JACC: CARDIOVASCULAR INTERVENTIONS VOL. 3, NO. 4, 2010

ISSN 1936-8798/10/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2010.01.012

Timing of In-Hospital Coronary Artery Bypass Graft Surgery for Non–ST-Segment Elevation Myocardial Infarction Patients

Results From the National Cardiovascular Data Registry ACTION Registry–GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With The Guidelines)

Shailja V. Parikh, MD,* James A. de Lemos, MD,* Michael E. Jessen, MD,† Emmanouil S. Brilakis, MD, PhD,* E. Magnus Ohman, MD,‡ Anita Y. Chen, MS,‡ Tracy Y. Wang, MD, MHS,‡ Eric D. Peterson, MD, MPH,‡ Matthew T. Roe, MD, MHS,‡ Elizabeth M. Holper, MD, MPH,* on behalf of the CRUSADE and ACTION Registry–GWTG Participants

Dallas, Texas; and Durham, North Carolina

Objectives The aim of this study was to examine timing of in-hospital coronary artery bypass graft surgery (CABG) for non–ST-segment elevation myocardial infarction (NSTEMI) patients.

Background Although practice guidelines recommend delaying CABG for a few days after presentation for ST-segment elevation myocardial infarction patients, current guidelines for NSTEMI patients do not address optimal CABG timing.

Methods We evaluated rates and timing of in-hospital CABG among NSTEMI patients treated at U.S. hospitals from 2002 to 2008 with the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) (January 2002 to December 2006) and ACTION Registry–GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With The Guidelines) (January 2007 to June 2008) programs. Analyses designed to study the clinical characteristics and outcomes of early (≤48 h, n = 825) versus late (>48 h, n = 1,822) CABG focused upon more recent NSTEMI patients from the ACTION Registry–GWTG.

Results Both the rate (11% to 13%) and timing (30% early and 70% late) of in-hospital CABG remained consistent from 2002 to 2008. In the ACTION Registry–GWTG program, NSTEMI patients undergoing late CABG tended to have a higher risk profile than those undergoing early CABG. In-hospital mortality (3.6% vs. 3.8%, adjusted odds ratio: 1.12, 95% confidence interval: 0.71 to 1.78) and the composite outcome of death, myocardial infarction, congestive heart failure, or cardiogenic shock (12.6% vs. 12.4%, adjusted odds ratio: 0.94, 95% confidence interval: 0.69 to 1.28) were similar between patients undergoing early versus late CABG.

Conclusions Most NSTEMI patients undergo late CABG after hospital arrival. Although these patients have higher-risk clinical characteristics, they have the same risk of adverse clinical outcomes compared with patients who undergo early CABG. Thus, delaying CABG routinely after NSTEMI might increase resource use without improving outcomes. Additionally, the timing of CABG for NSTEMI patients might be appropriately determined by clinicians to minimize the risk of adverse clinical events. (J Am Coll Cardiol Intv 2010;3:419–27) © 2010 by the American College of Cardiology Foundation

From the *Department of Internal Medicine, Division of Cardiology, and the †Department of Cardiothoracic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas; and the ‡Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina. The Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership and Schering-Plough Corporation are founding sponsors of the ACTION Registry–GWTG.

Manuscript received August 10, 2009; revised manuscript received January 4, 2010, accepted January 11, 2010.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 4, 2010
APRIL 2010:419–27

More than 40% of patients with an acute coronary syndrome have multivessel coronary artery disease identified at the time of coronary angiography (1). Thus, coronary artery bypass graft surgery (CABG) might be recommended for revascularization. Because a number of previous studies have reported increased mortality associated with early CABG after ST-segment elevation myocardial infarction (STEMI) (2–12), the American College of Cardiology/American Heart Association STEMI guidelines recommend delaying CABG in stable patients to minimize risk (13). However, the optimal timing of CABG after non–ST-segment elevation myocardial infarction (NSTEMI) is not addressed in the most recent American College of Cardiology/American Heart Association Guidelines for Unstable Angina and NSTEMI (14).

See page 428

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery

CHF = congestive heart failure

CK-MB = creatine kinase-myocardial band

IQR = interquartile range

MI = myocardial infarction

NSTEMI = non–ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

We used the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) and ACTION Registry–GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With The Guidelines) databases to determine whether the use and timing of in-hospital CABG for NSTEMI patients has changed over the past 6 years and to examine the influence of the timing of CABG on in-hospital outcomes.

Methods

Data sources. The NCDR (National Cardiovascular Data, Registry) ACTION Registry–GWTG represents a merger of the prior National Registry for Myocardial Infarction and CRUSADE registries. The ACTION Registry–GWTG is a national database that currently has 291 participating sites in the U.S., with data collection beginning January 1, 2007. The CRUSADE registry is a voluntary quality improvement initiative that began data collection on unstable angina and NSTEMI patients in November 2001 (with retrospective data collection from January 2001) and ended December 31, 2006, and had 568 nationally participating sites (15).

Patient inclusion criteria. Between January 1, 2002, and December 31, 2006, 175,394 NSTEMI patients were included in the CRUSADE initiative. Between January 1, 2007, and June 30, 2008, 47,971 NSTEMI patients were included in the ACTION Registry–GWTG. The NSTEMI patients in both the CRUSADE and ACTION Registry–GWTG programs were designated by the following criteria: ischemic symptoms within 24 h of presentation with elevation of creatine kinase-myocardial band (CK-MB) and/or troponin I/T levels above the local laboratory upper limit of normal.

