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Acute Clopidogrel Use and Outcomes in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes Undergoing Coronary Artery Bypass Surgery

Rajendra H. Mehta, MD, MS, FACC,* Matthew T. Roe, MD, MHS, FACC,* Jyotsna Mulgund, MS,* E. Magnus Ohman, MD, FACC,† Christopher P. Cannon, MD, FACC,‡ W. Brian Gibler, MD,§ Charles V. Pollack, Jr, MD, MA,‖ Sidney C. Smith, Jr, MD, FACC,† T. Bruce Ferguson, MD,¶ Eric D. Peterson, MD, MPH, FACC*

Durham and Chapel Hill, North Carolina; Boston, Massachusetts; Cincinnati, Ohio; Philadelphia, Pennsylvania; and New Orleans, Louisiana

OBJECTIVES We sought to characterize patterns of clopidogrel use before coronary artery bypass grafting (CABG) and examine the drug's impact on risks for postoperative transfusions among patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS).

BACKGROUND Adherence in community practice to American College of Cardiology/American Heart Association guidelines for clopidogrel use among NSTE ACS patients has not been previously characterized.

METHODS We evaluated 2,858 NSTE ACS patients undergoing CABG at 264 hospitals participating in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) Initiative. We examined the patterns of acute clopidogrel therapy and its association with bleeding risks among those having "early" CABG ≤5 days and again among those having "late" surgery >5 days after catheterization.

RESULTS Within 24 h of admission, 852 patients (30%) received clopidogrel. In contrast to national guidelines, 87% of clopidogrel-treated patients underwent CABG ≤5 days after treatment. Among those receiving CABG within ≤5 days of last treatment, the use of clopidogrel was associated with a significant increase in blood transfusions (65.0% vs. 56.9%, adjusted odds ratio [OR] 1.36, 95% confidence interval [CI] 1.10 to 1.68) as well as the need for transfusion of ≥4 U of blood (27.7% vs. 18.4%, OR 1.70, 95% CI 1.32 to 2.19). In contrast, acute clopidogrel therapy was not associated with higher bleeding risks if CABG was delayed >5 days (adjusted OR 1.18, 95% CI 0.54 to 2.58).

CONCLUSIONS Despite guideline recommendations, the overwhelming majority of NSTE ACS patients treated with acute clopidogrel needing CABG have their surgery within ≤5 days of treatment. A failure to delay surgery is associated with increased blood transfusion requirements that must be weighed against the potential clinical and economic impacts of such delays. (J Am Coll Cardiol 2006;48:281–6) © 2006 by the American College of Cardiology Foundation

A large randomized trial has demonstrated that the acute administration of clopidogrel—a long-acting antiplatelet therapy—to patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS) can reduce subsequent risk for death, myocardial infarction, or stroke by 20% when continued for a mean duration of nine months (1). However, single-center case series have demonstrated that, in patients requiring coronary artery bypass graft (CABG) surgery, the use of clopidogrel is associated with increased risk of perioperative bleeding and a need for transfusion (2–6). This risk appears to be time dependent. For example, post-hoc data analysis from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial revealed that bleeding risks were increased when patients had CABG surgery within 5 days of clopidogrel treatment but not when surgery was delayed for >5 days after treatment with clopidogrel (1). These findings are reflected in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the acute management of patients with NSTE ACS, which endorse the acute use of clopidogrel but also recommend withholding clopidogrel for at least 5 days before CABG surgery (7).

Adherence in community practice to this guidelines recommendation has not been characterized previously. The

From the *Division of Cardiology and the Duke Clinical Research Institute, Durham, North Carolina; †University of North Carolina School of Medicine, Chapel Hill, North Carolina; ‡TIMI Study Group, Brigham and Women's Hospital, Boston, Massachusetts; §University of Cincinnati College of Medicine, Cincinnati, Ohio; ‖University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and the ¶Louisiana State University Health Science Center, New Orleans, Louisiana. CRUSADE is a national quality improvement initiative of the Duke Clinical Research Institute. CRUSADE is funded by Millennium Pharmaceuticals, Inc. and Schering Corporation. The Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership provides additional funding support.

