


Optimal timing of coronary artery bypass after acute myocardial infarction: A review of California discharge data

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 Supplemental material is available online.

Objective: The optimal timing for coronary artery bypass grafting after acute myocardial infarction is not well established. The California Discharge Database facilitates the study of this issue by providing data from a large patient cohort free of institutional bias. We examine the timing of coronary artery bypass grafting after acute myocardial infarction on short-term outcomes.

Methods: We reviewed California Discharge Data to identify 40,159 patients who were hospitalized for acute myocardial infarction (day 0) and underwent subsequent coronary artery bypass grafting. Patients were stratified by the timing of coronary artery bypass grafting to "early" (days 0–2) and "late" groups (day 3 or later). The primary outcome variable was all-cause hospital mortality. Multiple logistic and linear regression and propensity analyses assessed the risk of adverse events, controlling for factors associated with preoperative clinical acuity, including the Charlson Comorbidity Index, shock, mechanical ventilation, and the use of intra-aortic balloon counterpulsation.

Results: Of 9476 patients identified, 4676 (49%) were in the early coronary artery bypass grafting group and 4800 (51%) were in the late coronary artery bypass grafting group. A total of 444 patients (4.7%) died during hospitalization, with a peak mortality rate of 8.2% among patients undergoing coronary artery bypass grafting on day 0, declining to a nadir of 3.0% among patients undergoing coronary artery bypass grafting on day 3. The mean time to coronary artery bypass grafting was 3.2 days. Patients undergoing early coronary artery bypass grafting experienced a higher mortality rate than those undergoing late coronary artery bypass grafting (5.6% vs 3.8%, $P < .001$). Early coronary artery bypass grafting was an independent predictor of mortality after controlling for clinical acuity and on propensity analysis (odds ratio 1.43, $P = .003$).

Conclusion: Patients undergoing coronary artery bypass grafting within 2 days of hospitalization for acute myocardial infarction experienced higher mortality rates than those undergoing coronary artery bypass grafting 3 or more days after acute myocardial infarction, independently of clinical acuity. This suggests that coronary artery bypass grafting may best be deferred for 3 or more days after admission for acute myocardial infarction in nonurgent cases.

Much attention has focused on the outcomes of coronary artery bypass grafting (CABG) in the setting of acute myocardial infarction (AMI).¹⁻³ Although it seems clear that patients who undergo CABG after AMI possess a higher risk of short-term mortality compared with patients who undergo elective CABG, the optimal timing of surgical revascularization remains controversial.^{1,4-6} Recent randomized controlled trials and meta-analyses performed in the setting of AMI have convincingly demonstrated that primary percutaneous coronary interventions (PCIs) yield superior results to thrombolytic therapy with decreased rates of death, reinfarction, and stroke.⁷⁻⁹ Consequently, an increased number of patients

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Abbreviations and Acronyms

AMI	= acute myocardial infarction
CABG	= coronary artery bypass graft
IABP	= intra-aortic balloon pump
ICD-9-CM	= International Classification of Diseases, Ninth Revision, Clinical Modification
OR	= odds ratio
PCI	= percutaneous coronary intervention

are receiving coronary angiography in the setting of AMI.^{10,11} This, in turn, has led to an increase in identification of candidates for surgical coronary revascularization (ie, in the setting of failed angioplasty or left main/multivessel disease). With this focus on CABG in the context of AMI and new trends in early management, the optimal timing of CABG after AMI should be scrutinized.

Although no definitive recommendation exists regarding the appropriate timing of CABG after recent AMI, the notion that these patients assume greater risk for short-term mortality is gaining consensus.^{5,12-14} This is not surprising given that the majority of patients who undergo early CABG present with a higher degree of clinical acuity, which, in turn, translates to higher mortality rates. For the stable patient post-AMI for whom the culprit lesion has been effectively treated with PCI, it is common practice to discharge the patient to recover for some time before undergoing CABG electively. Less certain, however, is the optimal management of patients post-AMI who cannot be discharged from the hospital before CABG because of a tenuous PCI result, disease severity, unstable angina, or compromised ventricular function. The optimal timing for CABG in these patients post-AMI was the focus of this study in which we performed a retrospective review with multivariable and propensity-based adjustments. We hypothesize that by controlling for both clinical acuity and early surgical propensity, an optimal time interval between AMI and CABG can be identified such that early postoperative mortality is reduced.

Materials and Methods**Data Source**

The State of California Office of Statewide Health Planning and Development (Healthcare Quality and Analysis Division) provided hospital discharge data for the years 1999 to 2005. The State of California requires all licensed hospitals to submit data on all discharged patients every 6 months. These records thus comprise a 100% sampling of California nonfederal hospital discharges. All data are de-identified and include demographic information, including age, gender, race, information on primary and concomitant diagnoses recorded and procedures performed, discharge information (eg, disposition to skilled nursing facility, death), and administrative information (eg, costs, payer information, length of stay, level of care). Unlike many other databases, the California discharge

database discriminates between prior and new diagnoses with respect to each hospital admission and identifies the dates of procedures and operations performed. These features facilitated the examination of outcomes related to the timing of CABG after AMI. Because individual patients are not identified in this multicenter registry report, the need for consent and institutional review board approval is waived at The Johns Hopkins Medical Institutions.