For the analysis of temporal changes in the rate and timing of CABG, after exclusions, we yielded a sample size of 109,169 NSTEMI patients (Fig. 1). To analyze the impact of the timing of CABG on in-hospital clinical outcomes in the ACTION Registry–GWTG, after exclusions, we yielded a sample size of 21,470 patients (Fig. 2). We used only the ACTION Registry–GWTG database to explore timing of CABG on in-hospital outcomes, because of difficulties in merging the CRUSADE and ACTION databases due to differing data elements in the earlier version of the CRUSADE case report form.

Data collection and study definitions. No consensus time specification exists to define early versus late CABG after NSTEMI. Because several prior studies defined early CABG as occurring ≤48 h and late CABG as >48 h after hospital admission (5–7,12), we prospectively used this definition, categorizing the time to CABG as the time from hospital arrival to first skin incision.

Data were abstracted by a trained data collector at each hospital. Reported descriptive data include demographic and historical information (including age, sex, race, history of hypertension, diabetes, peripheral arterial disease, dyslipidemia, prior myocardial infarction [MI], prior revascular-

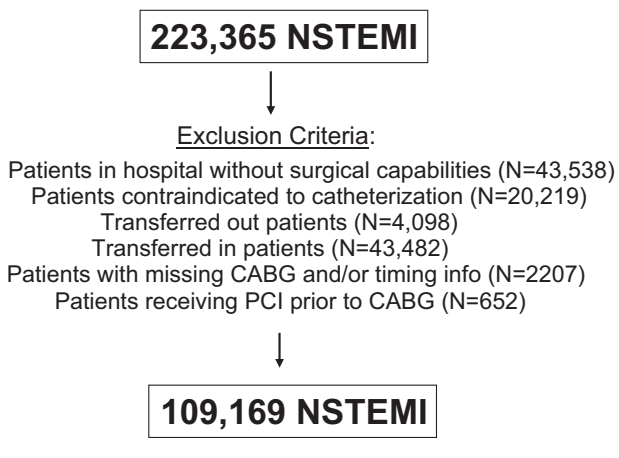

Figure 1. Patient Criteria for Rate and Timing of CABG in the CRUSADE and ACTION Registries

ACTION = Acute Coronary Treatment and Intervention Outcomes Network; CABG = coronary artery bypass graft surgery; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

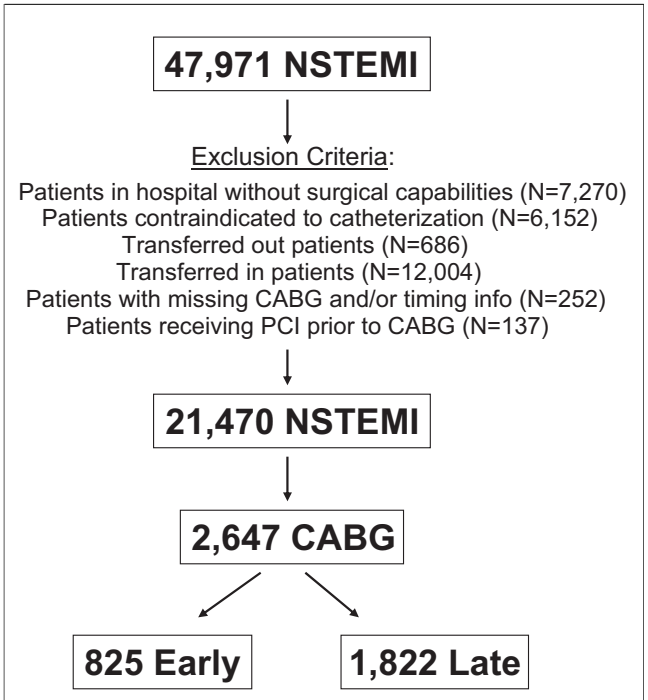

Figure 2. Patient Criteria for Timing of CABG in ACTION Registry–GWTG

GTWG = Get With The Guidelines; other abbreviations as in Figure 1.

ization, prior stroke, current/recent smoker, insurance status, and home medications); physical findings and laboratory data present at arrival to the hospital (including heart rate, blood pressure, signs of congestive heart failure [CHF], initial hematocrit, and serum creatinine); and in-hospital medications administered, including acute medications (within 24 h of hospital arrival) and medications used any time during hospital stay.

In-hospital outcomes were recorded by site data collectors, including all cause mortality, myocardial (re)infarction, cardiogenic shock, CHF, stroke, and bleeding defined as units of red blood cells transfused; however, these outcomes were not independently adjudicated. A composite outcome of death, MI, cardiogenic shock, or CHF was defined as the primary efficacy outcome. Myocardial (re)infarction was defined as clinical signs and symptoms of ischemia distinct from the presenting ischemic event, either occurring before CABG or spontaneously >72 h after CABG. For spontaneous MI, patients were required to have either new ischemic Q waves on electrocardiogram or an elevated CK-MB or troponin above the upper limit of normal, at least ≥25% above the most recent value if the most recent cardiac markers before MI were normal or ≥50% above the most recent value if the cardiac markers were above the upper limit of normal. For MI within the first 72 h after CABG, either new pathologic Q waves on electrocardiogram or an increase in biomarkers >5 times the upper limit of normal per the local laboratory was required. If patients had cardiac biomarkers above the upper limit of normal before CABG, then the increase in CK-MB had to be ≥50% above the most recent value.