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Abbreviations and Acronyms

ACC/AHA = American College of Cardiology/American Heart Association
CABG = coronary artery bypass graft
CI = confidence interval
CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines Initiative
CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events trial
GP = glycoprotein
NSTE ACS = non–ST-segment elevation acute coronary syndromes
OR = odds ratio
RBC = red blood cell
RR = relative risk

purposes of this study were to characterize patterns of clopidogrel use before CABG and to examine the time-dependent risks for postoperative transfusion among NSTE ACS patients treated at 264 hospitals participating in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) National Quality Improvement Initiative (8,9).

METHODS

Patient population. We reviewed the CRUSADE data from patients with NSTE ACS who underwent CABG surgery during their initial hospital stay. Patients with NSTE ACS were defined as having ischemic symptoms within 24 h of presentation and either ST-segment depression, transient ST-segment elevation, or positive cardiac markers (elevated troponin I or T and/or creatine kinase-MB greater than the upper limit of normal for participating institutions) (8,9). We excluded patients from hospitals without CABG capabilities; patients who were transferred in from other institutions or who were transferred out from the initial institution (because data on presentation characteristics, acute treatments, clinical outcomes, and use and timing of invasive procedures were not available for those patients); patients in whom information on clopidogrel treatment was not available; and those who received transfusion before CABG.

Of a total of 42,156 patients with NSTE ACS admitted to CABG-capable hospitals, 3,977 (9.4%) underwent CABG between January 2003 and September 2004 in 264 hospitals participating in the CRUSADE Initiative. After allowing for the aforementioned exclusions, 2,858 patients undergoing CABG constituted the study population for this analysis.

Data collection. The institutional review board of each institution approved participation in the CRUSADE Initiative. Data were collected in an anonymous fashion during the initial hospitalization and included baseline clinical characteristics, use of acute medications (<24 h of hospital arrival), contraindications to specific therapies, use and timing of invasive cardiac procedures, laboratory results, in-hospital clinical outcomes, and discharge therapies and interventions.

Statistical analysis. Patients were divided into four groups for analysis: Specifically, we looked at patients receiving clopidogrel therapy or not among those going to CABG "early," i.e., within 5 days of cardiac catheterization. We also examined the effects of clopidogrel therapy on outcomes among those going to "late CABG" defined as more than 5 days after catheterization. In these analyses, we conservatively assumed that the use of clopidogrel initiated acutely was continued until the time of cardiac catheterization but stopped afterwards (when coronary anatomy became known and treatment plans for CABG were formulated).

Continuous variables were described using mean or median values, and categorical variables were described as percentages. The Wilcoxon test was used to test for differences in continuous variables, and the chi-square test was used to detect global differences in categorical variables. We used generalized estimating equations to determine the effect of the use and timing of clopidogrel on the need for red blood cell (RBC) transfusions and the number of units transfused (10). Both models were adjusted for age, baseline hematocrit, gender, and signs of congestive heart failure on presentation. Also, for the need for transfusion outcome, we adjusted for body mass index, previous percutaneous coronary intervention, previous congestive heart failure, renal insufficiency, heart rate, and positive cardiac markers. For the RBC units' transfused outcome, we adjusted for blood pressure and hospital region. Race, insurance status, family history of coronary artery disease, ST-segment deviation, diabetes, current/recent smoking, hypercholesterolemia, previous myocardial infarction, previous stroke, hypertension, previous CABG, specialty of the caring physician, availability of cardiac catheterization laboratories and revascularization procedures, and academic status of the hospital were nonsignificant in both models and, thus, no adjustments were made for these variables. Two sets of pair-wise adjusted comparisons were made to examine the effects of clopidogrel therapy versus not among the "early CABG" group (within 5 days) and the "late CABG group" (>5 days). A p value of <0.05 was established as the level of statistical significance for all tests. All statistical analyses were performed using SAS software (version 8.2, SAS Institute, Cary, North Carolina).

