Clopidogrel to Treat Patients With Non–ST-Segment Elevation Acute Coronary Syndromes After Hospital Discharge

Pierluigi Tricoci, MD; Matthew T. Roe, MD, MHS; Jyotsna Mulgund, MS; L. Kristin Newby, MD, MHS; Sidney C. Smith, Jr, MD; Charles V. Pollack, Jr, MD, MA; Dan J. Fintel, MD; Christopher P. Cannon, MD; Deepak L. Bhatt, MD; W. Brian Gibler, MD; E. Magnus Ohman, MD; Eric D. Peterson, MD, MPH; Robert A. Harrington, MD

Background: Clopidogrel added to aspirin improved outcomes after hospitalization in patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS) in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, regardless of in-hospital treatment approach. The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for treating NSTE ACS thus recommend prescribing clopidogrel plus aspirin at discharge for all patients, not just for those undergoing percutaneous coronary intervention (PCI).

Methods: We studied 61 052 patients with high-risk NSTE ACS (defined as the presence of positive cardiac markers and/or ischemic ST-segment changes) from January 2002 through December 2003 at 461 US hospitals participating in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) Quality Improvement Initiative. We evaluated temporal trends of clopidogrel use at discharge since the ACC/AHA 2002 Guidelines update and examined variables associated with clopidogrel use in patients who did not undergo PCI.

Results: A total of 34 319 patients (56.2%) received clopidogrel when they were discharged from the hospital. Among patients who did not undergo PCI, variables associated with receiving clopidogrel at discharge included prior PCI, coronary artery bypass grafting (CABG), stroke, or myocardial infarction; hypercholesterolemia; elevated cardiac markers; and cardiology inpatient care. By late 2003, 96.3% of patients who underwent PCI received clopidogrel at discharge, compared with 42.8% of patients who did not undergo cardiac catheterization and 23.5% of the patients who underwent CABG, although clopidogrel prescription at discharge increased in each of these treatment groups from 2002 to 2003.

Conclusion: Since release of the ACC/AHA Guidelines recommendations for treatment of NSTE ACS, prescription of clopidogrel at hospital discharge in patients with NSTE ACS who are treated with medical therapy alone and in those who undergo CABG has increased, but most of these patients still do not receive clopidogrel at discharge.

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Author Affiliations: Division of Cardiology, Duke University School of Medicine, and Duke Clinical Research Institute, Durham, NC (Drs Tricoci, Roe, Newby, Peterson, and Harrington and Ms Mulgund); University of North Carolina School of Medicine, Chapel Hill (Drs Smith and Ohman); Pennsylvania Hospital, Philadelphia (Dr Pollack); Northwestern University School of Medicine, Chicago, Ill (Dr Fintel); TIMI Study Group, Brigham and Women's Hospital, Boston, Mass (Dr Cannon); Cleveland Clinic Foundation, Cleveland, Ohio (Dr Bhatt); and University of Cincinnati School of Medicine, Cincinnati, Ohio (Dr Gibler).

Non–ST-segment elevation acute coronary syndromes (NSTE ACS) result in approximately 1.4 million admissions to US hospitals each year.[1] In the past decade, antiplatelet and antithrombotic drugs for the treatment of NSTE ACS that have shown benefits in randomized clinical trials have been incorporated into clinical practice guidelines.[2-5]

Clopidogrel bisulfate inhibits platelet aggregation by irreversibly modifying the platelet adenosine diphosphate receptor and blocking its pro-aggregatory effects.[6] In the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, adverse cardiac events were reduced when clopidogrel was used with aspirin in addition to other standard therapies for up to 9 to 12 months, regardless of the in-hospital treatment approach.[4] Thus, the 2002 revision of the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for treatment of patients with NSTE ACS recommends the use of clopidogrel in addition to aspirin at discharge for 1 month (class IA) and up to 9 months (class IB).[7] However, temporal trends in application of the revised guidelines in routine practice have not been systematically studied.

