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EDITORIAL COMMENT

Bypass Surgery After Non–ST-Segment Elevation Myocardial Infarction

Better Early Than Late?*

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The Clinical Question

In addressing the question of timing of coronary artery bypass graft (CABG) surgery after ST-segment elevation myocardial infarction (STEMI), the 2004 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with STEMI (1) gives the following Class IIa recommendation: "In patients who have had a STEMI, CABG mortality is elevated for the first 3 to 7 days after infarction, and the benefit of revascularization must be balanced against this increased risk. Patients who have been stabilized (no ongoing ischemia, hemodynamic compromise, or life-threatening arrhythmia) after STEMI and who have incurred a significant fall in LV function should have their surgery delayed to allow myocardial recovery to occur. If critical anatomy exists, revascularization should be undertaken during the index hospitalization. (Level of Evidence: B)". The text then continues: "the Writing Committee believes that if stable STEMI patients with preserved LV function require surgical revascularization, then CABG can be undertaken within several days of the infarction without an increased risk."

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No other specific recommendations on timing of CABG after STEMI or non–ST-segment elevation myocardial infarction (NSTEMI) are made in the 2007 and recently published 2009 focused guideline updates for management of STEMI (2,3), in the ACC/AHA 2007 UA/NSTEMI guidelines (4), or in the ACC/AHA 2004 guidelines update for coronary artery bypass surgery (5). This last reference does state that the "risk of CABG in patients with unstable angina, post-infarction angina, early after non-STEMI and during acute MI is increased several fold relative to patients with stable angina, although the risk is not necessarily higher than that of medical therapy in these patients" (5). The CABG writing committees in 2004 and the earlier 1999 version (6) provide multiple references reporting an increased risk of mortality after CABG across the acute coronary syndromes spectrum, and they generalize that operative mortality decreases as time to operation increases. However, previous studies frequently have lumped together NSTEMI with STEMI and urgent with nonurgent cases, and the few teasing out NSTEMI have provided conflicting results on the safety of early CABG (7–11).

Given the confusion about the optimal timing of CABG in stable NSTEMI patients, advances in medical and surgical therapy, and the ongoing challenge of optimizing both patient outcomes and resource utilization, the current paper by Parikh et al. (12) in this issue of *JACC: Cardiovascular Interventions* is of considerable contemporary interest.

Study Summary

Parikh et al. (12) use merged major national databases that enrolled NSTEMI patients between January 1, 2002, and June 30, 2008, to address key questions about temporal trends in CABG use, timing, and clinical outcomes. The first 2 questions were addressed by a merger of the earlier CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) registry and the ongoing ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry–GWTG (Get With The Guidelines) database, which yielded 109,169 eligible patients from 475 centers. The third question was addressed by the ACTION registry–GWTG database, which yielded 2,647 CABG operations with timing information among 21,470 qualifying patients in 202 centers. Early CABG was defined as occurring ≤48 h and delayed CABG as >48 h after hospital arrival (7,9). The primary outcome was a composite of death, MI, cardiogenic shock, or heart failure. Increased bleeding after CABG was defined as transfusion of ≥2 red blood cell units. Patient risk profile was characterized by the GRACE (Global Registry of Acute Coronary Events) score (13). Generalized estimating equations methods were used to explore the relationship between CABG timing and in-hospital outcomes.

In-hospital CABG rates after NSTEMI (11% to 13%) and the proportion undergoing early (30%) versus later CABG (70%) did not change significantly between 2002 and 2008. Early CABG occurred at medians of 29 (early CABG) and 102 h (delayed CABG), and angiography, at 9

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and 28 h after admission, respectively. Three-vessel disease (in 73%) and median peak troponin were similar in the 2 subgroups. Late CABG patients were older, more often women, had a higher risk profile except for cardiogenic shock, and more frequently received in-hospital clopidogrel and low molecular weight heparin.

Despite the differences in baseline characteristics, subgroup outcomes were similar. The composite adverse clinical end point occurred in 12.6% of early and 12.4% of delayed subgroup patients, and each component of the end point was similar, including death (3.6% vs. 3.8%). This largely equivalent profile persisted after multivariable adjustment. Delayed surgery patients had a slightly greater chance of receiving ≥2 red cell units (55% vs. 48%), and their hospital stays were longer (11 vs. 7 days).

Clinical Interpretation and Implications

Parikh et al. (12) are to be congratulated for investigating an important, poorly defined area of decision making in coronary care. To do this, they took advantage of uniquely large, rich, and overlapping contemporary U.S. databases. A first observation, that CABG surgery rates after NSTEMI have been maintained over the past 6 years, came as a surprise, given the decade-plus trend of increasing percutaneous coronary intervention and decreasing CABG rates. The increasing use of an invasive strategy and persistently high rates of 3-vessel disease (73%) were offered as an explanation. The further finding of a >2:1 preference for delayed surgery may reflect an extension of STEMI recommendations into NSTEMI decision making. These observations argue for new evidence to guide decision making in NSTEMI.

Also, perhaps surprisingly, clinical outcomes after early and later CABG were similar. However, the early and delayed groups differed in many respects, raising concern about the impact of selection bias. To address this, the investigators applied sophisticated statistical modeling (i.e., the generalized estimating equations method), enabling adjustment for correlations within centers and correlations and variations among centers. Multivariable analyses were adjusted for 21 patient-specific baseline variables. Despite these exhaustive adjustments, outcomes remained equivalent.

Exploring upstream "process" factors that might influence timing, the investigators found a 19-h median delay to coronary angiography and increased pre-operative use of clopidogrel (14) and low molecular weight heparin (15) in the delayed CABG subgroup, which current guidelines recommend withholding for 5 to 7 days and 12 to 24 h, respectively, before nonurgent CABG (4).

The study has several limitations, including the possibility of residual confounding, which can be argued both ways: accounting for survivor bias (favoring the delayed group) would reinforce the safety of early surgery, whereas incomplete adjustment for higher risk characteristics of the delayed group would inappropriately favor early CABG. The short (in-hospital) follow-up is a further limitation, and the intermediate patient risk leaves open the question of the safety of early, nonurgent CABG in high-risk patients. The cut point of 48 h between early and delayed surgery is arbitrary and another cut point might be optimal. Time from onset of MI symptoms would be of interest in addition to time of admission. Finally, observational studies are limited to discovering associations rather than establishing cause-effect relationships.

Despite these limitations, this study sheds much new light on the question of timing of CABG after NSTEMI, which importantly differs from STEMI in pathology, prognosis, and initial management. Limitations of earlier studies have led to uncertainty about the relative benefits and risks of early versus delayed surgery. Into this confusing knowledge gap, this study provides the most objective, compelling observational data yet. The investigators argue that delaying surgery *routinely* in all patients after *uncomplicated* NSTEMI is not warranted and may increase resource utilization without improving outcomes. Randomized clinical trials should be pursued to definitively address the issue of optimal timing; nevertheless, these observations argue that, pending these trials, the decision on timing of CABG after NSTEMI, including upstream planning, may be individualized based on the judgment of experienced physicians and surgeons in an effort to optimize both patient outcomes and resource utilization.

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