Study Design

A retrospective review of California discharge data was performed for the years 1999 to 2005. We identified all adult patients (>17 years of age) who were admitted to a California hospital with the primary diagnosis of AMI as identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes (410.x).¹⁵ We combined these patients with those who underwent CABG of any type during their hospitalization (also identified by ICD-9-CM procedure codes 36.x).

Patients were excluded if they had valvular pathology (ie, stenosis, insufficiency or active endocarditis of the mitral, aortic, pulmonary, or tricuspid valves) or underwent any concomitant cardiac surgical procedures such as mitral or aortic valve repair or replacement, ventricular remodeling, or ventricular assist device placement. In addition, patients were excluded if they presented with "do not resuscitate" status on admission or if they were transferred from another hospital (because we did not have information on the timing of AMIs in these patients) (Table E1).

Creation of Variables

Variables crucial to the analysis not present in the data set were derived using existing data set variables and known ICD-9-CM codes. The primary derived variable was the timing of CABG after AMI. The data set parameters yielded time intervals expressed in "days" rather than finer time intervals of hours or minutes. In this analysis, we designated day 0 as the initial day of hospital admission. Baseline independent variables describing medical status and outcome variables (other than death) were developed from ICD-9-CM coding and are subsequently listed in Table E2. We used the Charlson scoring system¹⁶ with Deyo adaptation¹⁷ as a standardized index reflecting the overall burden of comorbidities in the study population. Our primary outcome variable was all-cause in-hospital mortality.

Patient Groups

Because of the lack of standardized timing intervals for the performance of CABG after AMI, we grouped patients into "early" and "late" groups on the basis of the median time to CABG for our study population (day 3). Early CABG was thus defined as CABG performed on hospitalization day 0, 1, or 2, and late CABG was defined as CABG occurring on or after day 3. We also examined differences in outcomes dichotomized between other time points such as day 0 versus day 1 and after, day 0 and 1 versus day 2 and after, and so forth.

Statistical Analysis

Comparisons of baseline characteristics between study groups were performed using the Student *t* test for continuous variables and the chi-square test for categorical variables. Mortality was first assessed for all risk factors using a univariate model. Significant predictors of mortality (both chronic and acute) were incorporated into

a multivariable logistic regression model in a stepwise fashion to assess the effect of timing of CABG on mortality. Operative timing and mortality were plotted for all time points present to determine whether an optimal time for the performance of CABG after AMI exists.

To assess selection bias not controlled for in our multivariate model and to counter the censoring that occurs from early mortality, we used a propensity-adjustment model. We developed propensity scores (based on the likelihood of receiving early CABG on days 0, 1, or 2) derived from a logistic regression model incorporating 35 potential predictors of operative timing (Table E3). We incorporated the resultant propensity scores into a logistic regression model to negate selection bias in examining the effect of propensity for early CABG on in-hospital mortality. We also used quintile stratification for both internal validation of our technique and examination of the effects of timing in different subsets of propensity.

All odds ratios (ORs) are presented with 95% confidence intervals. All statistical analysis was performed with the aid of STATA software (version 9.0, StataCorp LP, College Station, Tex).

Results

Between 1999 and 2005, California hospitals recorded a total of 443,069 patient discharges with the primary diagnosis of AMI. Of these patients, 40,159 underwent CABG during their hospitalization. After exclusion of children (<18 years of age), hospital transfers, patients with concomitant cardiac procedures, and patients with incomplete data, 9476 patients were included in the final study population.

We noted that 75% of CABG ($n = 7086$) procedures were performed during the first 5 days of hospitalization (Figure 1). The median time to CABG was 3 days (mean 3.2 ± 3.0). By stratifying according to this median, 4676 patients (49%) were classified as the early CABG group (CABG performed on days 0, 1, or 2) and 4800 patients were classified as the late group (CABG performed on day 3 or later). The early group consisted of a lower percentage of female patients compared with the late group (28% vs 33%, $P < .001$). Both groups had

similar baseline comorbidities with mean Charlson scores of 5.2 and 5.8, respectively ($P < .001$) (Table 1). As expected, patients in the early CABG group were of higher acuity with greater proportions presenting with shock and requiring intra-aortic balloon pump (IABP) counterpulsation. Of note, the early group had a lower percentage of subendocardial infarcts (45% vs 61%, $P < .001$).

In-hospital mortality for the entire study period was 4.7% (444 patients). Patients undergoing CABG on their initial day of admission had an 8.2% mortality rate. Plotting of mortality over time revealed a nadir for patients undergoing CABG on hospital day 3 with a mortality rate of 3.0% (Figure 1). This low mortality rate persisted for those receiving CABG on days 4 and 5 but increased thereafter. Patients who underwent CABG between days 14 and 28 experienced a 12.5% in-hospital mortality rate ($P < .01$). The greatest decline in mortality in a 1-day period occurred for patients undergoing CABG on the first hospital day. A 3.7% decline in mortality ($P < .05$) was observed when CABG was performed on hospital day 1 compared with the day of admission.

