Aortic valve replacement (AVR) for aortic stenosis (AS) is the most common cardiac valve operation and is often performed in combination with coronary artery bypass grafting (CABG) surgery.1 The natural history of significant AS and a failing ventricle is known and survival is poor,2,3 making the surgical treatment of significant AS a class I indication. 4 Although prior work has demonstrated a correlation between reduced preoperative ejection fraction (EF) and risk of mortality after cardiac surgery,5 a thorough analysis of outcomes after AVR for AS in the setting of reduced preoperative EF is lacking.

Several single center reports suggest favorable survivalship for patients who underwent an AVR in the setting of reduced preoperative EF.68 However, generalizability of these studies to daily practice is limited owing to small samples at single institutions. Furthermore, despite evidence indicating decreased survival in the AVR+CABG population,10–12 studies failed to stratify by procedure (AVR and AVR+CABG).7,9 Thus, accurately describing estimated survival after AVR on severe AS patients with reduced preoperative EF is limited. As a result, the appropriate management of patients with severe AS and left ventricular (LV) dysfunction is unclear.

Background—The survival of patients who undergo aortic valve replacement (AVR) for severe aortic stenosis with reduced preoperative ejection fractions (EFs) is not well described in the literature.

Methods and Results—Patients undergoing AVR for severe aortic stenosis were analyzed using the Northern New England Cardiovascular Disease Study Group surgical registry. Patients were stratified by preoperative EF (≥50%, 40%–49%, and <40%) and concomitant coronary artery bypass grafting. Crude and adjusted survival across strata of EF was estimated for patients up to 8 years beyond their index admission. A total of 5277 patients underwent AVR for severe aortic stenosis between 1992 and 2008. There were 727 (14%) patients with preoperative EF <40%. Preoperative EF had minimal effect on postoperative morbidity. There was no difference in 30-day mortality across EF strata among the isolated AVR cohort. Preserved EF conferred 30-day survival benefit among the AVR+coronary artery bypass grafting population (EF≥50%, 96%; EF<40%, 91%; P=0.003). Patients with preserved EF had significantly improved 6-month and 8-year survival compared with their reduced EF counterparts.

Conclusions—Survival after AVR or AVR+coronary artery bypass grafting was most favorable among patients with preoperative preserved EF. However, patients with mild to moderately depressed EF experienced a substantial survival benefit compared with the natural history of medically treated patients. Furthermore, minor reductions of EF carried equivalent increased risk to those with more compromised function suggesting patients are best served when an AVR is performed before even minor reductions in myocardial function. (Circ Cardiovasc Qual Outcomes. 2013;6:1-7.)

Key Words: aortic stenosis ■ aortic valve replacement ■ left ventricular function
WHAT IS KNOWN
• Medical management of severe aortic stenosis, regardless of ventricular function, is associated with poor survival.

WHAT THE STUDY ADDS
• Aortic valve replacement in patients with severe aortic stenosis and reduced preoperative ejection fraction (EF) offered improved survival compared with the natural history of the disease. However, even minor reductions in preoperative EF resulted in reduced survival as compared with patients having preserved EF.

An accurate estimation of long-term survival among a surgical cohort is timely, especially given the evolving treatment modalities for AS.

With this in mind, we undertook a regional prospective observational study of 5277 patients with severe AS who underwent AVR at 8 medical centers in Northern New England between 1992 and 2008. We investigated whether patients’ preoperative EF affects their short- and long-term survival.

Methods
The Northern New England Cardiovascular Disease Study Group is a voluntary research consortium composed of clinicians, research scientists, and hospital administrators, representing all medical centers in Maine, Vermont, and New Hampshire, where cardiac surgery is performed. Since 1987 the Northern New England Cardiovascular Disease Study Group has maintained a prospective registry of all patients undergoing cardiac surgery in the region. The group fosters continuous improvement in the quality of care of patients with cardiovascular disease in the region through the pooling of process and outcome data and the timely feedback of data to clinicians.

