Outcome of Patients With Low Ejection Fraction Undergoing Coronary Artery Bypass Grafting

Renal Function and Mortality After 3.8 Years

Graham S. Hillis, MBChB, PhD; Kenton J. Zehr, MD; Amy W. Williams, MD; Hartzell V. Schaff, MD; Thomas A. Orzulak, MD; Richard C. Daly, MD; Charles J. Mullany, MD; Richard J. Rodeheffer, MD; Jae K. Oh, MD

Background—There are few data regarding medium-term outcome of coronary artery bypass grafting (CABG) in patients with severe left ventricular (LV) systolic dysfunction, particularly in the modern era, and even less assessing preoperative factors that might identify patients at highest risk.

Methods and Results—Three hundred seventy-nine consecutive patients with LV ejection fraction ≤35%, who underwent isolated first CABG between 1995 and 1999 were studied. Potential preoperative and perioperative predictors of outcome were recorded and patients followed-up for a median of 3.8 years. The primary study end-point was all-cause mortality. The 30-day, 1-year, and 3-year survival rates were 94.5%, 88%, and 81%, respectively. The independent predictors of mortality were preoperative estimated glomerular filtration rate (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.97 to 0.99 per mL/min/1.73m²; P<0.001) and age (HR, 1.03; 95% CI, 1.01 to 1.06 per year; P=0.005).

Conclusions—Patients with significant LV systolic dysfunction undergoing isolated CABG using contemporary techniques have a good medium-term survival. Renal dysfunction is the strongest independent predictor of mortality. (Circulation. 2006;114[suppl I]:I-414–I-419.)

Key Words: coronary disease • kidney • surgery • survival

Major randomized control studies comparing medical therapy with coronary artery bypass grafting (CABG) did not recruit patients with a left ventricular (LV) ejection fraction <35%. They did, however, demonstrate improved survival in surgically treated patients with milder degrees of LV systolic dysfunction. Likewise, cohort studies and data on nonrandomized patients from the Coronary Artery Surgery Study registry have also favored surgical revascularization over medical therapy. These data suggest that CABG may improve prognosis in selected patients with coronary heart disease and severely impaired systolic function, and it is frequently performed on this patient population. It is, however, associated with a modest increase in risk compared with patients with normal LV function, with some older publications reporting extreme variations in outcome. Nevertheless, previous studies have primarily addressed early (in-hospital and/or 30-day) outcome, with limited contemporary data regarding longer-term mortality and morbidity. Likewise, there are few data assessing the preoperative factors that might identify patients who are at highest risk. To address these issues, the current study reports the medium-term outcome of a large cohort of consecutive patients with LV ejection fraction ≤35%, who underwent isolated first CABG surgery between 1995 and 1999, and the factors influencing this.

Methods

Patients

The study was approved by the Mayo Foundation Institutional Review Board. All patients who underwent isolated first CABG at the Mayo Clinic, Rochester, Minnesota between January 1, 1995 and December 31, 1999, and whose preoperative LV ejection fraction was ≤35%, were identified (n=379). In 195 patients (51%) this was determined by echocardiography, in 169 (45%) left ventriculography and in 15 (4%) by radionuclide scanning. Patients undergoing re-do CABG, concomitant valvular surgery, cardioverter-defibrillator implantation, aneurysmectomy, or ventricular septal defect repair were excluded.

Measures

Demographic and clinical data were recorded, including the preoperative Canadian Cardiovascular Society (CCS) angina class and the New York Heart Association (NYHA) functional class. Preoperative hemoglobin and creatinine and levels were documented (using the sample taken immediately before surgery) and the glomerular filtration rate estimated (eGFR) using the Modification of Diet in Renal Disease equation. Using this equation the eGFR (mL/min/1.73m²) = 186 × (serum creatinine level [mg per deciliter]) ^(-1.154) × (age [years]) ^(-0.203). The product of this equation was multiplied by a correction factor of 0.742 for women and 1.212 for blacks. Patients were categorized into 4 groups dependent on their eGFR (≥75 mL/min/1.73m², 60 to 74 mL/min/1.73m², 45 to 59 mL/min/1.73m², <45 mL/min/1.73m²), as described by the US National Kidney Disease Outcome Quality Initiative.
Angiographic data and operative details were recorded, with an angiographic stenosis of \( \geq 50\% \) considered significant.

Follow-Up
Patients were followed-up between January and June 2002. Initially, a review of Mayo Clinic records was performed. Patients were then contacted by telephone to confirm the recorded data and ensure that events treated at other institutions were documented. A scripted telephone interview was used to determine symptom status (CCS angina score and NYHA class). When telephone contact could not be established, a mailed questionnaire was used. If necessary the patient’s cardiologist or primary physician was contacted to acquire missing information, confirm the data, and/or obtain updated contact details. If the patient could not be contacted, vital status was established using the Social Security Index.