RESULTS

Of the 2,858 patients in our study, 852 (30%) received clopidogrel within 24 h of their admission. Of those patients treated with clopidogrel, 739 (87%) underwent CABG within 5 days of their last dose of clopidogrel, whereas the remaining 113 (13%) underwent CABG surgery >5 days after discontinuing clopidogrel. Similarly, the

Table 1. Clinical and Hospital Characteristics by Clopidogrel Use in Patients Undergoing CABG

Characteristics	Early CABG ≤5 Days*		Late CABG >5 Days*	
	No Clopidogrel (n = 1,826)	Clopidogrel (n = 739)	No Clopidogrel (n = 180)	Clopidogrel (n = 113)
Age (yrs)†	65 (56, 74)	65 (56, 74)	68 (60, 75)	67 (59, 76)
Female gender	28.6	30.0	27.8	27.4
BMI (kg/m^2)†	28.5 (25, 32)	28.3 (25, 32)	28.8 (26, 33)	28.3 (25, 32)
White race	84.1	85.0	76.7	85.0
Hypertension	68.7	66.4	71.7	73.5
Diabetes mellitus	32.2	34.6	35.6	41.6
Obesity (BMI >30 kg/m^2)	38.7	35.5	40.6	40.7
Current/recent smoker	31.4	29.8	35.0	29.2
Previous MI	20.1	21.9	23.9	35.4
Previous PCI	13.4	19.1	14.4	26.6
Previous CABG	5.0	5.6	5.0	13.3
Previous revascularization	17.3	22.2	17.8	35.4
Previous CHF	6.0	6.8	16.1	17.7
Previous stroke	6.8	6.6	8.9	16.8
Peripheral vascular disease	8.6	11.5	13.3	11.5
Renal insufficiency‡	7.2	5.0	10.0	10.6
Presenting characteristics				
Heart rate (beats/min)†	82 (70, 98)	80 (70, 96)	86 (72, 102)	89 (73, 105)
SBP (mm Hg)†	148 (129, 169)	148 (130, 170)	145 (123, 168)	146 (129, 165)
Hypotension	2.0	1.8	3.3	4.4
ST-segment depression	39.5	42.4	37.2	41.6
Transient ST-segment elevation	8.6	7.6	15.6	4.4
Positive cardiac markers	87.7	91.2	88.9	93.8
CHF at presentation	18.0	17.7	25.6	31.0

Data presented as percentages except where indicated. *From the time of cardiac catheterization. †Presented as median values with interquartile range. ‡Defined as creatinine >2.0 mg/dl, calculated creatinine clearance <30 ml/min, or need for chronic renal dialysis.

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

majority of patients not treated with clopidogrel underwent CABG >5 days of their cardiac catheterization (91%).

The baseline clinical characteristics of the 4 patient groups are shown in Table 1. Patients who underwent CABG >5 days with or without clopidogrel had more high-risk features, including older age, a history of previous revascularization, previous stroke, renal insufficiency, and a higher prevalence of diabetes compared with the respective group of patients undergoing early CABG with or without clopidogrel. Patients with delayed surgery also were more likely to present with clinical characteristics associated with a greater risk of adverse outcomes, such as signs of congestive heart failure, higher heart rate, positive cardiac enzymes, or severe left ventricular systolic dysfunction. In contrast, there were no significant differences between the clinical characteristics and presenting features of patients who did not receive clopidogrel and underwent early CABG and those who received CABG within 5 days of clopidogrel. Similarly, there were no significant differences in the baseline and presenting clinical features between patients undergoing late CABG with and without clopidogrel. Although the use of acute medications was similar in the four groups of patients, those who received clopidogrel within 5 days of CABG surgery were more likely to receive intravenous glycoprotein (GP) IIb/IIIa inhibitors (Table 2).

