Surgery

Timing of nonemergent coronary artery bypass grafting and mortality after non-ST elevation acute coronary syndrome

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Background The purpose of this study was to determine the association between time to coronary artery bypass grafting (CABG) and mortality among patients admitted with non-ST elevation acute coronary syndrome (NSTEACS). Patients are increasingly being referred for CABG soon after NSTEACS, although few data exist to guide the optimal timing of bypass surgery.

Methods We identified a cohort of all patients who underwent nonemergent CABG within 60 days of hospitalization for NSTEACS in the province of Alberta, Canada, from 2000 to 2004. Time from admission to CABG was categorized as early (2-7 days), intermediate (8-14 days), or late (15-60 days—reference group). The primary outcome was mortality occurring within 30 days of surgery.

Results Of the total cohort of 1,454 patients, 213 (14.6%) underwent early, 637 (43.8%) underwent intermediate, and 707 (48.6%) underwent late CABG surgery. In the final adjusted model time to CABG was not statistically significant as an independent predictor of short-term mortality. Compared to late CABG, there was a nonsignificant increased risk of mortality for those undergoing early (hazard ratio 2.36, 95% CI 0.72-7.76) and intermediate (hazard ratio 1.68, 95% CI 0.76-3.72) CABG surgery.

Conclusions Time from admission to CABG was not associated with an increased risk of short-term mortality. However, there was a trend toward increased mortality with early CABG, and this study does not exclude the presence of a modest risk association between timing of CABG and short-term mortality. (Am Heart J 2010;159:490-6.)

Guidelines for management of non-ST elevation acute coronary syndrome (NSTEACS) advocate early angiography for patients at risk for adverse events.[1,2] Consequently when surgical anatomy is evident, patients are increasingly being referred for coronary artery bypass grafting (CABG) soon after admission, even when clinically stable. Up to 21% of patients with NSTEACS will undergo CABG during their hospital admission,[3-6] yet there is little evidence to guide the optimal timing of nonemergent bypass surgery after NSTEACS.

The rationale for early nonemergent CABG after NSTEACS is primarily to reduce the risk of recurrent myocardial ischemia or infarction and death. Early CABG may also confer benefits with respect to improved ventricular function and decreased arrhythmia.[7] However, early CABG is not without potential consequences; cardiopulmonary bypass may exacerbate inflammation and platelet dysfunction associated with atherosclerotic plaque rupture,[8,9] and early CABG has been associated with increased bleeding if carried out within 5 to 7 days of thienopyridine administration.[10,11]

Previous observational studies evaluating timing of CABG and its impact on postoperative mortality have produced conflicting results. Some studies have found no association between timing of surgery and adverse outcomes,[12-17] whereas others have shown increased mortality when CABG is performed within 3 to 7 days.[18-22] However, most studies failed to differentiate NSTEACS from ST elevation myocardial infarction (STEMI) and were conducted before the adoption of early angiography into routine clinical practice.

Multiple randomized clinical trials have evaluated a strategy of early angiography in the NSTEACS population[3-5,23-25]; however, they provided little information regarding timing of CABG. Only two of these trials gave specific recommendations as to when CABG should be performed,[23,25] and the median time to CABG varied

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greatly between trials. Furthermore, in three of the trials, there were trends toward increased postoperative mortality after CABG in the early angiography arms.[3,4,23]

Therefore, there remains considerable uncertainty as to the optimal timing of nonemergent CABG after NSTEACS in the era of early angiography. Given this uncertainty, we sought to determine the association between timing of CABG post-NSTEACS and mortality using a large prospective cohort of patients referred for isolated, nonemergent CABG.

Methods

Ethical approval

This study was compliant with the Declaration of Helsinki. Approval for this study was obtained from the institutional review boards of the University of Alberta, Edmonton, Canada, and the University of Calgary, Calgary, Canada. No extramural funding was used to support this work.

Study population and data sources

We identified the study population using the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) database that captures all patients undergoing angiography or cardiac surgery in the province of Alberta, Canada.[26] All subjects undergoing CABG within 60 days of index admission for NSTEACS from January 1, 2000, to December 31, 2004, were eligible for inclusion. The diagnosis of NSTEACS was made by the responsible physician(s), and positive biomarkers were not required. Index admission was defined as the first hospital admission for NSTEACS, taking into account interhospital transfers and discharges home to await CABG, as determined from administrative databases from the 2 Alberta health regions where CABG was performed. In cases where the date of admission could not be determined from the administrative data, manual review of medical records was performed.