Using the database from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Quality Improvement Initiative, we sought to characterize the use of clopidogrel to treat patients with NSTE ACS at discharge from the hospital. Specifically, we evaluated prescription of clopidogrel at discharge by in-

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hospital treatment strategy (revascularization vs no revascularization), variables associated with prescription of clopidogrel at discharge, and temporal trends in the prescription of clopidogrel at discharge since the release of the revised guideline recommendations.

METHODS

DATA COLLECTION

Patients included in the national ongoing CRUSADE Quality Improvement Initiative have ischemic symptoms at rest within 24 hours of presentation (lasting for at least 10 minutes) and high-risk characteristics, including ST-segment depression, transient ST-segment elevation, and/or positive cardiac markers (troponin I or T and/or creatine kinase-MB levels greater than the upper limit of the reference range for assays used at participating institutions).[8]

Data were collected in an anonymous fashion (without informed consent) only during the index hospitalization, and the institutional review board of each institution approved participation in the CRUSADE initiative. Data collection included baseline clinical characteristics, use of acute medications (within 24 hours of hospital admission), use and timing of invasive cardiac procedures, laboratory results, in-hospital clinical outcomes, and discharge therapies and interventions. Decisions about the use of medications and invasive procedures were made by the treating physicians. Contraindications to specific therapies given class IA or IB recommendations by the ACC/AHA Guidelines were recorded.

STUDY POPULATION

We included patients treated at 461 hospitals in the United States between January 1, 2002, and December 31, 2003, who survived the hospitalization. From this population, we excluded patients with any contraindications to clopidogrel or aspirin recorded in the data collection form, including active or recent bleeding, allergy, platelet count of less than 100 000/mm^3, gastric ulcer or serious gastrointestinal/genitourinary bleeding, or severe comorbid illness. We also excluded patients who were transferred to other hospitals (because their discharge treatment information was not available), those without discharge medications listed on the data collection form, and patients with missing information on procedures performed during their hospitalization.

STATISTICAL ANALYSIS

For the descriptive analysis, patient baseline demographics, clinical characteristics, care patterns, and in-hospital outcomes of patients who were prescribed clopidogrel at discharge vs those who were not were compared. Median values were used to describe continuous variables, and percentages were reported for categorical variables. The Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables were used to test for differences.

Comparisons of patients who were prescribed clopidogrel at discharge were based on in-hospital treatment approaches and the occurrence of nonfatal clinical events. Patients were stratified by treatment approach: no cardiac catheterization, cardiac catheterization with no revascularization, percutaneous coronary interventions (PCI), and coronary artery bypass grafting (CABG). The group of patients with cardiac catheterization and no subsequent revascularization was further stratified by whether they had insignificant coronary artery disease (≤50% stenosis in all coronary lesions) or significant coronary artery disease (>50% stenosis in at least 1 coronary lesion). The entire group of patients who did not undergo a PCI or CABG was considered to have been medically treated. Temporal changes in discharge patterns during the study period (the first quarter of 2002 through the fourth quarter of 2003) were analyzed according to treatment approach and by primary inpatient service (cardiology and noncardiology). Finally, we compared prescribing clopidogrel at discharge based on the occurrence of in-hospital reinfarction, nonhemorrhagic stroke, and the composite outcome of these events to determine how nonfatal recurrent ischemic events during the hospitalization influence whether clopidogrel is prescribed.

We observed that most patients undergoing PCI received a coronary stent and were very likely to receive clopidogrel at discharge; thus, we analyzed variables associated with receiving clopidogrel *only* in patients who had not undergone PCI. We did not include postadmission events or procedures in the model. We used the generalized estimating equations method.[9] Identification of all baseline patient and hospital characteristics that were likely to have an impact on clopidogrel prescription was based on clinical judgment. Then, we conducted univariate analyses to determine which factors could be expected to have an independent effect on whether clopidogrel was prescribed. We then tested all variables in multivariable analyses and evaluated the results sequentially; we eliminated nonsignificant variables (those the investigator did not consider to be important) and retained significant variables (those the investigator considered to be important). We used the generalized estimating equations method to adjust for correlations among clustered responses (eg, within hospital correlations). The correlation occurs due to factors such as hospital peculiarities or characteristics common to patients visiting that hospital. The technique renders not only unbiased but also more accurate estimates of the parameters associated with the variable of interest and covariates.