The primary study end-point was all-cause mortality. In addition, data were collected regarding nonfatal myocardial infarction (defined using standard criteria pertaining at the time it occurred\(^9\,10\)), further myocardial revascularization, cardiac transplantation, and symptom status at follow-up.

Statistical Analyses
Continuous data are expressed as median (interquartile range) and categorical data as absolute values (percentage). Survival was plotted using the Kaplan-Meier method and compared using the log-rank statistic. Estimations of risk were performed using the Cox proportional hazard method. Potential independent predictors of outcome were identified by univariable analyses. Univariable predictors were entered in a stepwise manner into a multivariable model of survival, with entry and retention set at a significance level of \( \leq 0.05 \). SPSS version 9.0 (SPSS Inc, Chicago, Ill) was used for all analyses.

Results
Patient Population
The clinical characteristics of the study cohort are shown in Table 1. At the time of surgery, 150 patients (40\%) had CCS class I angina, 43 (11\%) class II, and 186 (49\%) CCS class III or IV. Sixty-eight of the 201 (34\%) patients with NYHA functional class III or IV symptoms had little or no angina (CCS class I) at the time of surgery.

Fifty-nine patients had undergone 75 previous percutaneous coronary interventions. One patient was receiving renal replacement therapy before surgery and 1 patient had a pre-existing implantable cardioverter-defibrillator.
Preoperative Investigations and Operative Details

Results of preoperative investigations are shown in Tables 1 and 2. Of the total cohort, 337 patients (89%) had either significant (≥50%) left main stem stenosis or 3-vessel coronary artery disease or both (Table 2). Sixteen patients (4%) underwent surgery without the use of cardiopulmonary bypass (“off pump”). Total bypass and aortic cross-clamp times for the remaining patients are shown in Table 2.

Follow-Up

Vital status data were obtained on all patients a median of 3.8 (2.5 to 5.3) years after surgery. The 30-day mortality rate was 5.5% (21/379). Four of these deaths occurred within 1-day of surgery. There were 86 late (after 30-days) deaths. The 1- and 3-year survival rates were 88% and 81%, respectively. Among the 272 survivors, 21 patients sustained a total of 22 nonfatal acute myocardial infarctions and 16 patients underwent further myocardial revascularization (15 percutaneous coronary interventions and 1 re-do CABG). No patients underwent cardiac transplantation during follow-up. Two patients required renal replacement therapy within 7 days of surgery. At follow-up, the CCS angina class was available in 235 patients (87% of survivors) and NYHA functional class in 236 patients (87%). Only 12 surviving patients had a CCS angina class ≥II, in comparison to 105 of the same patients at baseline. Thirty-nine survivors were in NYHA class III or IV, compared with 122 of the same patients at baseline.

Univariable Predictors of Mortality

The most powerful predictors of mortality during long-term follow-up were renal function and age (Table 1 and Figures 1 and 2).

**TABLE 2. Angiographic and Operative Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=379)</th>
<th>Alive (n=272)</th>
<th>Died (n=107)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main stem stenosis</td>
<td>121</td>
<td>84 (31%)</td>
<td>37 (35%)</td>
<td>1.17 (0.79–1.74)</td>
<td>0.44</td>
</tr>
<tr>
<td>Three vessel coronary artery disease</td>
<td>307</td>
<td>222 (82%)</td>
<td>85 (79%)</td>
<td>0.88 (0.55–1.40)</td>
<td>0.59</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>31 (25–33)</td>
<td>31 (25–33)</td>
<td>30 (25–33)</td>
<td>1.00 (0.95–1.05)</td>
<td>0.89</td>
</tr>
<tr>
<td>End diastolic pressure (mm Hg)</td>
<td>26 (19–32)</td>
<td>27 (20–33)</td>
<td>25 (17–28)</td>
<td>0.97 (0.94–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Operative details</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IABP preoperatively</td>
<td>54</td>
<td>36 (13%)</td>
<td>18 (17%)</td>
<td>1.34 (0.81–2.23)</td>
<td>0.26</td>
</tr>
<tr>
<td>Three or more grafts</td>
<td>315</td>
<td>230 (85%)</td>
<td>85 (79%)</td>
<td>0.63 (0.39–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Internal mammary graft used</td>
<td>352</td>
<td>260 (96%)</td>
<td>92 (86%)</td>
<td>0.41 (0.23–0.70)</td>
<td>0.001</td>
</tr>
<tr>
<td>Bypass time (minutes)*</td>
<td>88 (66–114)</td>
<td>87 (65–112)</td>
<td>93 (69–118)</td>
<td>1.00 (1.00–1.01)</td>
<td>0.35</td>
</tr>
<tr>
<td>Cross-clamp time (minutes) *</td>
<td>50 (34–61)</td>
<td>50 (36–61)</td>
<td>49 (33–62)</td>
<td>1.00 (0.99–1.01)</td>
<td>0.76</td>
</tr>
<tr>
<td>‘Off-pump’ CABG</td>
<td>16</td>
<td>12 (4%)</td>
<td>4 (4%)</td>
<td>0.75 (0.27–2.04)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

*Excludes surgery performed “off-pump” (n=16).
IABP indicates intra-aortic balloon pump.