Timing of CABG surgery

The timing of nonemergent CABG was at the discretion of the treating health care providers but was also dependent on triage status (incorporating clinical status) and operating room availability. Both surgical sites used the same scoring tool for surgical triage.[27] We restricted the cohort to clinically stable patients with NSTEACS by excluding subjects if they underwent emergency CABG or CABG within 2 days of admission, required placement of an intraaortic balloon pump, or underwent concomitant surgical procedures such as valve replacement.

The time to CABG surgery was defined as the number of calendar days from index admission to surgery. For the primary analysis, time to CABG was divided into 3 categories: early CABG (2-7 days), intermediate CABG (8-14 days), and late CABG (15-60 days—reference group). These were felt to be clinically relevant time frames, and previous studies have suggested increased risk when CABG is performed within 1 to 2 weeks after MI.[18-20,22] In secondary analyses, time to CABG was treated as a continuous variable and also dichotomized by its median.

Study outcomes and follow-up

The primary outcome was all-cause mortality at up to 30 days after surgery. The secondary outcome was all-cause mortality with at least 1 year of follow-up after surgery. The APPROACH database uses a linkage with the Alberta Bureau of Vital Statistics in ascertainment of mortality.[26]

Statistical analysis

Comparison of baseline subject characteristics across categories of time to CABG was performed using Pearson χ^2 testing or 1-way analysis of variance as appropriate. Times to events for survival analyses were measured from the date of CABG surgery. To adjust for baseline differences in covariates, we used a Cox proportional hazards regression model. Initially, all covariates of interest (demographics, comorbidities, and clinical variables at presentation and angiography) were assessed in a univariate fashion. Data regarding the ethnicity of subjects were not available. It was decided a priori to include the variables age, previous CABG, a history of renal disease, and ejection fraction in the final models, regardless of statistical significance, as these variables have previously been shown to be important predictors of outcome in CABG performed after MI.[28-32] The regression models were further developed using forward stepwise selection of covariates. The linearity of continuous covariates with the log hazard and the proportionality of hazards were assessed, and these assumptions were met. Risk-adjusted survival curves were plotted from the proportional hazards model using the corrected group prognosis method.[33] Given the linear relationship between time to CABG (in days) and all-cause mortality, in a secondary analysis, we explored the mortality risk per day from hospital admission to CABG surgery.

All statistical analyses were carried out using STATA v9.2 (Statacorp, College Station, TX).

The authors are solely responsible for the design and conduct of this study, all analyses, and the drafting and editing of the article and its final contents.

Results

Baseline characteristics

A total of 2,758 subjects underwent CABG after NSTEACS in the province of Alberta during the study period. Of these, 214 had emergent procedures, 182 had concomitant valvular surgery, and 48 were found to have actually had an STEMI. A further 735 subjects were excluded because they underwent CABG within 2 days of admission (presumed emergent CABG) or >60 days from admission resulting in a final study population of 1,557 subjects. The median time to CABG was 14 days (interquartile range 10-19 days). Overall, 208 subjects (13.7%) underwent early CABG (within 2 to 7 days), 637 (40.9%) underwent intermediate CABG (8-14 days), and 707 (45.4%) underwent late CABG (15-60 days).

The baseline characteristics for each group are shown in Tables I and II. Patients who underwent late CABG were older and more likely to have had a history of MI, congestive heart failure, diabetes mellitus, and cerebrovascular disease and an impaired ejection fraction. In