Statistical significance was established at $P<.05$ for all tests. We used SAS software (version 8.2; SAS Institute, Cary, NC) to perform all statistical analyses.

RESULTS

STUDY POPULATION AND CHARACTERISTICS OF PATIENTS AND HOSPITALS

The initial population for this analysis consisted of 83 790 patients with high-risk NSTE ACS who were treated at 461 US hospitals between January 1, 2002, and December 31, 2003. We excluded 2302 patients whose information regarding procedure use was missing, 3370 who died during the hospitalization, 10 130 who were transferred to other hospitals, 2631 who did not have reported discharge medications, 811 who had contraindications to clopidogrel, and 3494 who had contraindications to aspirin. The final population for our analysis was thus 61 052 patients.

During the study period, 34 319 patients (56.2%) were discharged with a prescription for clopidogrel and 26 733 (43.8%) were not. Patients receiving clopidogrel at discharge were younger, more frequently male, and more commonly had a history of PCI and CABG, but they less frequently had a history of congestive heart failure or congestive heart failure on presentation (**Table 1**). They also more frequently were admitted to a cardiology inpatient unit and more frequently were treated at hospitals with full capabilities for performing revascularization, including CABG facilities (Table 1).

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Table 1. Clinical Characteristics of Patients and Hospitals*

Characteristic	Did Not Receive Clopidogrel at Discharge (n = 26 733)	Received Clopidogrel at Discharge (n = 34 319)	*P* Value
Age, mean (SD), y†	70 (57-79)	65 (55-76)	<.001
Women	42.9	36.8	<.001
BMI†	27.4 (24.0-31.8)	28.1 (24.8-32.1)	<.001
Nonwhite race	21.4	16.2	<.001
Insurance status			
HMO or private	41.7	49.4	<.001
Medicaid or Medicare	50.7	42.6	
Self-insured or no insurance	6.4	6.8	
Family history of CAD	34.0	39.2	<.001
Hypertension	71.1	68.0	<.001
Diabetes mellitus	34.2	30.8	<.001
Current or recent smoker	25.4	30.5	<.001
Hypercholesterolemia	44.1	52.8	<.001
Medical history			
MI	30.3	30.8	.25
PCI	17.7	26.2	<.001
CABG	19.2	21.9	<.001
CHF	21.4	13.5	<.001
Stroke	10.9	9.3	<.001
Renal insufficiency‡	15.1	10.6	<.001
Presenting characteristics			
Heart rate, beats/min†	84 (71-100)	80 (68-93)	<.001
SBP, mm Hg†	145 (124-166)	146 (126-166)	<.001
ST depression	36.9	36.2	.008
Transient ST elevation	8.9	11.0	<.001
Positive cardiac markers	86.4	90.5	<.001
CHF at presentation	25.5	16.2	<.001
Hospital characteristics			
Procedural capabilities			
No cath laboratory	4.4	1.7	<.001
Cath laboratory only	9.6	5.5	
PCI, no CABG	5.9	3.8	
PCI and CABG	80.0	89.0	
Cardiology care§	52.2	68.5	<.001
Hospital beds†	378 (257-524)	397 (279-526)	<.001
Teaching hospital	30.9	29.4	<.001
Hospital region			
Northeast	22.1	19.2	<.001
South	33.0	31.9	
West	11.8	11.5	
Midwest	33.1	37.4	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CABG, coronary artery bypass grafting; CAD, coronary artery disease; cath, catheterization; CHF, congestive heart failure; HMO, health maintenance organization; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

*All data are given as percentages except where indicated.

†Median values (25th and 75th percentiles).

‡Defined as creatinine levels greater than 2.0 mg/dL (176.8 μmol/L), calculated creatinine clearance less than 30 mL/min (0.501 μL/s), or need for chronic renal dialysis.