For the outcomes of cardiogenic shock and CHF, only new shock or CHF was included as an end point event such that individuals presenting with shock or heart failure could not meet the end point of new shock or heart failure. Historically, postoperative bleeding in CABG patients has been defined by the number of required transfused red blood cell units. Thus, the prospective definition of bleeding used for the present analyses was transfusion ≥2 red blood cell units. Secondary bleeding definitions included the proportion receiving any red blood cell transfusion and the proportion receiving ≥4 red blood cell units.

The GRACE (Global Registry of Acute Coronary Events) risk score, a validated prognostic indicator of in-hospital events (16), was calculated for patients in the ACTION Registry–GWTG to better characterize the risk profile of patients in the early and late CABG groups. Because the ACTION Registry–GWTG collects signs (yes/no) and severity of heart failure (mild, severe, shock), for the variable of Killip class, we defined Killip 1 as no heart failure, Killip 2 as mild heart failure, Killip 3 as severe, and Killip 4 as cardiogenic shock. Because the variable of cardiac arrest on admission was not collected, this was not included in the calculated GRACE scores.

Statistical analysis. Baseline patient characteristics, clinical factors, hospital characteristics, in-hospital care patterns, and in-hospital outcomes were compared between early and late CABG groups. In addition, graphical displays of rates of CABG and timing of CABG (e.g., rates of early CABG) across the study period were presented. Median values with interquartile ranges (IQRs) (IQR: 25th, 75th percentiles) were used to describe continuous variables, and percentages were reported for categorical variables. Continuous and ordinal categorical variables were compared with stratum-adjusted Wilcoxon rank sum test, whereas nominal categorical variables were compared with stratum-adjusted chi-square test for trend where stratification is by hospital.

To explore the relationship between early CABG (vs. late CABG) and in-hospital clinical outcomes, the generalized estimating equations method for estimating marginal effects of timing of CABG (early vs. late) status was used. This method produces estimates similar to those from ordinary logistic regression, but the estimated variances are adjusted for the correlation of outcomes within a hospital. An exchangeable correlation structure was used for this analysis (17,18). Furthermore, the analyses accounted for both within-center correlation and among-center variation.

Patient-specific variables in the models included age, male sex, body mass index, white race, hypertension, diabetes, smoking status, hypercholesterolemia, prior peripheral artery disease, prior MI, prior percutaneous coronary intervention (PCI), prior CABG, prior CHF, prior stroke,

current dialysis, baseline serum creatinine, signs of CHF at presentation, heart rate, and systolic blood pressure on admission. Additionally, home clopidogrel (daily prescribed clopidogrel), acute clopidogrel (prescribed within first 24 h), acute clopidogrel contraindications, and time of presentation on weekday or weekend (8:00 AM to 4:00 PM, 4:00 PM to 12:00 AM, or 12:00 AM to 8:00 AM) were included.

To determine factors associated with delayed CABG, a multivariable logistic generalized estimating equations model was used adjusting for the aforementioned covariates (except for home clopidogrel, acute clopidogrel contraindications, and time of presentation), including other medications (aspirin, beta blocker, low molecular weight heparin, unfractionated heparin, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and statin) and provider and hospital characteristics (physician specialty, total number of hospital beds, region of the country, and type of hospital [academic or nonacademic]). All the variables listed are included in each outcome model; furthermore, the variables were determined through clinical input from the investigators of this study.

A p value of ≤0.05 was considered statistically significant for all tests, and all tests of statistical significance were 2-tailed. All analyses were performed with SAS software (version 9.2, SAS Institute, Cary, North Carolina).

Results

Temporal trends in CABG use and timing from 2002 to 2008. In-hospital CABG rates after NSTEMI did not change significantly from 2002 to 2008 (p_{trend} = 0.08), ranging between 11% and 13% (Fig. 3A). There was also no significant difference in the mean proportion of patients undergoing early (30.4%) or late (69.7%) CABG across time (p_{trend} = 0.28) (Fig. 3B).

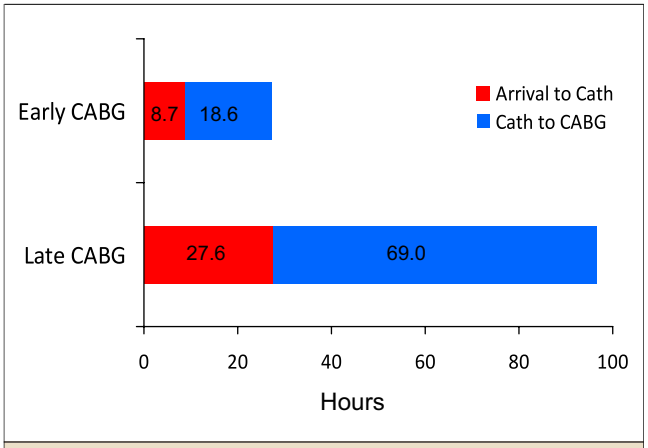

Figure 4. Median Time From Arrival to CABG by Timing of CABG

cath = catheterization; other abbreviations as in Figure 1.