Table I. Baseline demographic and historical characteristics

Baseline characteristics	Total cohort (n = 1557)	Time to CABG: Late: 15-60 d (n = 707)	Time to CABG: Intermediate: 8-14 d (n = 637)	Time to CABG: Early: 2-7 d (n = 213)	P*
Demographic					
Age (y), mean ± SD	66.5 ± 10.5	67.5 ± 10.6	66.2 ± 10.6	64.1 ± 9.4	<.001
≥75 y, n (%)	366 (23.5)	190 (26.9)	148 (23.2)	27 (12.7)	<.001
Females, n (%)	352 (22.6)	171 (24.2)	132 (20.7)	49 (23.0)	.313
Historical, n (%)					
CABG	59 (3.8)	31 (4.4)	21 (3.3)	7 (3.3)	.533
MI	949 (61.0)	465 (65.8)	369 (57.9)	115 (54.0)	.001
PCI	126 (8.1)	52 (7.4)	60 (9.4)	14 (6.6)	.261
Current smoker	433 (27.8)	205 (29.0)	173 (27.2)	55 (25.8)	.592
Hypertension	1082 (69.5)	498 (70.4)	439 (68.9)	145 (68.1)	.741
Dyslipidemia	1230 (79.0)	546 (77.2)	514 (80.7)	170 (79.8)	.284
Diabetes mellitus	459 (29.5)	241 (34.1)	168 (26.4)	50 (23.5)	.001
Congestive heart failure	254 (16.3)	144 (20.4)	90 (14.1)	20 (9.4)	<.001
Cerebrovascular disease	178 (11.4)	99 (14.0)	62 (9.7)	17 (8.0)	.011
Peripheral vascular disease	180 (11.6)	95 (13.4)	65 (10.2)	20 (9.4)	.102
Pulmonary disease	252(16.2)	121 (17.1)	101 (15.9)	30 (14.1)	.550
Renal disease	76 (4.9)	43 (6.1)	28 (4.4)	5 (2.4)	.065

PCI, Percutaneous coronary intervention.
* *P* value < .05 by Pearson χ^2 testing for categorical or 1-way analysis of variance for continuous variables.

Table II. Baseline clinical and angiographic characteristics

Baseline characteristics	Total cohort (n = 1557)	Time to CABG: Late: 15-60 d (n = 707)	Time to CABG: Intermediate: 8-14 d (n = 637)	Time to CABG: Early: 2-7 d (n = 213)	P*
Clinical					
ACS type					
NSTEMI	595 (38.2)	283 (40.0)	231 (36.3)	81 (38.0)	
Unstable angina	962 (61.8)	424 (60.0)	406 (63.7)	132 (62.0)	.365
CCS angina class, n (%)					
IVa	1127 (72.4)	535 (75.7)	449 (70.5)	143 (67.1)	.003
IVb	160 (10.3)	55 (7.8)	79 (12.4)	26 (12.2)	.054
IVc	89 (5.7)	30 (4.2)	41 (6.4)	18 (8.5)	.124
Presenting ECG, n (%)					
Atrial fibrillation	61 (3.9)	36 (5.1)	19 (3.0)	6 (2.8)	.176
ST depression	424 (27.2)	172 (24.3)	181 (28.4)	71 (33.3)	.037
LBBB	62 (4.0)	29 (4.1)	27 (4.2)	6 (2.8)	.614
Angiographic					
Ejection fraction, n (%)					
>50%	921 (59.2)	377 (53.3)	389 (61.1)	155 (72.8)	<.001
35%-50%	426 (27.4)	219 (31.0)	175 (27.5)	32 (15.0)	<.001
<35%	107 (6.9)	63 (8.9)	35 (5.5)	9 (4.2)	.041
Coronary anatomy, n (%)					
1/2-Vessel disease	260 (16.7)	109 (15.4)	110 (17.3)	41 (19.3)	.580
3-Vessel disease	846 (54.3)	395 (55.9)	346 (54.3)	105 (49.3)	.488
Left main disease	442 (28.4)	200 (28.3)	177 (27.8)	65 (30.5)	.837
Composite					
Urgency rating score, mean ± SD	4.95 ± 1.02	5.02 ± 0.95	4.91 ± 1.07	4.85 ± 1.08	.054

NSTEMI, Non-STEMI; *CCS*, Canadian Cardiovascular Society; *ECG*, electrocardiogram; *LBBB*, left bundle branch block.
* *P* value < .05 by Pearson χ^2 testing for categorical or 1-way analysis of variance for continuous variables.

contrast, those undergoing early CABG were more likely to have ST depression on their presenting electrocardiogram and also had worse average Canadian Cardiovascular Society angina class.[34] Notably, there were no differences between groups with respect to the composite Urgency Rating Score, a risk stratification and triage tool for CABG.[27] Furthermore, the proportion of patients with left main disease was similar across groups.

Table III. Adjusted risk of mortality within 30 days, by time to CABG

Variable	Adjusted* hazard ratio	95% CI
Time to CABG, categorized		
Early CABG (2-7 d)	2.36	0.72-7.76
Intermediate CABG (9-14 d)	1.68	0.76-3.72
Late CABG (15-60 d)	Reference	
Age (per 1-y increase)	1.07	1.02-1.13
Previous CABG	3.56	1.22-10.44
Pulmonary disease	2.33	1.07-5.07
Renal disease	4.15	1.54-11.19
Ejection fraction		
>50%	Reference	
35%-50%	1.38	0.57-3.32
<35%	4.19	1.62-10.78

* Adjusted for all other variables in the table.