Univariate analysis revealed early CABG to be highly associated with an increased risk of mortality (5.6% vs 3.8%, $P < .001$). This positive association was confirmed with multivariable logistic regression analysis controlling for gender, baseline comorbidities as assessed by the Charlson index, and markers of clinical acuity, including IABP, shock, cardiac arrest on admission, and ventilation before CABG (Table 2). The OR of 1.43 corresponds to a 43% increase in the risk of death among patients who underwent early CABG, controlling for the aforementioned markers of clinical acuity. Other strong predictors of death included IABP, shock on admission, cardiac arrest on admission, female gender, and Charlson index.

After we controlled for the propensity to undergo early surgery (C-index 0.76), CABG performed before day 3 continued to be positively associated with mortality risk (OR

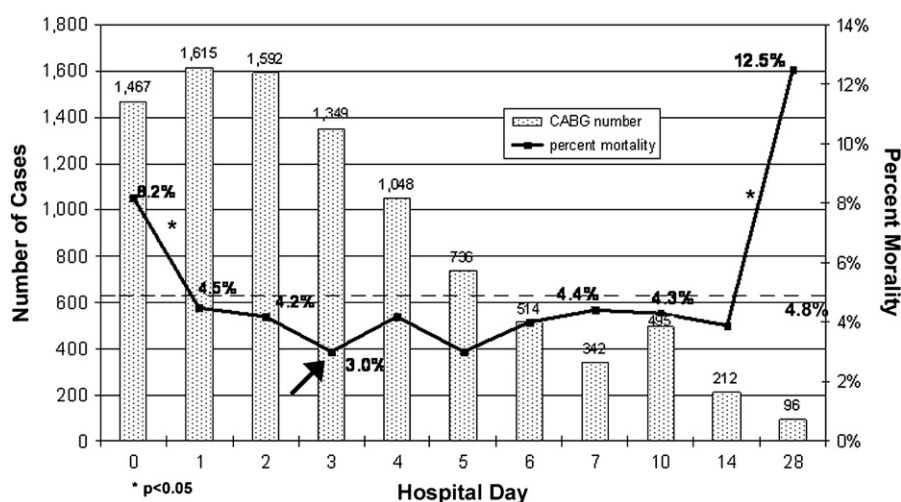


Figure 1. CABG volume and mortality over time. Distribution of CABG volume (left Y-axis, number of cases per day) and percent mortality (right Y-axis) per day of hospitalization. Dashed horizontal line represents total mortality over the study period (4.8%). Black arrow points to nadir of mortality occurring on day 3. CABG, Coronary artery bypass graft.

TABLE 1. Baseline demographics and acuity between early and late coronary artery bypass graft groups

	Early CABG N = 4676	Late CABG N = 4800	P value*
N (%) or mean (SD)			
Mean age (SD)	66.6 (11)	68.6 (11)	<.001
Female (%)	1306 (28)	1566 (33)	<.001
Black, Hispanic, Native American, Asian/Pacific Islander ±	930 (20)	1312 (27)	<.001
Obesity	623 (13)	602 (13)	.26
Charlson index (SD)	5.2 (1.8)	5.8 (1.9)	<.001
Subendocardial infarct	2114 (45)	2927 (61)	<.001
Cardiac arrest on admission	65 (1)	78 (2)	.35
Shock	314 (7)	166 (3.4)	<.001
IABP before CABG	469 (10)	412 (8.6)	.02
V-Fib on admission	81 (1.8)	91 (1.9)	.78
A-Fib on admission	570 (12)	774 (16)	<.001
Angiogram before CABG	4213 (90)	4592 (96)	<.001
Coronary stent before CABG	493 (11)	457 (10)	.1
Bypass (4 vessels)	1261 (27)	1245 (26)	.26
Bypass (3 vessels)	1552 (33)	1711 (36)	.01
Bypass (2 vessels)	1319 (28)	1288 (27)	.13
Bypass (1 vessels)	452 (10)	435(9)	.31

CABG, Coronary artery bypass graft; SD, standard deviation; IABP, intra-aortic balloon pump; V-Fib, ventricular fibrillation; A-Fib, atrial fibrillation. *P value is based on comparison between 2 groups by either chi-square or Student t test. ± Race or ethnic group was a variable present in the data set.

1.40, $P = .03$) (Table 2). Propensity scores were associated with early CABG (mean score 0.61 vs 0.37, $P < .001$) confirming that they did, in fact, predict early surgery. When stratified into propensity quintiles, only the lowest propensity group retained this positive association. Therefore, those patients with the least need to undergo early CABG had a 2-fold risk of death if they underwent early CABG (OR 1.58, $P = .03$). By performing serial propensity-adjusted analyses for all combinations of early and late CABG, we found that the relationship between early CABG and increased mortality ceased on hospital day 4 (OR for death if CABG performed on days 0–3 vs ≥ 4 , 0.92, $P = .45$). Thus, hospital day 3 seemed to be the cutoff point whereby further delay to CABG did not improve survival.