Angiography and CABG timing in ACTION Registry–GWTG. Of the 2,647 (12.3%) NSTEMI patients who underwent in-hospital CABG in the ACTION Registry–GWTG from 2007 to 2008, 825 (31.2%) underwent early CABG and 1,822 (68.8%) underwent late CABG. Overall, the median time from arrival to CABG for NSTEMI patients was 72.9 h (IQR: 42.0 to 121.8). The median time to CABG was 28.9 h (IQR: 18.5 to 40.4) for early CABG patients and 101.8 h (IQR: 70.8 to 147.1) for late CABG patients. The median time from hospital arrival to cardiac catheterization for early and late groups was 8.7 h (IQR: 3.0 to 17.6) and 27.6 h (IQR: 16.2 to 50.2), respectively. The median time between cardiac catheterization and CABG for early and late groups was 18.6 (IQR: 5.1 to 23.3) and 69.0 h (IQR: 44.3 to 110.2), respectively (Fig. 4).

Clinical characteristics associated with CABG timing. Baseline characteristics and presenting physical findings strati-

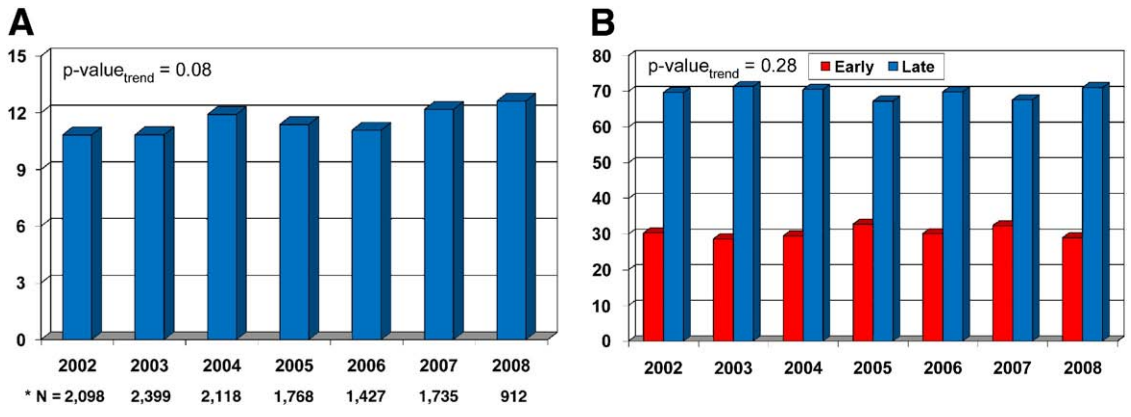

Figure 3. Rate of In-Hospital CABG by Year of Presentation and by Timing in the CRUSADE and ACTION Registries

(A) Rate of in-hospital CABG by year of presentation in the CRUSADE and ACTION registries. **(B)** Rate of in-hospital CABG by timing in the CRUSADE and ACTION registries. *N = number of patients undergoing in-hospital CABG. Abbreviations as in Figure 1.

fied by CABG timing are shown in Table 1. Compared with NSTEMI patients undergoing early CABG, patients undergoing late CABG had a higher-risk clinical profile and a slightly higher median GRACE risk score (127 vs. 121, p = 0.03). Compared with patients undergoing early CABG, those undergoing late CABG after NSTEMI were more likely to have signs of CHF on arrival. The NSTEMI patients treated with earlier CABG were more likely to have cardiogenic shock on presentation, although not statistically significant in the comparison of types of CHF.

In-hospital medications. In-hospital medications administered within 24 h of hospital arrival are shown in Table 2. Compared with patients undergoing early CABG, those undergoing late CABG were more likely to have received clopidogrel, statins, low molecular weight heparin, and angiotensin-converting enzyme inhibitors. However, early

Table 1. Clinical Characteristics of Patients Undergoing Early Versus Late CABG

	Early (n = 825)	Late (n = 1,822)	p Value
Age (yrs)*	63.0 (55.0, 72.0)	65.0 (57.0, 75.0)	0.02
Sex (%)			0.002
Male	75.5	68.3	
Female	24.5	31.7	
Race (%)			0.33
Caucasian	86.3	83.6	
Black	5.1	8.3	
Hispanic	3.4	2.0	
Asian	4.0	4.2	
Hypertension (%)	66.7	76.6	<0.0001
Diabetes (%)	31.2	39.5	<0.0001
Dyslipidemia (%)	56.2	58.1	0.47
Peripheral artery disease (%)	7.8	12.7	0.001
Prior myocardial infarction (%)	16.7	21.6	0.01
Prior percutaneous coronary intervention (%)	15.8	17.9	0.08
Prior coronary artery bypass grafting (%)	3.2	4.9	0.03
Prior congestive heart failure (%)	4.0	10.1	<0.0001
Prior stroke (%)	5.7	8.8	0.04
Baseline creatinine (mg/dl)*	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)	0.005
Baseline hematocrit (%) *	42.5 (38.9, 45.4)	41.2 (37.4, 44.5)	<0.0001
Admission systolic blood pressure (mm Hg)*	147.0 (129.0, 166.5)	150.0 (130.0, 170.0)	0.27
Admission heart rate (beats/min)	84.0 (71.5, 97.0)	86.0 (73.0, 101.5)	0.02
Signs of heart failure (%)	12.1	21.8	<0.0001
Type of heart failure (%)			0.14
Mild	53.0	66.1	
Severe	26.0	29.9	
Cardiogenic shock	15.0	1.8	
Left ventricular ejection fraction (%)			0.44
≥50%	52.4	53.1	
≥40%–50%	24.4	22.2	
≥25%–40%	19.3	19.9	
<25%	3.9	4.5	
Hospital type (%)			0.08
Academic	23.5	26.7	
Nonacademic	76.5	73.3	
Insurance status (%)			0.96
Health maintenance organization/private	60.5	54.7	
Medicare	25.8	30.8	
Medicaid	2.4	4.3	
Military/Veterans Affairs Medical Center	0.7	1.2	
Self/none	10.1	8.3	