Short-term mortality

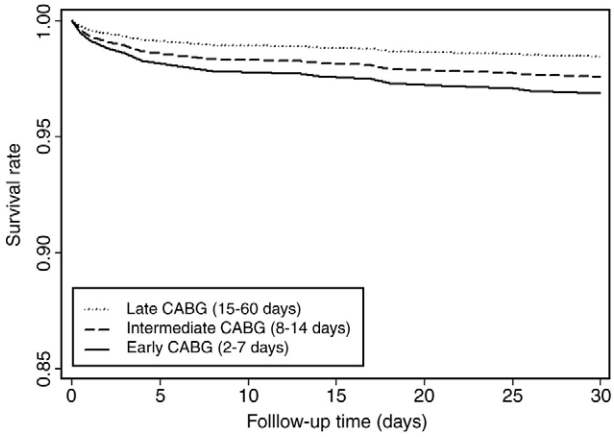
There were a total of 36 deaths (2.31%) at up to 30 days post-CABG surgery. The crude mortality rate was 2.35% (95% CI 0.31%-4.39%) for early, 2.98% (95% CI 1.66%-4.31%) for intermediate, and 1.70% (95% CI 0.74%-2.65%) for late CABG surgery. These differences were not significant (Pearson χ^2 P = .293).

In the univariate analysis, time to CABG was not a statistically significant predictor of mortality within 30 days. The unadjusted hazard ratio for death at 30 days, using late CABG as a reference, was 1.39 (95% CI 0.49-3.95) for early and 1.77 (95% CI 0.86-3.64) for intermediate CABG surgery.

Age, prior CABG, pulmonary disease, renal disease, and ejection fraction remained independent predictors of short-term mortality in the multivariate analysis. In the final model adjusted for these variables, time to CABG was not associated with an increased risk of mortality at up to 30 days post-CABG. However, there was a trend toward increased mortality with early CABG (P = .158). Using the late (15-60 days) CABG group as the reference, the estimated adjusted hazard ratio for death at 30 days was 2.36 (95% CI 0.72-7.76) for early CABG (2-7 days) and 1.68 (95% CI 0.76-3.72) for intermediate CABG (8-14 days) (Table III). The adjusted survival curves for the final model, according to timing of surgery are shown in Figure 1. There was no significant interaction by gender in the multivariate analysis.

Time to CABG remained nonsignificant as a predictor of short-term mortality when treated as a continuous variable. The adjusted hazard ratio per 1-day delay in CABG was 0.97 (95% CI 0.92-1.02). When time to CABG was dichotomized by its median of 14 days, a similar trend of a nonsignificant increased risk of mortality with early CABG was evident. Compared to late CABG (15-60 days), patients undergoing earlier CABG (between 2 and 14 days) experienced a nonsignificant increased risk of mortality (adjusted hazard ratio 1.78 [95% CI 0.84-3.81]).

Figure 1



Adjusted survival curves by timing of CABG using the corrected group prognosis method. The survival curves were adjusted for the variables of age, previous CABG surgery, a history of pulmonary disease, a history of renal disease, and ejection fraction. Note that the y-axis is truncated for clarity.

Long-term mortality

The median duration of follow-up was 3.7 years. In the unadjusted analysis, those undergoing early CABG had significantly lower long-term mortality compared to late CABG with a hazard ratio of 0.43 (95% CI 0.23-0.78, P = .008). In the final model adjusted for age, history of renal failure, previous CABG, diabetes mellitus, and atrial fibrillation, time to CABG was not a significant predictor of long-term mortality (P = .520). Using the late CABG group as the reference, the adjusted hazard ratio for death for the early CABG group was 0.69 (95% CI 0.35-1.35) and for the intermediate CABG group was 0.99 (95% CI 0.71-1.37). When time to CABG was dichotomized by its median or treated as a continuous variable, it remained a nonsignificant predictor of long-term mortality.

Discussion

In this large inception cohort of subjects undergoing nonemergent CABG after admission for NSTEACS, we found that the time from index admission to surgery was not associated with a significantly increased risk of short-term mortality at 30 days post-CABG surgery. Nonetheless, there was a trend toward higher postoperative mortality when CABG was performed within 1 to 2 weeks of admission. On long-term follow-up of >3 years, this trend did not persist, and there was no influence of timing of CABG on mortality.