To determine optimal operative timing in patients with AMI presenting with high clinical acuity, we examined those patients with transmural infarctions (ie, acute infarctions not coded as "subendocardial") who were classified as having shock or who underwent IABP placement. Among these patients, we noted that the lowest mortality rates were observed when CABG was performed on hospital day 3 (Figure 2). As for the entire study population, mortality rates increased after day 4 among patients in this high-acuity group. The overall

TABLE 2. Risk factors for mortality determined from multivariable logistic regression analysis

Risk factor	OR (95% CI)	P value*
Multivariable analysis without propensity adjustment		
Day of CABG (across entire study period)	0.99 (0.95–1.02)	.65
Early CABG (days 0–2)	1.43 (1.12–1.18)	.003
Female gender	1.46 (1.16–1.85)	.002
Charlson index	1.29 (1.20–1.39)	<.001
Shock	3.58 (2.41–5.32)	<.001
Cardiac arrest on admission	3.23 (1.59–6.54)	<.001
IABP before CABG	1.51 (1.09–2.1)	.01
Ventilated before CABG	1.25 (0.79–1.98)	.32
V-Fib on admission	1.03 (0.45–2.23)	.98
Anterolateral infarct	1.08 (0.47–2.29)	.93
Multivariable analysis with propensity adjustment		
Early CABG (days 0–2)	1.40 (1.12–1.74)	.003
Propensity score	1.32 (0.87–2.01)	.18
Risk of death with early CABG as stratified by propensity quintile		
Quintile 1 (Pscore 0.03–0.32)	1.58 (1.05–2.34)	.03
Quintile 2 (Pscore 0.32–0.36)	1.21 (0.75–1.94)	.43
Quintile 3 (Pscore 0.39–0.46)	1.46 (0.83–2.58)	.19
Quintile 4 (Pscore 0.46–0.60)	1.39 (0.77–2.5)	.28
Quintile 5 (Pscore 0.60–0.90)	3.80 (0.42–34.3)	.23

OR, Odds ratio; CI, confidence interval; CABG, coronary artery bypass graft; V-Fib, ventricular fibrillation; IABP, intra-aortic balloon pump; Pscore, propensity score. This analysis was performed with and without propensity adjustment and with quintile propensity stratification. *P value is based on multivariable logistic regression analysis, using all factors significant on univariate analysis.

in-hospital mortality rates for patients presenting with shock and IABP placement were 24% (90/480 patients) and 7% (65/881 patients), respectively.

Discussion

Although the debate regarding the optimal timing of CABG after AMI is not yet settled, the findings of this study lend support to an increasing body of medical literature demonstrating increased risks of urgent surgical coronary revascularization in the setting of AMI. As in many issues in cardiac surgery, this topic has undergone evolution as technology has improved and mortality rates for CABG have declined. Studies conducted in the early 1980s by DeWood and colleagues^{18,19} focusing on this question showed a benefit to performing early CABG. Although valid at the time, these studies were conducted in an era before the widespread institution of PCI and thrombolysis in the setting of AMI.

More recently, retrospective examinations have concluded that CABG should be deferred, when possible, for 3 or more days after AMI.^{12,13,20} Lee and colleagues^{13,20} have conducted several studies describing the appropriate timing of CABG after AMI. By using the state of New

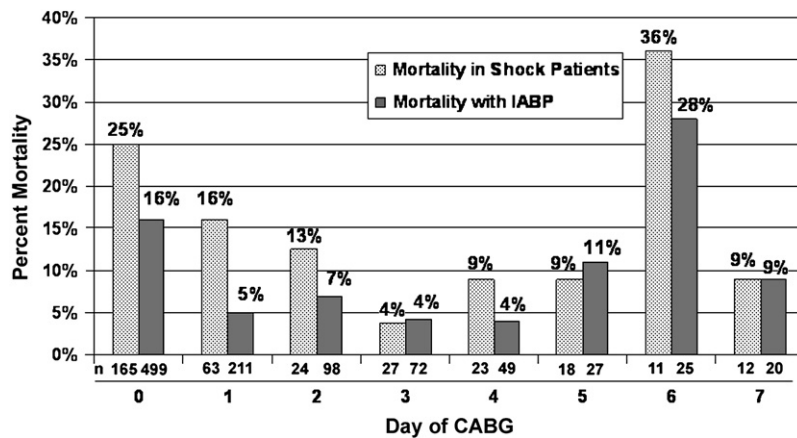


Figure 2. Mortality in patients undergoing acute CABG. Percent mortality for those patients with transmural AMI (defined as acute infarctions not coded as "subendocardial") and shock (*light grey bars*) or IABP placement preoperatively (*dark grey bars*). Note that for both patient sets, the nadir of mortality occurs on hospital day 3. Total patient numbers for each day (n) are given below each bar. *IABP*, Intra-aortic balloon pump; *CABG*, coronary artery bypass graft.

York database, the authors showed that the risk of early CABG is substantially higher before hospital day 3, with a doubling of mortality risk compared with patients who underwent later surgery. This positive association between early CABG and mortality was seen to be particularly important for transmural infarcts. Another study by Voisine and associates¹² concluded that CABG is best deferred for a period of 7 days after AMI. One should note, however, that this study examined only 77 subjects from a single institution (1991–2005) who underwent CABG within 24 hours of admission.