Figure 1. The effect of age on survival after coronary artery bypass grafting.
Receipt of an internal mammary artery graft was also associated with improved survival.

When patients who had sustained an acute myocardial infarction in the month before their index CABG (n=145, 38%) were excluded, the univariable predictors of mortality were age (hazard ratio [HR], 1.05 per year; 95% confidence interval [CI], 1.02 to 1.08; \( P = 0.001 \)), creatinine (HR, 1.56 per mg/dL; 95% CI, 1.20 to 2.04; \( P = 0.001 \)), eGFR (HR, 0.97 per mL/min/1.73m\(^2\); 95% CI, 0.96 to 0.99; \( P < 0.001 \)), creatinine \( \geq 1.5 \) mg/dL (HR, 1.76; 95% CI, 1.06 to 2.90; \( P = 0.03 \)), CCS class 3 or 4 angina (HR, 1.65; 95% CI, 1.02 to 2.68; \( P = 0.04 \)), and receipt of an internal mammary artery graft (HR, 0.32; 95% CI, 0.14 to 0.75; \( P = 0.008 \)).

### Multivariable Predictors of Mortality

Serum creatinine and eGFR are mathematically related. In this cohort, however, eGFR was a stronger univariable predictor of mortality (\( \chi^2 = 25.9 \) versus 20.6; \( P = 0.02 \)), and

![Figure 2. The effect of creatinine on survival after coronary artery bypass grafting.](image-url)

![Figure 3. The effect of estimated glomerular filtration rate on survival after coronary artery bypass grafting.](image-url)
TABLE 3. Multivariable Predictors of Mortality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>Wald $\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR 0.98*</td>
<td>0.97–0.99</td>
<td>17.57</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age 1.03†</td>
<td>1.01–1.06</td>
<td>8.01</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>IMA graft 1.82</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Hazard ratio per mL/min/1.73m². 
†Hazard ratio per year.
IMA indicates internal mammary artery.

when this was used creatinine provided no additional prognostic information. Estimated GFR was, therefore, used in a stepwise multivariable model that included other univariable predictors of outcome ($P<0.05$: age and receipt of an internal mammary artery graft). The independent predictors of mortality were eGFR and age (Table 3 and Figures 1 and 3). Patients with an eGFR of $<45$ mL/min/1.73m² were at particularly high risk (Table 4 and Figure 3).

When the 145 patients who had sustained an acute myocardial infarction in the month before their index CABG were excluded, the independent predictors of mortality were eGFR (HR, 0.98 per mL/min/1.73m²; 95% CI, 0.96 to 0.99; $\chi^2$ 9.2; $P=0.002$), age (HR, 1.04 per year; 95% CI, 1.01 to 1.07; $\chi^2$ 6.0; $P=0.01$), and receipt of an internal mammary artery graft (HR, 0.41; 95% CI, 0.17 to 0.97; $\chi^2$ 4.2; $P=0.04$).

Discussion
Although patients with advanced LV systolic dysfunction frequently undergo CABG there are few contemporary data assessing the outcome of such individuals beyond the early postoperative period. Likewise, the predictors of medium-term outcome are poorly documented, as are the symptomatic benefits of such therapy. The main findings of the current study were that during a median of 3.8 years of follow-up 28% of patients had died, with a 30-day mortality rate of 5.5%. The independent predictors of mortality were increasing age and impaired renal function. The most powerful predictor was the preoperative eGFR.

Patient Characteristics, Preoperative Therapy, and Investigation
The cohort were elderly, with a high prevalence of cardiovascular risk factors. The majority of patients had significant limiting angina and/or a pattern of coronary artery disease, whereby CABG would be recommended in current guidelines. Likewise, the majority of patients were in NYHA functional class III or IV. Use of angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, $\beta$-blockers, and statins was lower than optimal, but higher than reported in other comparable cohorts and in large contemporary North American databases. Use of all of these agents was significantly higher during the second half of the study period (data not shown).

Predictors of Mortality
The increasing perioperative risks associated with CABG in elderly patients have been well-documented and some previous data suggest that the risks are particularly high in those with reduced LV ejection fraction. Others, however, have failed to demonstrate an independent relationship between age and outcome in this setting. Our data suggest it is an important determinant, with those dying within 30 days having a median age of 76 years compared with 69 years among survivors. In this cohort, patients 75 years of age and older had a 5-year survival of <30%.

