopnea, rales for more than one third of the lung fields, elevated jugular venous pressure, or pulmonary congestion on chest radiograph believed to be secondary to cardiac dysfunction. Stroke was defined as a new focal neurologic deficit that persisted >24 hours. Postadmission MI was defined as clinical signs and symptoms of a new infarction confirmed by new electrocardiographic changes or (re)elevation of cardiac biomarkers. Major bleeding was defined as hematocrit drop of $\geq 12\%$,

intracranial hemorrhagic stroke, retroperitoneal bleeding, baseline hematocrit of $\geq 28\%$ with red blood cell transfusion, or baseline hematocrit of $<28\%$ with red blood cell transfusion and witnessed bleeding event. To account for use pattern over time, a continuous clopidogrel use trend variable was used. The variable was defined as the year and quarter when patients arrived at a hospital.

Study population

The study population was drawn from 165,498 patients with unstable angina or NSTEMI admitted to 550 hospitals between January 2001 and December 2005. We excluded 20,567 patients who were transferred out; 8,744 with contraindications to early clopidogrel; 1,025 with missing information about early clopidogrel; 1,234 who received no short-term medications within 24 hours; 9,985 patients who only had ischemic ST-segment changes; and 317 patients who died within 24 hours of arrival. We also excluded 30,581 patients who had PCI within 24 hours as they would be expected to receive clopidogrel within 24 hours. The final study population consisted of 93,045 patients with NSTEMI from 545 US hospitals.

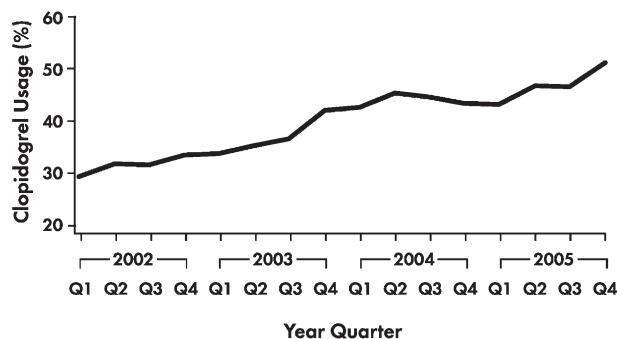
Statistical analysis

For descriptive analyses, comparisons between patients who did and did not receive clopidogrel within 24 hours were made for baseline characteristics, treatment profiles, procedure use, and clinical outcomes using Wilcoxon 2-sample tests for continuous variables and χ^2 tests for categorical variables. Continuous variables were presented as medians with interquartile percentiles, and categorical variables were expressed as percentages.

For early clopidogrel use trend analyses, the use rates in each year and quarter were calculated. Use rate was defined as the number of patients who received early clopidogrel over the total number of eligible patients in each year/quarter. Jonckheere-Terpstra test was used to test for use trend over time.

Because receiving clopidogrel within 24 hours is not randomly assigned in clinical practice, 2 statistical methods were used to adjust for potential confounding in our treatment and outcome comparisons. The first analysis used propensity methods to compare patient subgroups with similar baseline characteristics and thereby similar likelihood for receiving clopidogrel within 24 hours.¹¹ Specifically, 2 multivariable models—one for patients on clopidogrel at home and the other for patients not on clopidogrel at home—were developed to determine patient and hospital factors associated with receiving clopidogrel within 24 hours. The models were constructed using backward variable selection with significance level set at 0.3, using patient baseline characteristics and hospital features as candidate variables. Common covariates that stayed in both models were insurance status, heart rate, hypertension, dyslipidemia, prior MI, PCI, coronary artery bypass surgery (CABG), HF, renal insufficiency, signs of HF at presentation, physician specialty, clopidogrel use trend variable, number of hospital beds, and hospital region. Additional covariates used in the model for patients on clopidogrel at home were age and race. Other covariates used in the model for patients not on clopidogrel at home were body mass index (BMI), systolic blood pressure, family history of coronary artery disease (CAD), diabetes, current/recent smoker, ST-segment changes, and facility type. Patients were categorized into 5 equal groups

Figure 1



Trends in the use of early clopidogrel for patients not undergoing PCI in <24 hours.

ranging from those with lowest propensity (quintile 1) to those with the greatest propensity (quintile 5) for receiving clopidogrel within 24 hours. Categorizing was done separately for patients on clopidogrel at home and patients not on clopidogrel at home. Mortality rates across 5 propensity groups were compared between patients who received short-term clopidogrel and patients who did not receive short-term clopidogrel. For patients with and without home clopidogrel, the odds ratio (OR) of mortality associated with receiving clopidogrel within 24 hours (vs not receiving clopidogrel within 24 hours) was calculated separately controlling for propensity quintiles using Cochran-Mantel-Haenszel statistics.