§Admitted to a primary cardiology service.

Table 2. Invasive Procedures and Receiving Clopidogrel at Discharge*

Procedure*	Did Not Receive Clopidogrel at Discharge (n = 26 733)	Received Clopidogrel at Discharge (n = 34 319)
Cardiac catheterization	59.9	84.2
Catheterization <24 h	24.9	45.1
PCI	10.0	71.2
PCI, <24 h	4.8	37.7
CABG	26.6	3.9

Abbreviations: CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

*All data are given as percentages; *P*<.001 for all.

Table 3. Concomitant Discharge Medications and Interventions*

Characteristic	Did Not Receive Clopidogrel at Discharge (n = 26 733)	Received Clopidogrel at Discharge (n = 34 319)
Aspirin	86.3	93.3
β-Blocker	79.7	87.6
Lipid-lowering agent†	72.8	85.7
ACE inhibitor‡	56.7	64.5
Diet modification counseling	69.7	76.4
Smoking cessation counseling	62.0	72.6
Cardiac rehabilitation referral	38.6	48.4

Abbreviation: ACE, angiotensin-converting enzyme.

*Among patients without listed contraindications. Data are given as percentages. *P*<.001 for all.

†For patients with history of hypercholesterolemia or measured low-density lipoprotein greater than 100 mg/dL (2.59 μmol/L).

‡For patients with ejection fraction less than 40%, congestive heart failure, diabetes mellitus, or hypertension.

PROCEDURES USED AND CONCOMITANT DISCHARGE TREATMENTS

Patients who received clopidogrel at discharge more frequently underwent cardiac catheterization and PCI but less frequently underwent CABG (**Table 2**). Furthermore, 65.7% of the patients who were prescribed clopidogrel at discharge had received it during the first 24 hours of the hospitalization, whereas 15.8% of the patients who were not prescribed clopidogrel at discharge received it during the first 24 hours. Of the patients who underwent catheterization, 7.6% of those who received clopidogrel at discharge had insignificant coronary artery disease compared with 21.4% of those who did not receive it on discharge.

Patients who received clopidogrel at discharge more frequently were treated with other discharge medications recommended by the ACC/AHA Guidelines (**Table 3**). These patients also more frequently received secondary prevention interventions at discharge, such as counseling for smoking cessation and diet modification and referral for cardiac rehabilitation.

The variables most strongly associated with receiving clopidogrel at discharge in patients who had not undergone PCI included a prior PCI, CABG, stroke or myocardial infarction; hypercholesterolemia; elevated cardiac markers; slower heart rate; and cardiology inpatient care (**Table 4**). The receiver operating characteristic, also known as the c-index, of the model was 0.62.

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Table 4. Factors Associated With Receiving Clopidogrel at Discharge in Patients Who Did Not Undergo PCI*

Variable	χ^2	Adjusted OR (95% CI)	*P* Value
History of PCI	154.9	1.55 (1.45-1.66)	<.001
History of CABG	137.4	1.41 (1.33-1.49)	<.001
Hypercholesterolemia	77.4	1.25 (1.19-1.31)	<.001
History of stroke	72.5	1.33 (1.25-1.42)	<.001
Elevated cardiac markers	70.1	1.44 (1.32-1.57)	<.001
History of MI	53.7	1.21 (1.15-1.28)	<.001
Heart rate (per 10-min increase)	41.0	0.97 (0.96-0.98)	<.001
Cardiology care (vs noncardiology)	26.4	1.18 (1.11-1.26)	<.001
SBP (per 10–mm Hg increase)	19.7	1.02 (1.01-1.02)	<.001
Men (vs women)	18.0	0.90 (0.86-0.94)	<.001
Age (per 10-y increase)	13.5	1.04 (1.02-1.05)	<.001
Catheterization laboratory only (vs CABG†)	11.8	1.33 (1.14-1.56)	.008
No catheterization laboratory (vs CABG†)		0.90 (0.72-1.13)	
PCI only (vs CABG†)		0.98 (0.82-1.18)	
Signs of CHF	8.7	0.92 (0.88-0.97)	.003
White race (vs other)	7.6	1.10 (1.03-1.18)	.006
Renal insufficiency	5.0	1.07 (1.01-1.14)	.02
History of CHF	3.9	0.94 (0.88-1.00)	.049

Abbreviations: CABG, coronary artery bypass grafting; CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
*Model c-index, 0.62.
†Hospitals with both CABG and PCI services.