Although these prior studies are valuable in supporting the notion that delayed CABG is preferable under elective clinically stable circumstances, they have not specifically addressed patients with AMI presenting with higher clinical acuity. Kamohara and colleagues¹⁴ attempted to examine this issue by focusing on patients who underwent urgent CABG only. In their report, they conclude that patients who underwent early CABG (ie, within 6 hours of AMI) experienced higher mortality rates (9.1% vs 2.9%) than those who underwent CABG later in their course (ie, 6–24 hours after AMI). Although this study attempted to examine the effect of timing among acutely ill patients, it is a single-center report that did not include patients undergoing CABG 24 or more hours after AMI. It is possible that outcomes would have improved among these patients if CABG had been further delayed.

In our analysis, we attempted to bridge this gap in knowledge by focusing on hospitalized patients, identifying a modern cohort of patients among multiple centers who presented with higher clinical acuity than those reported in prior studies but did not require urgent CABG. We used this strategy to determine the optimal timing of surgery among patients with AMI who underwent CABG during their initial hospitalization.

Our study uniquely possesses an even distribution of post-AMI CABG timing intervals. With 1477 patients undergoing CABG on their initial hospital day, early CABG was well

represented in this sample. The fact that we only examined patients who required hospital admission may partially explain why the in-hospital mortality rate of 4.8% may be higher than previously reported mortality rates, typically ranging from 2.3% to 3.3%.^{12,20}

This study is also distinguished by the robust statistical methods we used to control bias inherent in its retrospective design. We addressed 2 important statistical problems. First, patients who underwent early CABG inherently assumed a greater mortality risk associated with their increased level of acuity, constituting a *selection bias*. Although traditional multivariate models can attempt to limit this risk, an obvious flaw is the difficulty of accounting for all potential confounders. Second, patients who underwent early CABG and died are excluded from being a part of the late CABG group. This effect, termed *censoring*, leads to relative inequality between the 2 groups and violates a fundamental assumption of multivariate models. Because those patients who die cannot be part of the late group, a bias that inflates late group survival occurs. In the absence of a gold standard blinded, randomized controlled trial, these effects are difficult to control.

We attempted to address these statistical concerns by using a propensity-adjusted analysis. The use of propensity scores represents another tool to help eliminate bias in a retrospective study and has been used successfully in other landmark surgical studies.^{21–23} The propensity score (ranging from 0–100) predicts which patients are likely to receive a treatment or, in this case, early CABG. Propensity scores are particularly useful when the primary outcome is rare. Unlike traditional multivariate analyses, the propensity-based approach addresses the issues of selection bias and censoring by adjusting for the likelihood of receiving early CABG, not simply by adjusting for known confounders. We think that the use of a propensity-based approach is an effective way to address the issue of timing in this analysis.

By using propensity-adjusted analysis, the findings of this study are consistent with previous reports showing that early CABG (before day 3) is associated with an increased risk of

mortality. We found an approximate doubling of mortality among those patients who underwent CABG before day 3 (5.6% vs 2.8%). This effect was independent of factors associated with acuity and propensity-based analysis. It is noteworthy that on quintile assessment, the effect seemed to be restricted to the lowest propensity quintile. In other words, those patients with low likelihood for undergoing early CABG derived the worst effect from receiving early CABG. These results suggest that early elective CABG in the setting of AMI is associated with a heightened postoperative mortality risk that might otherwise be ameliorated by deferring the operation. Our analysis suggests that 3 to 5 days seems to be an optimal timing window for performing an elective CABG after AMI.

An unexpected observation from this study showed that postoperative mortality rates trended upward after day 5. In fact, patients who underwent CABG between days 14 and 28 experienced a 12.5% risk of mortality. In contrast, previous studies have noted a steady downward trend in mortality with increasing time after AMI. In our cohort, among patients who underwent CABG after day 14, 16% presented in shock ($n = 7$), 29% required mechanical ventilation ($n = 13$), and 20% required IABP placement ($n = 9$) preoperatively. Thus, it is likely that our findings are reflective of sicker patients who required extended hospitalization after an AMI.

We also examined a critically ill population by examining only those patients with a transmural infarction who presented in hemodynamic shock or who underwent IABP placement. It is noteworthy that these patients also derived mortality benefit from waiting until day 3 to perform CABG but experienced increased mortality if CABG was performed after day 4. These findings support that, even in the setting of high-acuity patients, survival benefit may be derived from deferring CABG 2 to 3 days after AMI.

Use of the California Database

We chose to use the California statewide database in this analysis because of 2 key features. The first was the ability to gauge procedural timing, which was crucial to the analysis. The second was the discrimination between diagnoses present on admission to the hospital versus new diagnoses made during the hospitalization. This allowed us to determine whether a patient characteristic was preexistent or developed subsequent to CABG. For the purposes of retrospective analyses, a large database provides a large sample size that is free of institutional bias. Because individual institutional practices with respect to performing CABG after AMI differ dramatically, we think that this freedom from institutional bias gives our study added power.

Study Limitations

We recognize that there are several limitations in our study. First, our study is retrospective and cannot account for inherent undocumented differences in patient characteristics.