The secondary analysis used multivariable logistic regression modeling to estimate the independent effects of early clopidogrel. Generalized estimating equation method was used to account for within hospital clustering because patients treated at the same hospital are more likely to have similar outcomes relative to patients in other hospitals (ie, within-center correlation for response).¹² Five different risk adjustment models were created as follows: (1) unadjusted OR; (2) OR adjusted for baseline characteristics (to account for the differences in known patient and physician factors); (3) OR adjusted for baseline characteristics, propensity score (to account for the differences in the likelihood in receiving early clopidogrel), and home clopidogrel (this factor could influence the decision to administer early clopidogrel); (4) OR adjusted for baseline characteristics, propensity score, home clopidogrel, and 4 other early medications (aspirin, heparin, β -blocker, and glycoprotein IIb/IIIa inhibitors) (to account for differences in other guideline-based therapies); and (5) OR adjusted for baseline characteristics, propensity score, home clopidogrel, 4 other early medications, and diagnostic catheterization within 24 hours of arrival (this factor could influence the decision to administer early clopidogrel). Variables included in the baseline characteristics adjustment model were age, sex, race, BMI, heart rate, systolic blood pressure, family history of CAD, hypertension, diabetes, current/recent smoker, dyslipidemia, prior MI, PCI, CABG, HF or stroke, renal insufficiency, ST-segment changes, signs of HF, physician specialty, and clopidogrel use trend variable. Analyses were carried out with the same models as described above to examine the relationship between

Table I. Baseline characteristics of the study population

Characteristic	Clopidogrel (within 24 h) n = 35 880	No clopidogrel (within 24 h) n = 57 165	P
Age (y) *	70 (58, 80)	71 (59, 80)	<.01
BMI (median)	27.6	27.4	<.01
Male sex (%)	59.0	57.1	<.01
White race (%)	80.0	78.5	<.01
Family history of CAD (%)	34.9	31.1	<.01
Medical history			
Hypertension (%)	73.1	71.4	<.01
Diabetes mellitus (%)	36.1	35.0	<.01
Current/recent smoker (%)	25.4	24.0	<.01
Dyslipidemia (%)	53.5	45.0	<.01
Prior MI (%)	36.3	29.6	<.01
Prior PCI (%)	27.7	16.2	<.01
Prior CABG (%)	25.4	19.3	<.01
Prior HF (%)	20.6	22.3	<.01
Prior stroke (%)	13.2	11.5	<.01
Renal insufficiency (%)	16.6	16.4	.41
Presenting features			
Systolic blood pressure (mm Hg) *	144 (124, 166)	144 (123, 166)	<.01
HF (%)	25.2	28.7	<.01
ST depression (%)	30.4	29.2	<.01
Transient ST elevation (%)	5.1	4.5	<.01
Home medications			
Aspirin (%)	50.4	44.0	<.01
β -blocker (%)	45.1	38.4	<.01
Clopidogrel (%)	29.7	4.3	<.01
Hospital characteristics			
Region			
West (%)	9.4	12.6	<.01
Northeast (%)	22.2	22.2	
Midwest (%)	35.0	35.2	
South (%)	33.5	30.1	
Type of hospital			
No services (%)	3.0	4.4	<.01
Catheterization laboratory only (%)	6.2	6.5	
PCI, no surgical support (%)	3.5	4.7	
Surgical support (%)	87.3	84.5	
Teaching hospital			
Nonacademic (%)	68.9	68.7	.59
Academic (%)	31.1	31.3	
Total hospital beds *	383 (275, 536)	397 (266, 536)	<.01

BMI, body mass index; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*Presented as median (25th, 75th percentile).

non-CABG-related major bleeding and early clopidogrel treatment. Odds ratios and 95% CIs were presented for receipt of clopidogrel in 24 hours versus no receipt of clopidogrel in 24 hours to examine its influence on outcomes. A *P* value <.05 was considered significant for all tests. All analyses were performed using SAS software (version 8.2, SAS Institute, Cary, NC).