*Presented as median values (25th, 75th percentiles).
CABG = coronary artery bypass graft surgery.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 4, 2010
APRIL 2010:419–27

Table 2. Medications Within 24 Hours by Timing of CABG

	Early (n = 825)	Late (n = 1,822)	p Value
Aspirin (%)	98.4	97.8	0.18
Beta-blocker (%)	93.1	94.4	0.59
Angiotensin-converting enzyme inhibitor (%)	34.3	46.2	<0.0001
Statin (%)	46.7	59.5	<0.0001
Clopidogrel (%)	27.3	36.9	0.01
Glycoprotein IIb/IIIa inhibitor (%)	38.3	37.9	0.04
Anticoagulants (%)*			
Unfractionated heparin	72.5	61.5	<0.0001
Low molecular weight heparin	29.9	43.7	<0.0001
Bivalirudin	0.8	0.8	0.39

*Recorded as anytime during hospital stay rather than within 24 h.
Abbreviations as in Table 1.

CABG patients were more likely to receive glycoprotein IIb/IIIa inhibitors and unfractionated heparin than late CABG patients.

Severity of coronary disease and infarct size. Both the early and late CABG groups had primarily 3-vessel disease on coronary angiography (73.7% vs. 72.8%, p = 0.40). Although there were no differences in the median peak troponin levels between the early and late CABG groups (27.5× upper limit of normal vs. 23.2× upper limit of normal, p = 0.19), the median peak CK-MB was modestly higher in the early CABG group (5.1× upper limit of normal vs. 4.7× upper limit of normal, p = 0.01).

Multivariable analyses to identify factors associated with CABG timing. Factors associated with delayed CABG after multivariable adjustment are shown in Table 3 and include

Table 3. Multivariable Model of Factors Associated With Delayed CABG

	Odds Ratio	95% Confidence Interval	p Value
Demographic data			
Age (per 5-yr increase)	1.08	1.04–1.13	0.0003
Clinical characteristics			
Current/recent smoker	1.44	1.13–1.82	0.003
Signs of congestive heart failure	1.54	1.15–2.06	0.004
Hypertension	1.27	1.06–1.52	0.009
Baseline hematocrit (per 1% decrease)	1.02	1.01–1.04	0.009
Prior congestive heart failure	1.67	1.12–2.49	0.01
Dyslipidemia	0.79	0.63–0.97	0.03
Inpatient medications			
Acute statin	1.60	1.34–1.90	<0.0001
Acute clopidogrel	1.83	1.42–2.36	<0.0001
Acute angiotensin-converting enzyme inhibitor	1.46	1.19–1.79	0.0003
Acute angiotensin receptor blocker	1.67	1.21–2.32	0.002
Any unfractionated heparin	0.75	0.59–0.95	0.02
Any low molecular weight heparin	1.68	1.33–2.13	<0.0001

Abbreviations as in Table 1.

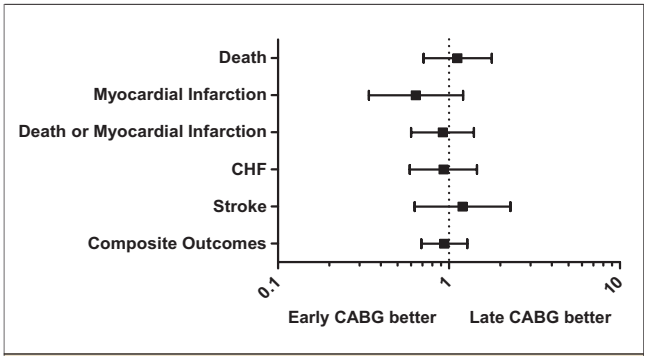

Figure 5. Adjusted Odds Ratios and 95% Confidence Interval for In-Hospital Outcomes for Early CABG (vs. Late CABG)

*Composite outcomes = death, myocardial infarction, congestive heart failure, or cardiogenic shock. CABG = coronary artery bypass graft surgery; CHF = congestive heart failure.

in-hospital administration of clopidogrel and low molecular weight heparin as well as older age, hypertension, smoking, evidence of CHF, and lower hematocrit.

Outcomes. There were no differences in unadjusted in-hospital adverse outcomes between those undergoing early versus late CABG, including death (3.6% vs. 3.8%, p = 0.56), MI (1.2% vs. 1.7%, p = 0.13), CHF (7.8% vs. 8.0%, p = 0.45), shock (5.9% vs. 4.0%, p = 0.06), or stroke (2.2% vs. 1.7%, p = 0.63). The primary composite outcome occurred in 12.6% of the early subgroup versus 12.4% of the late subgroup (p = 0.42). After multivariable adjustment, in-hospital outcomes remained similar for the early and delayed CABG subgroups (Fig. 5). Patients undergoing late surgery were more likely to receive a red blood cell transfusion (65.5% vs. 56.7%, p = 0.0001) including ≥2 U of packed red blood cells (54.9% vs. 48.1%, p = 0.006), but there were no differences in those receiving ≥4 U (28.0% vs. 23.8%, p = 0.41). Median length of hospital stay was significantly longer in the late CABG group (11 vs. 7 days, p < 0.0001) than in the early CABG group.