The proportion of patients requiring RBC transfusion in the four groups is as shown in Table 3. Among the early CABG group, clopidogrel therapy was associated with a significant increased need for RBC transfusion compared with those not receiving clopidogrel. This difference persisted after adjusting for differences in baseline clinical factors between the two groups (adjusted odds ratio [OR] 1.36, 95% confidence interval [CI] 1.10 to 1.68). If a higher cutpoint is used, 28% of patients receiving clopidogrel within 5 days of CABG required four or more units of RBCs compared with only 18% of patients not treated with clopidogrel and undergoing early surgery (adjusted OR 1.70, 95% CI 1.32 to 2.19). More patients who had CABG within 5 days of clopidogrel received any platelet transfusion (33.7%) compared with those not treated with clopidogrel and undergoing early CABG (22.3%; mean platelet units transfused 1.33 vs. 0.76, median 0 in both groups).

In contrast to these results, among those in whom CABG was delayed >5 days after catheterization, acute clopidogrel therapy was not associated with increased need for transfusion (adjusted OR 0.81, 95% CI 0.44 to ;1.48) or at risk for large transfusions of four or more units of RBCs (adjusted OR 1.18, 95% CI 0.54 to 2.58). No difference was observed in the need for platelet transfusions in the two late CABG groups (Table 3).

Table 2. Acute Care (<24 h) Patterns and In-Hospital Procedures by Clopidogrel Use in Patients Undergoing CABG Surgery*

Characteristics	Early CABG ≤5 Days†		Late CABG >5 Days†	
	No Clopidogrel (n = 1,826)	Clopidogrel (n = 739)	No Clopidogrel (n = 180)	Clopidogrel (n = 113)
Aspirin	94.9	96.6	90.5	95.5
Beta-blockers	88.2	89.0	87.4	95.2
Heparin—any	92.2	93.1	92.5	92.0
Unfractionated heparin	54.2	53.4	59.8	44.6
LMWH	46.0	49.3	45.4	53.6
GP IIb/IIIa inhibitor	39.2	45.0	36.1	40.8
Arrival to CABG‡	69 (40, 104)	73 (44, 104)	193 (162, 236)	203 (164, 251)
Number of diseased vessels				
2	22.8	27.9	21.5	28.2
3	72.1	65.7	72.9	59.1
LVEF				
Moderate (25%–40%)	17.2	16.7	27.7	27.9
Severe (<25%)	3.7	3.1	12.7	9.0

Data presented as percentages except where indicated. *Among patients without listed contraindications. †From the time of cardiac catheterization. ‡Presented as median (interquartile range).
CABG = coronary artery bypass graft; GP = glycoprotein; LMWH = low molecular weight heparin; LVEF = left ventricular ejection fraction.

Death rates generally were low in this population (Table 3). After adjusting for baseline clinical factors, there was no difference in in-hospital mortality in patients treated with clopidogrel versus not among those having early CABG surgery within 5 days of catheterization (adjusted OR 1.31, 95% CI 0.79 to 2.19). Among those undergoing CABG >5 days after catheterization, the in-hospital death rates were 5.3% versus 3.9% in the clopidogrel versus no-clopidogrel-treated patients. The small number of patients in these two late CABG groups precluded any multivariable adjustments. Other adjusted outcome measures such as death or nonfatal myocardial infarction, and cardiogenic shock were also similar in the two clopidogrel groups compared with the respective two no-clopidogrel groups. The median post-CABG length of stay was also similar in the four groups.

Because those patients receiving clopidogrel and early CABG also were more likely to be treated acutely with a GP IIb/IIIa inhibitor, a factor that may increase the risk for perioperative bleeding after early CABG (11), we performed a sensitivity analysis by excluding all patients treated within 18 h of surgery with a GP IIb/IIIa receptor antagonist. This interval was chosen to be consistent with the pharmacological impact of these agents on bleeding risks with surgery. This exclusion had a limited effect on the results, as patients receiving clopidogrel and early CABG continued to show an increased risk of requiring RBC transfusions compared with the early CABG-no clopidogrel group (adjusted OR 1.37, 95% CI 1.08 to 1.75). Similarly, if we extended our analysis to exclude all patients receiving GP receptor antagonists any time before their CABG, those receiving clopidogrel ≤5 days before CABG continued to have a greater need for transfusions compared with the early CABG-no clopidogrel group (adjusted OR 1.74, 95% CI 1.32 to 2.29).