Results

In the study population, 35,880 (38.6%) patients who did not undergo PCI within 24 hours of arrival received

Table II. Factors associated with receiving early (<24 hours) clopidogrel among patients on home clopidogrel

Variable	Adjusted			
	χ^2	OR	95% CI	P
Prior PCI	42.47	1.37	1.24-1.50	<.01
Prior MI	4.450	1.11	1.01-1.22	.04

Variables that were not significant in the model were age, insurance status, dyslipidemia, hypertension, cardiologist (vs noncardiologist), white race (vs other races), signs of heart failure, renal insufficiency, and prior heart failure. Variables that were significant but not shown in the table were prior CABG, age, heart rate, clopidogrel use trend variable, number of hospital beds, and hospital region.

Table III. Factors associated with receiving early (<24 hours) clopidogrel among patients not on home clopidogrel

Variable	Adjusted			
	χ^2	OR	95% CI	P
Cardiologist (vs noncardiologist)	156.5	1.39	1.32-1.46	<.01
Prior HF	85.80	0.83	0.79-0.86	<.01
Signs of HF at admission	75.05	0.83	0.80-0.87	<.01
Prior PCI	55.54	1.16	1.12-1.21	<.01
Current/recent smoker	32.44	1.10	1.06-1.14	<.01
Dyslipidemia	31.08	1.09	1.06-1.13	<.01
ST depression (vs neither)	29.28	1.07	1.03-1.11	<.01
Transient ST elevation (vs neither)		1.26	1.15-1.37	
Both (vs neither)		1.21	1.07-1.36	
Prior CABG	24.21	1.10	1.06-1.14	<.01
Systolic BP (per 10 mm Hg increase)	22.58	1.01	1.01-1.02	<.01
Renal insufficiency	13.71	0.92	0.88-0.96	<.01
Hypertension	13.65	0.94	0.91-0.97	<.01
No service hospital (vs tertiary)	9.196	0.67	0.50-0.90	.03
Catheterization laboratory only hospital (vs tertiary)		0.84	0.66-1.09	
PCI hospital (vs tertiary)		0.79	0.59-1.07	
Diabetes	8.590	0.95	0.92-0.98	.03
Northeast*	8.215	0.93	0.76-1.13	.04
West*		0.73	0.58-0.92	
Midwest*		0.85	0.70-1.04	
Family history of CAD	7.257	1.05	1.01-1.09	.01

Variables that were not significant in the model were prior MI, body mass index, and number of hospital beds. Variables that were significant in the model but not shown in the table were insurance status, heart rate, and clopidogrel use trend variable.
*Versus south region.

early clopidogrel. Use of early clopidogrel increased from approximately 30% in 2002 to 50% in 2005 ($P < .01$ for trend) (Figure 1). Patients receiving early clopidogrel were younger, more likely male, and more often had prior stroke, MI, PCI, and CABG (Table I). Patients who were on early clopidogrel therapy at home were more likely to receive early clopidogrel therapy if they had a history of MI or PCI (Table II). Patients who were not on home clopidogrel therapy were more likely to receive early clopidogrel if they were primarily taken care of by cardiologists; had a history of smoking, dyslipidemia,

Table IV. Concomitant medications and invasive procedures

Medication/procedure	Clopidogrel (within 24 h)	No clopidogrel (within 24 h)	P
	n = 35 946	n = 57 416	
Aspirin	95.5	90.8	<.01
Heparin	87.7	81.6	<.01
β -Blockers	88.2	80.2	<.01
ACE inhibitors	51.8	43.2	<.01
GP IIb/IIIa inhibitors	34.7	24.9	<.01
Catheterization, overall	77.4	65.5	<.01
Catheterization (<24 h)	23.9	19.4	<.01
PCI, overall	36.6	21.4	<.01
CABG	11.0	16.6	<.01

Data are presented as percentages. ACE, Angiotensin-converting enzyme; GP, glycoprotein.