Discussion

Recent trends in the management of NSTEMI include increasing application of an early invasive treatment strategy. Among individuals with extensive coronary artery disease for whom CABG was previously the preferred treatment option, PCI—particularly with drug-eluting stents—has become a commonly employed revascularization alternative (19). Surprisingly, in the present study we found that in-hospital CABG rates after NSTEMI did not change between 2002 and 2008. This finding was unexpected, because prior studies have revealed an increase in PCI use over time with a reduction in the rates of CABG (18–20). However, our study extends findings by Gogo et al. (20), who analyzed patients from 2002 to 2005 in the CRUSADE registry and found no change in CABG rates

among patients with severe coronary disease receiving in-hospital CABG. We also found no change in the timing of CABG, with a consistent 30% of individuals undergoing early (≤48 h) CABG from 2002 to 2008.

Several potential factors might contribute to the failure of the expected decline in CABG rates. First, as use of cardiac catheterization for NSTEMI has increased over time (21,22), so has the diagnosis of extensive coronary artery disease. Thus, the proportion of patients undergoing surgical revascularization after an NSTEMI might have remained stable as the pool of patients identified with severe coronary artery disease has increased. Second, the debate over whether patients with multivessel disease fare better with PCI versus CABG is ongoing and remains particularly contentious in the subset of diabetic patients (23–29). Almost three-quarters of the patients in this study had 3-vessel coronary artery disease on coronary angiography, and over 30% of patients were diabetic. Recommendations favoring CABG over PCI in this subgroup of patients likely contributed to persistent high use of CABG.

Factors influencing the timing of CABG after NSTEMI. Late CABG was associated with a higher risk profile, along with increased statin, clopidogrel, angiotensin-converting enzyme inhibitor, and low molecular weight heparin administration during the hospital stay. Although the influence of statins and angiotensin-converting enzyme inhibitors is likely a reflection of existing cardiovascular disease, administration of clopidogrel and low molecular weight heparin might have directly affected CABG timing. Several studies have confirmed higher bleeding rates in patients receiving clopidogrel within 5 to 7 days before CABG (30–33). Additionally, prior studies have revealed higher bleeding rates in patients receiving low molecular weight heparin immediately before CABG (34–36), and the American College of Cardiology/American Heart Association Unstable Angina/NSTEMI practice guidelines recommend discontinuation of enoxaparin 12 to 24 h before CABG (14). Thus, decisions regarding CABG timing might be driven by physicians upstream of the cardiac surgeon, because early administration of clopidogrel and low molecular weight heparin by nonsurgeon physicians might contribute to delayed CABG.

Patients undergoing early CABG underwent catheterization a median of 18.9 h sooner after hospital arrival than patients undergoing late CABG. Thus, a key variable influencing CABG delay is delay to cardiac catheterization, a finding that further supports that decisions regarding CABG timing might be influenced by physicians upstream of the cardiac surgeon.

Association between CABG timing and outcomes. Unadjusted and adjusted analyses revealed no differences in outcomes between patients undergoing early or late CABG, and patients undergoing early CABG were less likely to receive red blood cell transfusions. Most studies examining the timing of surgery after an MI have not discriminated between STEMI and NSTEMI and have grouped patients under the umbrella of "acute myocardial infarction" (2–5,7,11,12,37–48). However, the distinction between STEMI and NTSTEMI is critical, because the treatments before CABG and early outcomes differ markedly between the 2 types of MIs. The few studies specifically examining the timing of surgical revascularization after an NSTEMI are conflicting. Deeik et al. (9) reported that waiting 3 to 5 days for CABG after a nontransmural MI resulted in similar postoperative outcomes of reinfarction and death as compared with a control group of patients undergoing CABG for stable coronary artery disease. However, Braxton et al. (6) found no difference in surgical mortality rates, comparing patients with non–Q-wave MI undergoing CABG within 48 h with those undergoing elective CABG. Our study is unique in that not only does it detail the outcomes specifically of NSTEMI patients but the patients in our study have been treated in the contemporary era of aggressive pharmacological and interventional therapy for NSTEMI.

Study limitations. This study has the inherent limitations of observational registries, because the timing of referral for both cardiac catheterization and CABG was left to the discretion of the treating physician. Furthermore, there might have been a survivor bias favoring the late CABG group, because patients who died early could not undergo late CABG. This limitation, however, only strengthens our finding of no apparent benefit associated with routine CABG delay. By contrast, the possibility of a selection bias favoring the early CABG group also exists, because patients undergoing late CABG had more high-risk clinical features. Although we attempted to account for these factors through comprehensive multivariable analyses, it is possible that other unmeasured factors could also have contributed to CABG timing and also influenced outcomes. Additionally, there was a lack of adjudication for outcomes. Moreover, only the time of first red blood cell transfusion was collected, so it is not possible to determine whether subsequent red blood cell transfusions were administered pre-operatively or post-operatively. This study only performed follow-up through hospital discharge, and additional study is needed to correlate findings with longer-term outcomes up to 12 months and beyond. The median GRACE risk score of the cohort was 125, well within the intermediate-risk range. Additional study is needed to determine whether delay in CABG is beneficial in higher-risk individuals. Potentially the outcome models could be overfitted and thus would fail to replicate in future samples.