Although we attempted to control for selection bias with propensity and multivariate statistical methods, we concede that a fundamental problem of any retrospective study examining interventional timing is the inherent heightened acuity of patients who undergo early CABG. Second, we were reliant on the variables provided by the California discharge database. Several markers of clinical acuity (eg, left ventricular ejection fraction) were not available and thus could not be included. Finally, administrative databases, including the one we used, and studies based on them are reliant on accurate coding. We acknowledge that the data presented here were not necessarily entered by individuals with clinical expertise. Subtle differences in coding definitions may exist between different institutions; neither the coding nor procedural timing included in the California discharge data has been validated for patients undergoing CABG. However, although errors and variance in the data undoubtedly exist, we have assumed that these are randomly distributed and should not lead to significant bias in our conclusions. Without a randomized controlled clinical trial, we thought that a retrospective study with compensatory statistical methods constituted a reasonable approach to address this issue.

Why Delayed CABG May Be Preferable

In light of the present findings and similar conclusions by others, we must ask the question of why delayed CABG leads to improved outcomes in the setting of AMI. Intuitively it seems that early reperfusion would lead to the preservation of myocardium, thus limiting infarct size. However, reperfusion injury can lead to increased damage to the vital myocardium beyond the ischemic insult.²⁴ Furthermore, it is known that during the acute phases of an infarct, whole body inflammatory states are increased with increased levels of C-reactive protein as a marker.^{25,26} It is possible that reperfusion-induced inflammatory states have systemic manifestations that increase mortality. Beyond biological explanations, on a programmatic level, it is also possible that outcomes are improved by operating in a planned and controlled setting where routine physician, nursing, and ancillary staff are present and rested. Whether these or other unknown factors contribute to reduced mortality by deferring CABG after AMI is still unclear and a subject of considerable interest.

Conclusions

In this analysis, we sought to determine the optimal CABG timing after AMI among patients who underwent surgery during the index hospitalization. We observed a reduced mortality rate when CABG was deferred until hospital day 3, consistent with previous reports. This effect was also observed among high-acuity patients who presented in hemodynamic shock or requiring IABP support. These results suggest that CABG may best be deferred for 3 or more days after admission for AMI under nonurgent clinical circumstances.

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Discussion

Dr Mitruka (Rancho Mirage, Calif). I think there is little question that early revascularization confers a survival advantage in patients with AMI. This has been demonstrated by the cardiologists performing PCI in this patient population. Indeed, the door to balloon time is now a benchmark for programmatic success. This early intervention has resulted, however, in many surgeons being cajoled or even coerced into performing high-risk operations earlier than may be beneficial. The optimal timing of surgical revascularization after AMI remains somewhat controversial, although it is generally accepted that waiting is better. This was demonstrated by the Columbia group evaluating New York State databases, and they showed that waiting to operate, especially in patients with transmural infarcts, results in better outcomes.

This retrospective study performed by the Johns Hopkins group using California discharge data adds to the growing body of literature that attempts to objectify the optimal timing of CABG after AMI. This group is to be congratulated for a statistical tour de force that overcame many of the inherent limitations and biases of a retrospective study in drawing meaningful conclusions. By using multiple logistic and linear regression, as well as propensity-adjusted multivariate analysis, the risk of adverse events could be assessed while controlling for factors associated with high preoperative clinical acuity. With this methodology, they were able to conclude that early CABG less than 3 days after an AMI was an independent predictor of mortality after controlling for clinical acuity and surgical propensity. Identifying the optimal timing of CABG after AMI to be 3 to 5 days to reduce postoperative mortality will be of clear clinical benefit. Furthermore, outlining that patients with higher acuity undergoing operation sooner will have higher morbidity will be beneficial in aligning outcome expectations between surgeons and our referring physicians. With that long-winded preamble, I have a few questions that you are invited to answer individually.

It is generally well accepted by most surgeons that preoperative assessment of left ventricular function, particularly after an AMI, is one of the best predictors of postoperative outcome. Yet, left

ventricular function in this particular study as a variable was not assessed. Could you comment as to why?

Dr Weiss. I agree with you that left ventricular function is important. The reason we were not able to include it was because it was simply not a component of the California discharge database. Clearly these administrative databases have limitations, the principle one being a limitation of the data and variables that would be present if you had an opportunity to design the study from the beginning and oversee data collection. If we had control of the data set, we certainly would be interested in examining ventricular function. In addition, there is selection bias associated with retrospective administrative databases and an inability to recognize undocumented inherent patient differences.

Rather than focusing on the weaknesses of these studies, I like to focus on the strengths, being that these types of studies provide a broad multi-institutional sample. They allow examination of outcomes that are applicable to both small centers and large academic institutions. They offer another tool for providing evidence-based guidelines for our patients. I think the best way to address variables that are not present in the data set is to conduct a secondary study, perhaps using institutional data where you can control what variables are present. In fact, we are in the process of conducting a similar study based on our own institutional data with patients undergoing CABG, and we hope that this will provide some of the answers that are not readily available using the California database.

Dr Mitruka. The anatomic location and size of the infarct are allegedly addressed by the comorbidity index, the Charlson index. However, it is also well recognized that patients with transmural infarcts that are perhaps anterior infarcts pose a higher risk in the perioperative period when operated on sooner rather than later. Was there any way to distinguish those patients in this database during your analysis to come up with a subgroup of patients who perhaps were at even higher risk?