Table V. Inhospital outcomes

Inhospital events	Clopidogrel (within 24 h)	No clopidogrel (within 24 h)	P
	n = 35 880	n = 57 165	
Death	3.5	5.3	<.01
Postadmission MI	2.3	3.0	<.01
Death or MI	5.4	7.6	<.01
Cardiogenic shock	2.0	2.5	<.01
Heart failure	8.1	11.0	<.01
Stroke	0.7	1.0	<.01
Major bleeding, any	16.0	20.6	<.01
Non-CABG major bleeding	9.5	9.5	.90
CABG major bleeding	83.5	81.8	.11
RBC transfusion, any	14.2	17.7	<.01
Non-CABG RBC transfusion	8.9	10.4	<.01

Data are presented as percentages. RBC, Red blood cell.

prior PCI, or CABG; had higher systolic blood pressure, ST-segment depression, transient ST-segment elevation; or had a family history of CAD but were less likely to receive early clopidogrel if they had hypertension, diabetes, renal insufficiency, and history or new signs of HF at presentation (Table III).

Concomitant medications and invasive procedures

Patients who received early clopidogrel were more likely to be treated with aspirin, heparin, β -blockers, angiotensin-converting enzyme inhibitors, and glycoprotein IIb/IIIa inhibitors within 24 hours (Table IV). They were also more likely to undergo diagnostic catheterization, PCI beyond 24 hours, and less likely to undergo CABG.

Inhospital outcomes

The use of early clopidogrel was associated with a lower risk of MI and inhospital mortality (Table V), a relationship that persisted after risk adjustment (adjusted OR 0.68, 95% CI 0.61-0.77, $P < .01$) (Table VI). Across all

Table VI. Logistic regression model for the association of early clopidogrel with inhospital mortality

Model	OR (95% CI)	P
(1) Unadjusted model	0.66 (0.61-0.71)	<.01
(2) Adjusted for baseline characteristics	0.78 (0.72-0.84)	<.01
(3) Adjusted for baseline characteristics + propensity score + home clopidogrel	0.74 (0.68-0.81)	<.01
(4) Basic adjusted model + propensity score + home clopidogrel + all short-term medications	0.71 (0.63-0.79)	<.01
(5) Basic adjusted model + propensity score + home clopidogrel + all short-term medications + catheterization <24 h	0.68 (0.61-0.77)	<.01

Variables in the model for baseline adjustment—year/quarter; male sex; white race; BMI—under (BMI <18.5), normal (18.5 ≤ BMI < 25), over (25 ≤ BMI < 30), obese (30 ≤ BMI < 40), extremely obese (BMI ≥ 40); age—linear spline with knots at 55, 65, 75, and 85; heart rate—linear spline with knots at 60, 90; systolic BP—linear spline with knots at 120, 140, 160, and 180; family history of CAD; hypertension; diabetes mellitus; current/recent smoker; dyslipidemia; prior MI; prior PCI; prior CABG; prior heart failure; prior stroke; renal insufficiency; ECG—ST depression, ST elevation, both, or neither; signs of heart failure on presentation; short-term medications— aspirin, β-blocker, any heparin, GP IIb/IIIa inhibitors, and catheterization <24 hours.

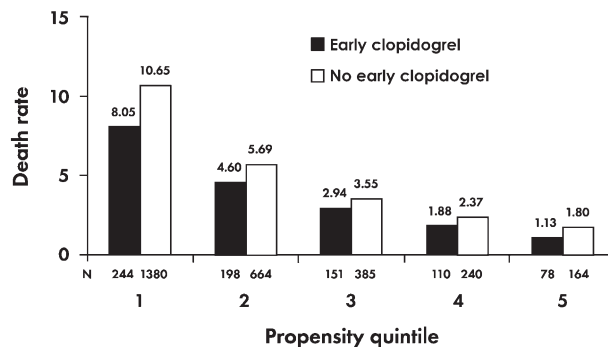
propensity quintiles, the use of early clopidogrel was associated with a lower risk of mortality among patients on home clopidogrel and those not on home clopidogrel (Figures 2 and 3).

The rate of major bleeding in patients not undergoing CABG was similar among the groups treated with and without early clopidogrel (9.5% vs 9.5%, $P = .90$), and the absence of an increased risk of bleeding persisted after risk adjustment (OR 0.92, 95% CI 0.81-1.04, $P = .17$) (Table VII). Analogously, the bleeding rate in CABG patients who received early clopidogrel was similar to those who did not receive clopidogrel (83.5% vs 81.8%, $P = .11$).

Discussion

Our study demonstrates the temporal trends in the short-term use of clopidogrel and its association with inhospital outcomes. The major findings of this retrospective cohort study are 3-fold. First, despite guideline recommendations, approximately half of NSTEMI patients do not receive early clopidogrel therapy. Second, early clopidogrel therapy in patients with NSTEMI not undergoing PCI within the first 24 hours is associated with a lower risk of inhospital mortality. Finally, early clopidogrel therapy is not associated with an increased risk of major bleeding in patients who do not undergo CABG.