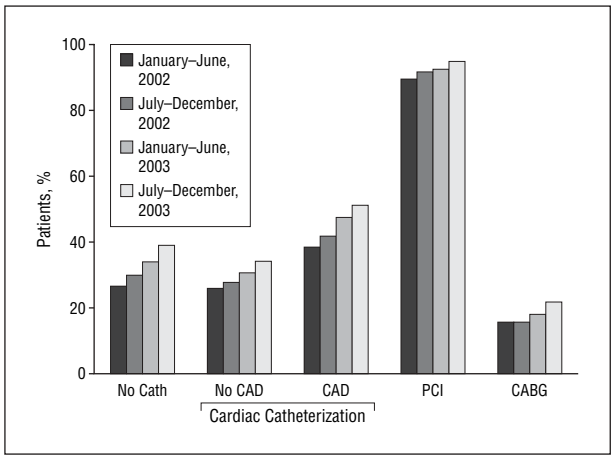

Figure 1. Temporal trends in prescribing clopidogrel at discharge over the 2-year study period by in-hospital treatment approach. Patients who underwent catheterization but who did not undergo revascularization are further distinguished as having insignificant CAD (no CAD; all coronary lesions ≤50%) or significant CAD (CAD; at least 1 coronary lesion >50%). CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; cath, catheterization; and PCI, percutaneous coronary intervention.

NONFATAL IN-HOSPITAL OUTCOMES

Reinfarction occurred in 2.4% of patients, hemorrhagic stroke in 0.5%, and the composite of reinfarction or nonhemorrhagic stroke in 2.8% of patients. Among those with reinfarction, 58.2% received clopidogrel on discharge and 41.8% did not. Among patients with nonhemorrhagic stroke, 42.7% received clopidogrel on discharge and 57.3% did not. Among patients with the composite of reinfarction or nonhemorrhagic stroke, 55.8% received clopidogrel on discharge and 44.2% did not.

TEMPORAL TRENDS IN DISCHARGE CLOPIDOGREL USE

By the last quarter of 2003, receiving clopidogrel at discharge had increased in each of the groups stratified by in-hospital treatment approach (**Figure 1**). However, fewer than 25% of patients who underwent CABG and fewer than 50% of patients who did not undergo catheterization received clopidogrel at discharge by the end of the study period. Use patterns and temporal trends in prescribing clopidogrel at discharge were similar among patients who were treated in cardiology and noncardiology inpatient services (**Figure 2**).

COMMENT

During the 2-year period of this study, we found that most patients who had not undergone PCI did not receive clopidogrel at discharge. However, encouraging trends for increased prescribing of clopidogrel at discharge were shown during the period, indicating an incremental adoption of the updated ACC/AHA Guidelines recommendations for patients with NSTE ACS.