Dr Weiss. We could identify the location of the infarct on the basis of the data we had. We incorporated that information into our propensity adjustment. On the multivariable logistic regression, we only used anterolateral infarct because that was the only factor that was a significant predictor of mortality on univariate analysis. So the answer to your question is yes, we did look at those variables. We incorporated them in a univariate model, and then we used them in our multivariable model accordingly.

Dr Mitruka. We, as clinical surgeons, oftentimes feel as though the longer we can wait, or we are taught to believe that the longer we can wait after an AMI before operating, the better, so I was a bit surprised to see that the longer you waited with patients, 2 to 3 weeks after an MI, the higher the mortality. We would have expected that the mortality decreases over the course of time. Would you comment on that?

Dr Weiss. As you pointed out, according to the studies done by the Columbia group, you would expect mortality to decrease over time. That has been shown in the past, and our findings would seem to contradict their findings. I think the difference lies in the fact that we looked at a subset of patients who were hospitalized and could not be discharged. Previous studies looked at patients who could be discharged. We thus examined a more acute cohort of patients, and I speculate that the reason some of these patients had higher mortality was because those who underwent operation

later possessed higher clinical acuity with more comorbidities. This is perhaps the type of patient who has brittle diabetes, congestive heart failure, or COPD. This is the type of patient who you would prefer not to operate on, but for one reason or another later on in their hospitalization your hand is forced. We do have data to back that up. We examined that subset of patients, the late patients, and we did see that their Charlson Index was a full point higher than that of the remainder of the study population, so they indeed had a higher comorbidity index. In addition, those patients had a higher percentage of shock, higher percentage of intraaortic balloon pump, so I suspect that the difference is that our patient population is slightly different and that those patients operated on later were more acutely ill.

Member of the audience: I just want to ask one quick question. Did you look at the mortality rate for AMI without surgery? Is this an effect that occurs because the highest death rate from AMI is early, and this is an effect maybe of the disease rather than surgery?

Dr Weiss. That is a good point. We did not specifically do the same analysis on AMI without surgery. We designed the study to capture data such that we only looked at those who received surgery. I agree with you, and I think it is probably true that this is a function of the disease process, but within that disease process, if we look at the subset of those who have required surgery, we should still be able to identify the optimal time for CABG surgery in that cohort.

Dr Vallieres (Seattle, Wash). I am not a cardiac surgeon but I was wondering if you had looked at which day of the week (eg, Monday, Tuesday) when the infarct occurred and correlated to the day of the week when the revascularization occurred and whether this had an impact on these variables.

Dr Weiss. We did not. It was not present in the data set, and we did not look at it.

Dr Cohen. I had a couple of questions, but as the discussion ensued they turned into comments. The first comment is that I have to take issue with the statement that there are patients early on who would have fared better had you waited to operate. I think the study of your design might have been better had you excluded some of the patients who were absolutely without question going to die early without operation because I think they would have died had you waited, and so I think that invalidates that statement.

The second thing is that I have to emphasize what our primary discussant said. I think that ventricular function in the face of AMI and in determining when that patient is going to undergo operation is absolutely crucial, and I think that might be the fatal blow in determining the validity of this study because this study is incredibly important. Heart surgeons are going to rely on studies such as this in determining how to make life and death decisions for patients. I just don't know how you can do it without knowing what the ventricular function is in the face of an AMI.

Dr Weiss. As I said, we are attempting to perform a second study using our own institutional data that may answer some of those questions.

Dr Slater (Portland, Ore). I have some quick data questions. Did you segregate the data for men and women? Is the day of hospitalization the same as the day of MI for your group or was there any variability in that some patients come in several days after their MI? You have the date of surgery, but did you break it down by patients who came in, had an AMI on say Monday, Tuesday, are catheterized, and you are operating Tuesday night, versus patients who

are catheterized and scheduled for surgery the following day, and they are done as an elective case?

Dr Weiss. We did not segregate on the basis of gender. We did look at gender in our multivariable model. Female gender was a predictor of worse outcomes, as has been shown previously.

The structure of the database does not really allow us to discriminate based on the hours at which you receive your CABG. It is only based on days. It is one of the limitations of the study, and we acknowledge that.

To answer your question about which patients presented and when they presented, these were all patients whose hospital day zero was their initial day of hospitalization, and it was also their day of presentation, the day that they had an AMI. We went to great efforts to identify patients who were admitted to the hospital solely with the principle diagnosis of AMI. For example, we excluded hospital transfers. We wanted to identify a group of patients for whom day zero truly was the day that they were admitted with AMI.