Conclusions

The rates of in-hospital CABG and timing of CABG after NSTEMI have not changed over the past 6 years. In the current era, CABG is delayed more often in higher-risk patients, and the delay seems to happen "upstream" of the cardiac surgeon. Process factors associated with delayed

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 4, 2010
APRIL 2010:419–27

CABG include delay to cardiac catheterization and treatment with clopidogrel and low molecular weight heparin. Importantly, unadjusted and adjusted outcomes seem similar between those undergoing early CABG and those undergoing delayed CABG. Moreover, with early CABG, bleeding rates are lower and hospital stay is shorter than with late CABG. In conclusion, most NSTEMI patients undergo late CABG more than 48 h after hospital arrival, and although these patients have higher-risk clinical characteristics, they have the same risk of adverse clinical outcomes compared with patients who undergo early CABG in this study. These results suggest that delaying surgery routinely in all patients after uncomplicated NSTEMI might increase resource use without improving outcomes. Additionally, the timing of CABG for NSTEMI patients might be appropriately determined by clinicians to minimize the risk of adverse clinical events.

Reprint requests and correspondence: Dr. Elizabeth M. Holper, University of Texas Southwestern Medical Center, Division of Cardiology, 5201 Harry Hines Boulevard, Dallas, Texas 75235. E-mail: Elizabeth.Holper@UTSouthwestern.edu.

REFERENCES

1. Brener SJ, Milford-Beland S, Roe MT, Bhatt DL, Weintraub WS, Brindis RG, American College of Cardiology National Cardiovascular Database Registry. Culprit-only or multivessel revascularization in patients with acute coronary syndromes: an American College of Cardiology National Cardiovascular Database Registry report. Am Heart J 2008;155:140–6.
2. Hill JD, Kerth WJ, Kelly JJ, et al. Emergency aortocoronary bypass for impending or extending myocardial infarction. Circulation 1971;43: 105–10.
3. Jones EL, Waites TF, Craver JM, et al. Coronary bypass for relief of persistent pain following acute myocardial infarction. Ann Thorac Surg 1981;32:33–43.
4. Kennedy JW, Ivey TD, Misbach G, et al. Coronary artery bypass graft surgery early after acute myocardial infarction. Circulation 1989;79: 173–8.
5. Tio RA, de Boer MJ, Hoorntje JC, Suryapranata H, Halebos MM, Zijstra F. Coronary artery bypass grafting early after acute myocardial infarction in patients initially treated with thrombolytic therapy or coronary angioplasty. Coron Artery Dis 1994;5:713–6.
6. Braxton JH, Hammond GL, Letsou GV, et al. Optimal timing of coronary artery bypass graft surgery after acute myocardial infarction. Circulation 1995;92:II66–8.
7. Creswell LL, Moulton MJ, Cox JL, Rosenbloom M. Revascularization after acute myocardial infarction. Ann Thorac Surg 1995;60:19–26.
8. Gersh BJ, Chesebro JH, Braunwald E, et al. Coronary artery bypass graft surgery after thrombolytic therapy in the Thrombolysis in Myocardial Infarction Trial, Phase II (TIMI II). J Am Coll Cardiol 1995;25:395–402.
9. Deeik RK, Schmitt TM, Ihrig TG, Sugimoto JT. Appropriate timing of elective coronary artery bypass graft surgery following acute myocardial infarction. Am J Surg 1998;176:581–5.
10. Lee DC, Oz MC, Weinberg AD, Lin SX, Ting W. Optimal timing of revascularization: transmural versus nontransmural acute myocardial infarction. Ann Thorac Surg 2001;71:1197–202.
11. Voisine P, Mathieu P, Doyle D, et al. Influence of time elapsed between myocardial infarction and coronary artery bypass grafting surgery on operative mortality. Eur J Cardiothorac Surg 2006;29: 319–23.
12. Weiss ES, Chang DD, Joyce DL, Nwakanma LU, Yuh DD. Optimal timing of coronary artery bypass after acute myocardial infarction: a review of California discharge data. J Thorac Cardiovasc Surg 2008; 135:503–11, 511.e1–3.
13. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol 2004;44:E1–211.
14. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-elevation Myocardial Infarction). J Am Coll Cardiol 2007;50:e1–157.
15. Hoekstra JW, Pollack CV, Roe MT, et al. Improving the care of patients with non-ST-elevation acute coronary syndromes in the emergency department: the CRUSADE initiative. Acad Emer Med 2002;9:1146–55.
16. Granger CB, Goldberg RJ, Dabbous O, et al., Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. Arch Intern Med 2003; 163:2345–53.
17. Berlin JA, Kimmel SE, Ten Have TR, Sammel MD. An empirical comparison of several clustered data approaches under confounding due to cluster effects in the analysis of complications of coronary angiography. Biometrics 1999;55:470–6.
18. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.
19. Hahn J, Lessard D, Yarzebski J, et al. A community-wide perspective into changing trends in the utilization of diagnostic and interventional procedures in patients hospitalized with acute myocardial infarction. Am Heart J 2007;153:594–605.
20. Gogo PB Jr., Dauerman HL, Mulgund J, et al., CRUSADE Investigators. Changes in patterns of coronary revascularization strategies for patients with acute coronary syndromes (from the CRUSADE Quality Improvement Initiative). Am J Cardiol 2007;99:1222–6.
21. Fox KA, Goodman SG, Anderson FA Jr., et al., GRACE Investigators. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes. The Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2003;24:1414–24.
22. Hahn J, Lessard D, Yarzebski J, et al. A community-wide perspective into changing trends in the utilization of diagnostic and interventional procedures in patients hospitalized with acute myocardial infarction. Am Heart J 2007;153:594–605.
23. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996;335:217-25.
24. Serruys PW, Morice MC, Kappetein AP, et al., SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
25. Booth J, Clayton T, Pepper J, et al., SoS Investigators. Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). Circulation 2008;118:381–8.
26. Serruys PW, Ong AT, van Herwerden LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol 2005;46:575–81.
27. Rodriguez AE, Baldi J, Fernandez Pereira C, et al. Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). J Am Coll Cardiol 2005;46:582–8.
28. Hueb W, Lopes NH, Gersh BJ, et al. Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation 2007;115:1082–9.