DISCUSSION

Our analysis is the first to provide insight into patterns of clopidogrel use and outcomes in the setting of CABG performed on patients with NSTE ACS. We found that as many as 30% of patients currently receive clopidogrel before

Table 3. In-Hospital Outcomes by Clopidogrel Use in Patients Undergoing CABG Surgery

Hospital Outcomes	Early CABG ≤5 Days*		Late CABG >5 Days*	
	No Clopidogrel, CABG <5 Days (n = 1,826)	Clopidogrel ≤5 Days Before CABG (n = 739)	No Clopidogrel, CABG >5 Days (n = 180)	Clopidogrel >5 Days Before CABG (n = 113)
Any RBC transfusion	56.9	65.0	67.2	61.1
RBC transfusion >4 U	18.4	27.7	26.5	25.7
RBC units transfused†	1.0 (0, 3)	2.0 (0, 4)	2 (0, 4)	2.0 (0, 4)
Any platelet transfusion	20.3	33.7	15.0	17.7
Death	2.9	3.5	3.9	5.3
Death or reinfarction	5.7	5.0	8.3	6.2
Cardiogenic shock	4.2	3.8	6.1	4.4
Stroke	1.4	1.6	0.6	1.8
Length of stay (days)†	9.0 (7, 13)	9.0 (7, 12)	15 (12, 19)	16.0 (13, 20)
Length of stay post-CABG (days)†	5	6	6	6

Data presented as percentages except where indicated. *From the time of cardiac catheterization. †Presented as median (interquartile range).
CABG = coronary artery bypass graft; RBC = red blood cell.

CABG surgery, and, of these, nearly 90% have surgery within 5 days of treatment, contrary to the ACC/AHA guidelines recommendations. Our data also showed that the performance of CABG within 5 days of clopidogrel treatment is associated with an increase in the proportion of patients requiring blood transfusion and a greater number of packed RBC units transfused. We confirmed that rate of transfusion requirement returned to normal (vs. rate of patients not treated with clopidogrel) if surgery was delayed >5 days after clopidogrel was stopped, results similar to those observed in the CURE study (1,7). Thus, our data support the ACC/AHA guidelines recommendations that encourage the discontinuation of clopidogrel >5 days before CABG to minimize the perioperative bleeding risk and the need for blood transfusion.

It could be hypothesized that the rush to early CABG is related to the high-risk features or unstable presenting features of the patients. However, contrary to these expectations, patients undergoing CABG within 5 days of clopidogrel treatment did not differ significantly from those who did not receive clopidogrel and underwent early CABG in the presence of high-risk features, such as diabetes, previous revascularization, prior stroke, and renal insufficiency, and with unstable presenting features, such as signs of congestive heart failure, higher heart rate, and elevated cardiac enzymes. This finding suggests that surgery was electively performed sooner than is recommended after the discontinuation of clopidogrel in the vast majority of patients. We did not collect information on the reasons for early or late surgery in patients receiving clopidogrel and thus can only speculate as to why this occurs. Higher-risk patients on clopidogrel wait longer for CABG because physicians may need more time to discuss the risks with them and their families, they may want the patients to be more stable before surgery, or they may hope to provide the best milieu to lower risk in these otherwise high-risk patients (i.e., by waiting until the effect of clopidogrel is completely gone—>5 days). In contrast, more stable patients may receive early CABG because of economic constraints and/or lessened concerns about bleeding with clopidogrel, especially with increasing experience among cardiac surgeons in the management of patients on clopidogrel, meticulous hemostasis during surgery, and the use of platelet transfusions and epsilon amino caproic acid or aprotinin in the perioperative period.

Our analyses also better quantitate the magnitude of transfusion risks among those receiving clopidogrel and early surgery. Specifically, we found that although the adjusted odds for transfusion are approximately 36% higher, the median absolute increase in total number of RBC units transfused was modest at one unit. Looked at another way, the absolute proportion of patients receiving four or more units of RBC (a large bleed) was increased by 10% with clopidogrel if surgery was performed within 5 days.