The CURE trial demonstrated the benefits of adding clopidogrel to standard therapy for NSTEMI.⁸ In patients who underwent revascularization procedures, the rates of ischemic events were 11.5% versus 13.9% in the placebo group, and in patients who did not undergo revascularization, the composite event rate was 8.1% versus 10.0% in the placebo group. Thus, the benefits of clopidogrel in reducing ischemic events were observed whether or not patients underwent revascularization.

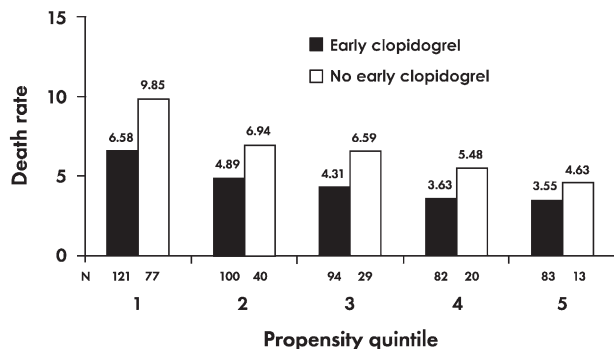
Figure 2

Death rate across propensity quintiles in patients not taking clopidogrel at home.

However, differences exist among the CURE trial and contemporary US patient populations. Specifically, the patient population in CURE tended to be younger (mean age 63 years vs 71 years in this analysis), with fewer diabetics (23% in CURE vs 35.4% in this analysis), less HF (8% in CURE vs 21.7% in this analysis), longer median time to cardiac catheterization (10 days vs 38 hours in this analysis), and a paucity of glycoprotein IIb/IIIa inhibitor use (6.6% in CURE vs 28.7% in this analysis). Our study, while observational, extends these clopidogrel experiences to a contemporary, higher-risk, and more aggressively treated US NSTEMI population. We found that the early use of clopidogrel in the setting of adherence to early guidelines-based therapy is associated with a lower risk of MI and death. The mortality benefit was seen across all propensity quintiles whether patients were on clopidogrel at home or not, suggesting that the early use of clopidogrel has a favorable impact even on patients less likely to be treated with clopidogrel. Factors such as having a cardiologist as the primary caregiver for patients not on clopidogrel at home significantly influenced whether those patients received early clopidogrel. Earlier work has shown that NSTEMI patients primarily cared for by cardiologists were more often younger, had fewer comorbidities, were more likely to receive evidence-based therapies, and had a lower risk of inhospital mortality.¹³ Nevertheless, the mortality difference persisted after adjustment for patient, physician, hospital factors, propensity to receive early clopidogrel, and other concomitant early medications. Our analysis could not precisely account for all factors that may have influenced mortality rates in the study population. The consistency of the results across all propensity quintiles, however, indicates that the benefits of early clopidogrel persist across a broad patient population.

Use of clopidogrel is generally accompanied by an increased bleeding risk in patients undergoing CABG.

Figure 3



Death rate across propensity quintiles in patients on clopidogrel at home.

Post hoc analysis from CURE demonstrated an increased bleeding risk when CABG was performed within 5 days of clopidogrel therapy—a finding that has been validated in a recent study.¹⁴ The widespread early use of clopidogrel poses a potential risk of increased bleeding in patients who require urgent CABG. Prior studies have shown that there is no reliable way to predict patients' need to undergo CABG after NSTEMI.^{15,16} In the United States, most patients who undergo CABG do so within 5 days of the last clopidogrel dose because of a variety of reasons. This practice contributes significantly to the bleeding risk, and the only way to mitigate the risk is to adhere to current guidelines. Given the recent evidence for increased risk of late stent thrombosis after drug-eluting stent implantation,¹⁷ it is possible that the use of CABG for revascularization of multivessel disease in the setting of acute coronary syndromes will increase. Thus, the timing of clopidogrel administration in relation to CABG is particularly relevant. In this present study, we could not determine the interval between clopidogrel administration and CABG or if clopidogrel was given before diagnostic catheterization. This study therefore does not answer the question of whether the timing of clopidogrel has an impact on bleeding risk in patients who undergo CABG, but it shows that there is no increased risk of bleeding in patients who do not undergo CABG.