29. Frye RL, August P, Brooks MM, et al., BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503–15.
30. Berger JS, Frye CB, Harshaw Q, Edwards FH, Steinhubl SR, Becker RC. Impact of clopidogrel in patients with acute coronary syndromes requiring coronary artery bypass surgery: a multicenter analysis. J Am Coll Cardiol 2008;52:1693–701.
31. Maltais S, Perrault LP, Do QB. Effect of clopidogrel on bleeding and transfusions after off-pump coronary artery bypass graft surgery: impact of discontinuation prior to surgery. Eur J Cardiothorac Surg 2008;34:127–31.
32. Pickard AS, Becker RC, Schumock GT, Frye CB. Clopidogrel-associated bleeding and related complications in patients undergoing coronary artery bypass grafting. Pharmacotherapy 2008;28:376–92.
33. Nurozler F, Kutlu T, Küçük G, Okten C. Impact of clopidogrel on postoperative blood loss after non-elective coronary bypass surgery. Interact Cardiovasc Thorac Surg 2005;4:546–9.
34. Kincaid EH, Monroe ML, Saliba DL, Kon ND, Byerly WG, Reichert MG. Effects of preoperative enoxaparin versus unfractionated heparin on bleeding indices in patients undergoing coronary artery bypass grafting. Ann Thorac Surg 2003;76:124–8, discussion 128.
35. Clark SC, Vitale N, Zacharias J, Forty J. Effect of low molecular weight heparin (Fragmin) on bleeding after cardiac surgery. Ann Thorac Surg 2000;69:762–5.
36. Jones HU, Muhlestein JB, Jones KW, et al. Preoperative use of enoxaparin compared with unfractionated heparin increases the incidence of re-exploration for postoperative bleeding after open-heart surgery in patients who present with an acute coronary syndrome. Circulation 2002;106:119–22.
37. Favaloro RG, Effler DB, Cheanvechai C, Quint RA, Sones FM Jr. Acute coronary insufficiency (impending myocardial infarction and myocardial infarction): surgical treatment by the saphenous vein graft technique. Am J Cardiol 1971;28:598–607.
38. Pifarré R, Spinazzola A, Nemickas R, Scanlon PJ, Tobin JR. Emergency aortocoronary bypass for acute myocardial infarction. Arch Surg 1971;103:525–8.
39. Dawson JT, Hall RJ, Hallman GL, Cooley DA. Mortality in patients undergoing coronary artery bypass surgery after myocardial infarction. Am J Cardiol 1974;33:483–6.
40. Berg R Jr., Kendall RW, Duvoisin GE, Ganji JH, Rudy LW, Everhart FJ. Acute myocardial infarction: a surgical emergency. J Thorac Cardiovasc Surg 1975;70:432–9.
41. Bolooki H, Vargas A. Myocardial revascularization after acute myocardial infarction. Arch Surg 1976;111:1216–24.
42. Levine FH, Gold HK, Leinbach RC, Daggett WM, Austen WG, Buckley MJ. Safe early revascularization for continuing ischemia after acute myocardial infarction. Circulation 1979;60:5–9.
43. Selinger SL, Berg R Jr., Leonard JL, Grunwald RP, O'Grady WP. Surgical treatment of acute evolving anterior myocardial infarction. Circulation 1981;64:II28–33.
44. Fudge TL, Harrington OB, Crosby VG, et al. Coronary artery bypass after recent myocardial infarction. Arch Surg 1982;117:1418–20.
45. Flameng W, Sergeant P, Vanhaecke J, Suy R. Emergency coronary bypass grafting for evolving myocardial infarction. Effects on infarct size and left ventricular function. J Thorac Cardiovasc Surg 1987;94:124–31.
46. Connolly MW, Gelbfish JS, Rose DM, et al. Early coronary artery bypass grafting for complicated acute myocardial infarction. J Cardiovasc Surg (Torino) 1988;29:375–82.
47. Amsel BJ, Walter PJ, Van der Mast M, Vander Sande J. Immediate bypass surgery (0.5–3 h) for evolving myocardial infarction. Adv Cardiol 1988;36:178–88.
48. Sintek CF, Pfeffer TA, Khonsari S. Surgical revascularization after acute myocardial infarction. Does timing make a difference? J Thorac Cardiovasc Surg 1994;107:1317–21.

Key Words: acute coronary syndrome ■ coronary artery bypass graft surgery ■ non–ST-segment elevation myocardial infarction.