These data demonstrating a modest increase in transfusion risk are generally lower than those seen in previous case series (2–6). This lower risk may in part reflect a more stable estimate of risks based on a much larger case sample in the CRUSADE Initiative. Alternatively, it is possible that as surgeons and anesthesiologists gain experience with perioperative management of patients treated with clopidogrel, risks have declined. This perioperative management could include more liberal use of platelet transfusions (as seen in our study), the use of procoagulant and platelet-protective drugs such as aprotinin and tranexamic acid, and closer attention to maintaining a dry surgical field prior to closure (4,12).

The use of GP IIb/IIIa antagonists was greater in patients who received clopidogrel and underwent early CABG. However, the relationship of clopidogrel with bleeding after CABG remained directionally and consistently the same even when patients with GP IIb/IIIa were excluded and argues against significant confounding by GP IIb/IIIa inhibitors.

The increase in bleeding observed in patients who received acute clopidogrel and CABG must be weighed against the potential benefits of administering clopidogrel while awaiting surgery. Data from the CURE trial suggest that the use of clopidogrel in patients with NSTE ACS is associated with very early effects on various outcome measures. Thus, the use of clopidogrel was associated with a lower incidence of in-hospital events, including myocardial infarction (relative risk [RR], 0.60; 95% CI 0.48 to 0.76), severe ischemia (RR, 0.74; 95% CI 0.61 to 0.90; $p = 0.003$) or recurrent angina (RR, 0.91; 95% CI 0.85 to 0.98; $p = 0.01$) (1,7). Our observational study, however, was not able to confirm these benefits because we did not have systematic postprocedural enzyme measurements or a rigorous clinical trials event committee. Additionally, the benefits of delaying CABG surgery for >5 days after the administration of clopidogrel must be weighed against the potential risks of events while waiting as well as the economic consequences of extended hospital length of stay.

Study limitations. First, we considered the time between cardiac catheterization and CABG surgery as a proxy for the time between the discontinuation of clopidogrel and CABG because the exact time of discontinuation of clopidogrel before CABG was not available. Second, we did not collect data on the incidence of re-exploration after CABG, although this has been done in previous studies (2–6). However, consistent with previous studies, when we looked at RBC transfusions requiring four or more units as a surrogate for reoperation, the risk was higher among patients on clopidogrel undergoing early CABG compared with those undergoing early CABG but not receiving clopidogrel. Third, serial hemoglobin values were not collected in our dataset at the time of the initiation of the CRUSADE Initiative, and therefore we are unable to provide the actual values of hemoglobin/hematocrit that led to transfusions. However, the similar levels of nadir hematocrit post-CABG in the four groups suggest that perhaps the threshold for transfusion was not significantly different

between the four groups (median nadir hematocrit post-CABG among patients who received any RBC transfusion-clopidogrel/early CABG group 25.1 %, clopidogrel/late CABG group 25.6%, no-clopidogrel/early CABG group 25.8%, and no-clopidogrel/late CABG group 25.9%). Perhaps other factors besides nadir hematocrit may be important in determining RBC transfusions, such as rate of bleeding or hemodynamic instability. Fourth, our comparisons of clinical outcomes by treatment strategy were observational. Although we adjusted all comparisons for baseline clinical factors, we cannot exclude any persistent unmeasured confounding. Nonetheless, because a randomized clinical trial evaluating the benefits and risks of patients undergoing early versus late CABG is unlikely to be undertaken as most physicians would consider this to be unethical in view of data from the CURE trial (1,7), this study is the first to provide insight into the scope of this issue at a national level.

Conclusions. When CABG is required, the majority (87%) of patients treated with acute clopidogrel did not have their surgery delayed for the recommended 5-day interval, contrary to current ACC/AHA guidelines. These patients demonstrated an increase in bleeding complications compared with patients who did not receive clopidogrel and underwent early CABG. However, these bleeding risks must be weighed against the benefits of clopidogrel use demonstrated in randomized clinical trials, as well as against the economic impact of delaying CABG surgery.

Reprint requests and correspondence: Dr. Rajendra H. Mehta, Box 17969, Duke Clinical Research Institute, Durham, North Carolina 27715. E-mail: mehta007@dcri.duke.edu.

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