Higher NYHA functional class was not associated with increased mortality. This is contrast to the findings from the Coronary Artery Bypass Grafting Patch Trial database. However, in this study, the excess risk was observed only when comparing an absence of heart failure symptoms with any degree of limitation and the increased risk was similar regardless of the severity of heart failure, with mortality among patients with grade IV symptoms slightly lower than those in class I, II, or III. Although other groups have reported an increased perioperative mortality among patients with severe symptoms of heart failure undergoing CABG, there is considerable variation between centers and several studies assessing long-term outcome have failed to find any such relationship.

Several other notable clinical factors did not influence mortality. These included patient gender, diabetes mellitus, hypertension, use of an intra-aortic balloon pump preoperatively, and recent acute myocardial infarction. The preoperative LV ejection fraction (measured either by left ventriculography or echocardiography) was also of no prognostic significance. This may reflect a declining influence on perioperative mortality but may also be caused by the relative homogeneity of the cohort in this respect. Certainly, LV ejection fraction is an important prognostic factor in less selected populations.

Renal Function and Outcome
Mortality rates after CABG in patients with end-stage renal disease are known to be higher. In addition, the importance of milder degrees of renal dysfunction is increasingly recognized. Nevertheless, the particular importance of renal impairment in the outcome of patients with depressed LV systolic function has not been well-documented. One previous study of 80 patients with a LV ejection fraction $\leq 30\%$ followed for a mean of 15 months demon-

---

**TABLE 4. Relative Unadjusted and Adjusted Risk for Mortality Stratified by Estimated Glomerular Filtration Rate**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI) Adjusted for Age and Gender</th>
<th>Hazard Ratio (95% CI) With Multivariable Adjustment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR $\geq 75$ mL/min/1.73m² (n=78)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>eGFR 60–74 mL/min/1.73m² (n=104)</td>
<td>1.81 (0.87–3.78)</td>
<td>1.72 (0.82–3.58)</td>
<td>1.71 (0.82–3.58)</td>
</tr>
<tr>
<td>eGFR 45–59 mL/min/1.73m² (n=120)</td>
<td>2.13 (1.05–4.33)</td>
<td>1.90 (0.92–3.89)</td>
<td>1.65 (0.80–3.41)</td>
</tr>
<tr>
<td>eGFR $&lt;45$ mL/min/1.73m² (n=77)</td>
<td>4.43 (2.21–8.88)</td>
<td>3.59 (1.76–7.32)</td>
<td>2.66 (1.14–6.20)</td>
</tr>
</tbody>
</table>

*Adjusted for age, creatinine, and use of an internal mammary artery graft.
strated that a creatinine of ≥180 μmol/L (2 mg/dL) was associated with a higher cardiac mortality, whereas others have reported a considerable increase in risk among patients with low ejection fraction requiring dialysis before CABG. The importance of renal dysfunction has not, however, been replicated in all studies. This is surprising, particularly because impaired renal function increases cardiovascular risk and is a powerful predictor of a poor prognosis in patients with LV systolic dysfunction. Certainly, the current data suggest that, among patients with significant LV systolic dysfunction undergoing CABG, renal function, measured using either serum creatinine or eGFR, is the single most powerful predictor of medium-term outcome. Further work is required to assess whether measures to improve renal function and correct associated abnormalities might improve surgical prognosis in this high-risk group.

Strengths and Limitations of the Current Study

The large cohort of consecutive patients ensures that total mortality can be used as the primary end-point. In addition, symptomatic status at follow-up is available in a large number of patients. However, the lack of data regarding myocardial function after surgery is a weakness and the study has the limitations inherent in a retrospective cohort design. Finally, the study cannot address the relative benefits of medical therapy alone versus a combination of medical therapy plus surgical revascularization in patients with severe ischemic LV dysfunction. This can only be adequately evaluated in a prospective study.

Conclusions

The current study demonstrates that patients with significant LV systolic dysfunction undergoing isolated first CABG using contemporary techniques have a good early and medium-term survival. In addition, the majority of survivors derive considerable symptomatic benefit. Renal dysfunction portends a very poor prognosis in this setting. Further work is required to determine strategies that can improve the outcome of these individuals at high risk.

Source of Funding

Dr Hillis was supported by the British Heart Foundation.

Disclosures

None.

References


Outcome of Patients With Low Ejection Fraction Undergoing Coronary Artery Bypass Grafting: Renal Function and Mortality After 3.8 Years
Graham S. Hillis, Kenton J. Zehr, Amy W. Williams, Hartzell V. Schaff, Thomas A. Orzulak, Richard C. Daly, Charles J. Mullany, Richard J. Rodeheffer and Jae K. Oh

Circulation. 2006;114:I-414-I-419
doi: 10.1161/CIRCULATIONAHA.105.000661

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/1_suppl/I-414

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/