VARIABLES ASSOCIATED WITH USE OF CLOPIDOGREL AT DISCHARGE

Prescription of clopidogrel at hospital discharge in the overall study population was concentrated in patients who underwent PCI and tended to be younger male patients with lower-risk features, but these characteristics define a low-risk population of patients with NSTE ACS who are more likely to undergo invasive procedures and PCI with expected widespread use of clopidogrel.[10] In the population who did not undergo PCI, however, variables indicating higher baseline risk and more extensive vascular disease (ie, prior revascularization procedures or stroke, hypercholesterolemia) and possible aspirin resistance (prior myocardial infarction with expected chronic aspirin use) were the variables most strongly associated with receiving clopidogrel at discharge. Clinicians may perceive that patients with NSTE ACS who have known vascular disease and those receiving ongoing antiplatelet therapy may have an enhanced benefit from a dual antiplatelet therapy. However, other high-risk features that correlate with left ventricular dysfunction, such as faster heart rate, lower blood pressure, and signs of congestive heart failure on admission, were negatively associated with receiving clopidogrel at discharge. These observed treatment patterns are similar to other studies that have documented treatment disparities in patients with ACS and concomitant heart failure.[11,12] Furthermore, even though cardiologists more frequently use evidence-based therapies for patients with acute myocardial infarction, patterns and trends for receiving clopidogrel at discharge were similar for patients who had received cardiology and noncardiology inpatient services.[13,14] Nonetheless, the c-index for the model identifying variables associated with prescribing clopido-

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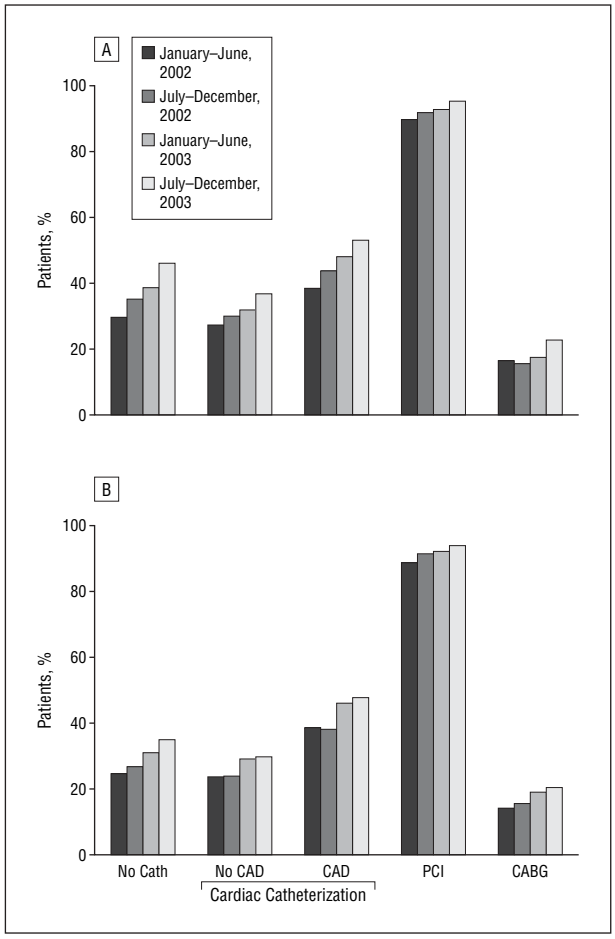

Figure 2. Temporal trends in prescribing clopidogrel over the 2-year study period by an in-hospital treatment approach according to primary inpatient service, cardiology (A) and noncardiology (B). Patients who underwent catheterization but who did not undergo revascularization are further distinguished as having insignificant CAD (no CAD; all coronary lesions, ≤50%) or significant CAD (CAD; at least 1 coronary lesion, >50%). CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; cath, catheterization; and PCI, percutaneous coronary intervention.

grel at discharge was low, which could indicate that factors influencing the decision to prescribe clopidogrel at discharge are difficult to ascertain and may reflect confusion in routine clinical practice regarding the indications for prescribing postdischarge clopidogrel for patients with NSTE ACS who do not undergo PCI.

IMPACT OF LONG-TERM CLOPIDOGREL USE

The benefits of long-term clopidogrel use were demonstrated in the large-scale CURE trial, which showed a 20% relative risk reduction in the composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke when patients received aspirin plus clopidogrel for 9 to 12 months after an episode of NSTE ACS.[4] The benefits of clopidogrel were established with a low overall use of invasive procedures (only 44% of patients underwent cardiac catheterization and 21% underwent PCI), but the treatment effect of clopidogrel was consistent across treatment strategies, including medical treatment, PCI, and CABG.[15] In addition, the Clopidogrel for the Reduction of Events During Observation (CREDO) trial[16] established that clopidogrel administered for up to 12 months after placement of a bare-metal stent reduced the risk of long-term recurrent ischemic events. In both the CREDO and CURE trials, the impact of clopidogrel was consistent in reducing long-term recurrent ischemic events.[4,16] Clopidogrel appears to provide added benefits to other standard discharge medications in patients with NSTE ACS, regardless of treatment strategy and revascularization approach. However, we observed temporal increases in clopidogrel use after discharge in patients with insignificant CAD, but the use of long-term, dual antiplatelet therapy in this population has not been studied carefully and thus may not be justified.[17]