The low crude mortality rates that we observed in each of the groups in this study, ranging from 1.70 (late CABG, 95% CI 0.74%-2.65%) to 2.98% (intermediate CABG, 95%

CI 1.66%-4.31%), suggest that CABG can be performed with relative safety in stable patients early after NSTEACS. Although these mortality rates remain higher than those observed for the elective CABG population, they are nonetheless comparable or lower than rates observed in previous studies of CABG after MI/ACS. The crude mortality rates in this observational study are comparable to those observed in the subgroups undergoing CABG after NSTEACS in the FRISC 2 and TACTICS-TIMI 18 trials.[4,23] The mortality rates in the present study were substantially lower in comparison with other contemporary cohorts undergoing CABG after ACS.[21,22] However, these studies did not exclude patients with STEMI or undergoing emergency CABG.

On the basis of the results of this study, we cannot exclude the presence of a modest increase in perioperative mortality when CABG is performed within 1 to 2 weeks after admission. The trend toward increased postoperative mortality with early CABG is consistent with the findings from the CABG subgroups in three of the randomized trials of early intervention in NSTEACS, though the median time to CABG varied widely between the trials.[3,4,23]

The period for enrolment in this cohort study, encompassing the years 2000 to 2004, was chosen to ensure a wide distribution of time from admission to CABG as routine early angiography for NSTEACS was being introduced into clinical practice at this time. The median time to CABG of 14 days in this study compares favorably with that seen in the previous randomized trials of early intervention for NSTEACS.[4,23,24] In comparison to previous observational studies, CABG was performed much earlier after admission in the present study, with the exception of the study of Weiss et al[22] (mean time to CABG of 3 days), whose cohort included a high proportion of STEMI and cardiogenic shock.[20-22] Overall, the earlier timing of CABG in this study (and even during the course of this study) supports our hypothesis that the adoption of early angiography after NSTEACS into routine clinical practice in this period has resulted in patients being increasingly referred for CABG soon after admission.

There are notable limitations to this study. First, the low event rate that we observed may have rendered this study underpowered to detect a small increase in mortality in those undergoing CABG soon after admission. Nevertheless, the results of this study should provide reassurance that mortality rates after early CABG remain low. Second, this study was observational in nature and consequently was subject to potential confounding by surgical bias in that health care providers may have chosen to operate earlier on patients at higher risk or with clinical deterioration. Despite this potential, we found a systematic bias toward delaying CABG in the elderly with comorbidities and in those with impaired cardiac function, all of whom are at high risk of deterioration without revascularization. We further attempted to minimize the influence of surgical bias by excluding patients undergoing emergent surgery and those with cardiogenic shock, as well as by adjustment for baseline differences in the analysis. Finally, we also could not account for the period from initial admission to surgery. The APPROACH database does not include information on subjects who died while awaiting CABG or who were referred for CABG but did not undergo surgery because of patient or physician refusal. Therefore, to be included in the present study, all subjects must have survived to the time of CABG. Mortality in the first 14 days after non-STEMI can occur relatively frequently, ranging from 1.0% to 6.5% depending on the underlying patient risk.[35] Therefore, patients who survived to undergo delayed CABG may have already proven themselves more robust and hence have experienced a lower short-term mortality rate after CABG.

Notwithstanding these limitations, we addressed many of the major methodological limitations of previous observational studies examining the association of timing of surgery with postoperative outcomes in the MI/ACS population. Most significantly, we restricted this study to NSTEACS only as indications for bypass surgery differ greatly in STEMI. Unlike prior studies, we excluded patients with cardiogenic shock or requiring emergency surgery. Ours was also one of the few studies to rigorously define timing of CABG using the date of index admission as time zero. Many previous studies have used onset of symptoms as the reference time point, but the validity of this is in the NSTEACS population is questionable, where symptoms are often atypical.[36] Furthermore, to our knowledge, only one other study also accounted for transfers from other hospitals in determining timing of CABG.[22]

Overall, we found no independent association between timing of bypass surgery after admission for NSTEACS and risk of postoperative mortality. Coronary artery bypass graft performed even within the first 2 weeks of admission carries with it a relatively low mortality risk. Nonetheless, we did observe a nonsignificant increase in mortality when surgery was undertaken during the first 1 to 2 weeks. Whether a small increased perioperative risk with early CABG would be offset by reduced recurrent ACS or death while awaiting CABG remains to be elucidated.

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