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TABLE E1. Exclusion criteria for study

Exclusion criteria	ICD-9-CM codes	No. of patients excluded (original N = 40,159)
Age < 18 y	NA	1
Hospital transfers	NA	15,276
Incomplete data, including no data on CABG timing available	NA	13,261
Diseases of mitral valve (stenosis and insufficiency)	394, 394.0, 394.1, 394.2, 394.9, 424.0	1108
Additional cardiac pathology		
Diseases of aortic valve (stenosis and insufficiency)	395, 395.0, 395.1, 395.2, 395.9, 424.1, 746.5, 746.6	439
Combination mitral and aortic disease	396, 396.0, 396.2, 396.3, 396.8, 396.9, 746.3, 746.4	184
Pulmonary valve disease	397.1, 424.3, 746.00, 746.01, 746.02, 746.09	2
Tricuspid valve disease	397, 397.0, 424.2, 746.1	69
Malfunctioning mechanical valve	996.02, 996.71	1
Concomitant procedures		
Mitral valve replacement/repair	35.1, 35.12, 35.2, 35.23, 35.24, 35.33, 35.98, 35.99	15
Aortic valve replacement/repair	35.01, 35.11, 35.21, 35.22	11
Heart transplantation	37.5, 37.51	0
Implantation of removal of ventricular assist device	37.64, 37.65, 37.66	318
Pulmonary valve replacement/repair	35.03, 35.13	0
Tricuspid valve replacement/repair	35.04, 35.14	0
Final study population		9476

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NA, not available.

TABLE E2. Independent and dependent variables generated from ICD-9 and ICD-9-CM coding

Primary variable day of CABG	
Baseline	
Independent variables	ICD-9-CM codes used
Charlson index*	See below
Diabetes mellitus (Y/N)	250, 250.0 250.1, 250.3, 250.7, 250.8, 250.9
COPD	491.2, 491.20, 491.21, 491.22 492, 492.0, 492.8
Hypertension	401, 401.1, 401.91
CRF	585, 588
History of stroke	431, 433, 433.3, 433.8, 433.9, 434, 434.0, 434.1, 434.9
Hyperlipidemia	272.2, 272.4
Obesity	278.0, 278.00, 278.01
PVD	443, 443.8, 443.89, 443.9
Type of AMI:	
Anterolateral	410, 410.0, 410.00, 410.01, 410.02, 410.1 410.10, 410.11, 410.12
Posterior	410.6, 410.60, 410.61, 410.62
Inferior	410.4, 410.40, 410.41, 410.42
Lateral	410.5, 410.50, 410.51, 410.52
Subendocardial	410.7, 410.70, 410.71, 410.72
Acuity variables	ICD-CM (for procedures) codes
CPR	99.63
IABP before CABG	376.1
Conduction disorder on admission	426, 426.0, 426.1, 426.10, 426.11, 426.12, 426.13, 426.2, 426.3, 426.4, 426.5, 426.50, 426.51, 426.52, 426.53, 426.54, 426.6, 426.8, 426.81, 426.89, 426.9
Ventricular fibrillation on admission	427.4, 427.41, 427.42
Cardiac arrest on admission	427.5, 779.85
Mechanical ventilation before CABG	967, 967.0, 967.1, 967.2, 960.4
Shock	785.51
Atrial fibrillation on admission	427.3, 427.31, 427.32
Ventricular tachycardia on admission	427.1
Coronary stent before CABG	00.45, 00.46, 00.47, 00.48, 00.66, 36.01 36.02, 36.05, 36.06, 36.07
Angiogram before CABG	88.5, 88.50, 88.51, 88.52, 88.53, 88.54, 88.55, 88.56, 88.57
Outcome variables	
Postoperative LOS	Present in database
Postoperative stroke	431, 433, 433.3, 433.8, 433.9, 434, 434.0, 434.1, 434.9
Prolonged ventilation (>96 h)	967.2
Postoperative ARF	584, 584.6, 584.7, 584.8, 584.9, 586 587, 588, 5880, 588.1, 588.8, 588.9
Postoperative new onset dialysis	125.5, 389.5, 392.7, 394.2, 399.5
Wound infection	998.5, 998.59

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; *CABG*, coronary artery bypass graft; *AMI*, acute myocardial infarction; *COPD*, chronic obstructive pulmonary disease; *PVD*, peripheral vascular disease; *CRF*, chronic renal failure; *ARF*, acute renal failure; *CPR*, cardiopulmonary resuscitation; *IABP*, intra-aortic balloon pump; *LOS*, length of stay. *Charlson Index includes a weighted compilation of 17 baseline comorbidities in multiple systems, including cardiovascular (ischemic disease and congestive heart failure), renal, endocrine (diabetes mellitus), cerebrovascular, peptic ulcer, rheumatologic, hepatic, oncologic (history of cancer or malignancies), and infectious (human immunodeficiency virus/acquired immune deficiency). A total of 1186 unique ICD-9 codes are used for the creation of the Charlson Index.

TABLE E3. Variables included in propensity analysis to assess the likelihood of undergoing early coronary artery bypass grafting

Category	Variable
Demographics	Age (y)
	Gender
	Race
	Charlson index score*
	Hypertension (not part of Charlson)
MI type	Anterolateral infarct
	Subendocardial infarct
Acuity	Shock
	Cardiac arrest on admission
	Thrombolysis before CABG
	Mechanical ventilation before CABG
	Conduction disorder
	Ventricular fibrillation on admission
	Ventricular tachycardia on admission
	Atrial fibrillation on admission
	Angina on admission
	Red blood cell transfusion before CABG
	Angiogram before CABG
Coronary stent before CABG	

MI, Myocardial infarction; *CABG*, coronary artery bypass grafting. *These variables include 17 Charlson index parameters to comprise the 35 variables used to create the propensity score.