BARRIERS TO DISCHARGE CLOPIDOGREL USE

Multifactorial issues seem to limit the use of clopidogrel to treat patients who have not undergone PCI. First, the high costs of long-term clopidogrel use, which are usually shifted directly to patients (who have increasingly limited prescription drug coverage), may have a significant impact on physicians' decisions at hospital discharge.[18] Second, the lack of widespread knowledge among some physicians about the long-term benefits of clopidogrel after an episode of ACS in patients who have not undergone PCI and confusion about the guideline recommendations for prescribing clopidogrel for patients undergoing CABG are likely obstacles to prescribing clopidogrel at discharge. The ACC/AHA Guidelines for patients with NSTE ACS recommend withholding clopidogrel for 5 to 7 days before a patient undergoes CABG, given the increased risk of bleeding found in the CURE trial when CABG was performed less than 5 days after clopidogrel was discontinued.[7] Even though this recommendation does not address use of clopidogrel after discharge, when the bleeding risks would be expected to be minimized after recovery from the CABG, there may be uncertainty among cardiac surgeons about guideline recommendations for prescribing clopidogrel after a patient undergoes a CABG (which are not clearly stated), as well as other evidence-based medications.[19] Finally, because prescribing clopidogrel at discharge was associated with higher uptake of other guideline recommendations, this practice may be a marker of hospitals with a greater commitment to quality improvement and better systems in place to ensure consistent, evidence-based discharge care.

During the observation period of our study (January 2002 to December 2003), hospitals participating in the CRUSADE initiative received quarterly data feedback and were offered quality improvement tools such as discharge checklists and educational programs to improve their understanding of the guidelines revisions. However, the relative temporal change in prescribing clopidogrel at discharge was modest over the study period. Therefore, novel approaches to quality improvement are needed to overcome the barriers that limit the use of clopidogrel and promote widespread adherence to guidelines for treating patients with NSTE ACS at all hospitals.[5]

STUDY LIMITATIONS

This study has certain limitations. First, data were collected by retrospective chart review, and valid reasons for not prescribing clopidogrel at discharge may not have

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been well documented. Second, hospitals involved in the CRUSADE initiative may not be representative of all US hospitals because participation is voluntary, and hospitals that agreed to participate may be more interested in adherence to guidelines and more receptive to quality improvement initiatives. Third, we could not ascertain when clopidogrel was prescribed at discharge for patients transferred from community hospitals to tertiary hospitals (most likely for invasive procedures) because current privacy regulations prohibit anonymous data collection after interhospital discharge. Finally, information on postdischarge medication compliance could not be collected in the CRUSADE initiative, so the impact and duration of long-term clopidogrel use was not assessed.

In conclusion, receiving clopidogrel at discharge for patients with NSTE ACS is concentrated in those undergoing PCI and is prescribed for fewer than half of patients who are medically treated despite guideline recommendations for consistent use of clopidogrel at discharge regardless of the in-hospital treatment approach. Because adherence to comprehensive guidelines at hospital discharge is associated with lower long-term mortality in patients with NSTE ACS, further investigation into the barriers that limit the prescription of clopidogrel at discharge and the key factors for successful quality improvement interventions at hospitals is needed to improve the treatment at discharge of patients with NSTE ACS.[5,20,21]

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Correspondence: Pierluigi Tricoci, MD, Duke Clinical Research Institute, Desk 7583, 2400 Pratt St, Durham, NC 27705 (trico001@dcri.duke.edu).
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