Study limitations

There are several important limitations to this study. First, as a retrospective analysis, the results are potentially confounded by unmeasured differences between groups. Important clinical characteristics, especially baseline risk status that may have influenced the decision to use clopidogrel were not collected in CRUSADE and could not be accounted for in this analysis. Despite this, we did attempt multiple analytic techniques to adjust for

Table VII. Logistic regression model for the association of early clopidogrel and major bleeding in patients not undergoing CABG

Model	OR (95% CI)	P
(1) Unadjusted model	0.98 (0.90-1.07)	.72
(2) Adjusted for baseline characteristics	1.04 (0.96-1.13)	.37
(3) Adjusted for baseline characteristics + propensity score + home clopidogrel	1.00 (0.91-1.10)	.98
(4) Basic adjusted model + propensity score + home clopidogrel + all short-term medications	0.92 (0.82-1.02)	.12
(5) Basic adjusted model + propensity score + home clopidogrel + all short-term medications + catheterization <24 h	0.92 (0.81-1.04)	.17

Similar variables used for adjustment as in Table VI.

measured confounders and the treatment effect remained significant among treatment groups. Second, neither the location nor the exact time of clopidogrel initiation in relation to in-hospital events was recorded. In addition, the dosing information for more than half of the patients was missing. It is unclear how these factors might have affected outcomes. Third, certain physicians wait until the coronary anatomy is defined before deciding on clopidogrel administration. This timing factor was not collected and not included in the propensity model. This unmeasured factor could have confounded the likelihood of receiving early clopidogrel. Fourth, hospitals involved in the CRUSADE initiative may not be representative of all US hospitals; participation was voluntary and may indicate more interest in adherence to guidelines and implementing quality improvement initiatives. Finally, we were only able to assess in-hospital outcomes following early clopidogrel therapy. The long-term outcomes associated with this therapy remain unknown.

Conclusions

Although the early use of clopidogrel increased significantly, approximately 50% of patients with NSTEMI who did not undergo PCI within 24 hours were still not treated according to ACC/AHA recommendations by the end of this analysis. Treatment with early clopidogrel was associated with a lower risk of in-hospital mortality in this nonrandomized, observational study. Therefore, prospective, randomized clinical trials of early clopidogrel in the setting of early, comprehensive, guideline-based care are needed to understand the impact of this therapy for NSTEMI patients treated in the United States.

We thank David Z. Bynum for his editorial support.

References

- Smith Jr SC, Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention: executive summary. *Circulation* 2001;103:3019-41.

2. Gibson CM, Dotani MI, Murphy SA, et al. Correlates of coronary blood flow before and after percutaneous coronary intervention and their relationship to angiographic and clinical outcomes in the RESTORE trial. *Am Heart J* 2002;144:130-5.
3. FRAGmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:708-15.
4. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.
5. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;319:1105-11.
6. PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;338:1488-97.
7. PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes. The PURSUIT Trial Investigators platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy. *N Engl J Med* 1998;339:436-43.
8. CURE trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
9. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-summary article: a report of the ACC/AHA task force on practice guidelines. *J Am Coll Cardiol* 2002;40:1366-74.
10. Roe MT, Ohman EM, Pollack CV, et al. Changing the model of care for patients with acute coronary syndromes. *Am Heart J* 2003;146:605-12.
11. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal events. *Biometrika* 1983;70:41-55.
12. Liang K, Zeger S. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13-22.
13. Roe MT, Chen AY, Mehta RH, et al. Influence of inpatient service specialty on care process and outcomes for patients with non ST-segment elevation acute coronary syndromes. *Circulation* 2007;116:1153-61.
14. Mehta RH, Roe MT, Mulgund J, et al. Acute clopidogrel use and outcomes in patients with non-ST-segment elevation acute coronary syndromes undergoing coronary artery bypass surgery. *J Am Coll Cardiol* 2006;48:281-6.
15. Sadanandan S, Cannon CP, Gibson CM, et al. A risk score to estimate the likelihood of coronary artery bypass surgery during the index hospitalization among patients with unstable angina and non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2004;44:799-803.
16. Mehta RH, Chen AY, Pollack Jr CV, et al. Challenges in predicting the need for coronary artery bypass grafting at presentation in patients with non-ST-segment elevation acute coronary syndromes. *Am J Cardiol* 2006;98:624-7.
17. BASKET-LATE investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006;48:2584-91.