All patients included in our analysis met American College of Cardiology/American Heart Association guidelines for severe AS with a valve area <1 cm² or mean gradient >40 mm Hg. We excluded patients who did not meet severe AS criteria, patients without a documented preoperative EF, patients with cancer, other concomitant procedures aside from CABG or aortic root replacement, or patients presenting with endocarditis. Our final cohort consisted of 5277 patients undergoing AVR (2693 isolated AVR and 2584 AVR+CABG) surgery for severe AS at any of the 8 medical centers in Northern New England between 1992 and 2008.

Data Collection
Previous publications by the Northern New England Cardiovascular Disease Study Group have discussed our data collection methodology and definitions in detail. We prospectively collected the preoperative variables displayed in Table 1. Comorbidities analyzed included diabetes mellitus, cerebrovascular disease (prior stroke, prior transient ischemic attack, prior carotid surgery, carotid stenosis, or carotid bruit), peripheral vascular disease (claudication, amputation, prior lower extremity bypass, absent pedal pulses, or lower extremity ulcers), treated chronic obstructive pulmonary disease, renal failure (diabetes or creatinine >2 mg/dL), cardiac heart failure (CHF) [this or prior admission]), cardiac anatomy and function (left main stenosis, number of diseased vessels, and preoperative EF), valve symptoms (angina, shortness of breath, CHF, syncope, or other symptoms), and pulmonary hypertension. Cardiothoracic surgeons assessed patient acuity (elective, urgent, and emergent) using definitions previously described.

Subject Stratification
Patients were stratified and analyzed according to procedure (AVR or AVR+CABG) and preoperative EF. Preoperative EF was stratified into 3 groups: ≥50%, 40% to 49%, and <40%. The type (mechanical versus tissue) and brand of valve were not controlled.

Outcome Data
Postoperative morbidity variables collected included intra-aortic balloon pump use, return to the operating room for bleeding, postoperative atrial fibrillation, time to extubation, and length of stay. Procedural counts in the registry within each medical center are validated against hospital billing data. Postprocedural mortality out to 8 years was obtained by linking our registry to the Social Security Administration’s Death Master File using a combination of first name, last name, date of birth, date last known alive, and Social Security number.

Statistical Analysis
We used standard statistical methods to compare the characteristics of patients having isolated AVR with those undergoing AVR+CABG, including ANOVA for continuous variables, χ² for categorical data, and logistic regression for ordered categories (reported as a P trend). We used the Wilcoxon rank sum test for non-parametric data.

The risk of death at predefined time periods (within 6 months and 8 years) associated with choice of procedure and degree of preoperative EF was compared using the Wald test within a Cox proportional hazards model. We report 8-year survival conditional on survival beyond 6 months. Survival was adjusted for covariates previously found to be associated with mortality, including age, sex, acuity, vascular disease, diabetes mellitus, prior MI, renal failure or creatinine >2 mg/dL, left main disease, chronic obstructive pulmonary disease, body mass index, medical center, and year. The time dependence of the hazard ratio (HR) was assessed by estimating the HR in separate windows of time after follow-up.

Crude survival curves were estimated using the Kaplan–Meier method. Survival adjusted for differences between patients across EF categories were estimated using the method of Zhang, as it does not force proportional hazards on the difference between patients across EF categories. Separate curves were created for AVR and AVR+CABG. Adjusted survival curves were created using Stata release 11.0 software.

Protection of Human Subjects
Institutional review board approval was obtained at each participating medical center. Institutional review boards of 7 of our 8 member centers have designated the Northern New England Cardiovascular Disease Study Group as a Quality Improvement Registry, and, therefore, patient consent was not required. Written patient consent was obtained for the one remaining center (Catholic Medical Center, Manchester, NH). The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the paper as written.

Results
Study Population
A total of 5277 (2693 isolated AVR and 2584 AVR+CABG) patients were analyzed. There were 28812 patient years of follow-up data (15 187 isolated AVR and 13 625 AVR+CABG). A total of 727 patients had EFs <40% (318 AVR and 409 AVR+CABG). The interquartile (25th–75th percentile) of EF in the AVR group was <40%: 25–35, 40% to 49%: 40–45, and ≥50%: 60–70, and the AVR group was <40%: 25–35, 40% to 49%: 40–45, and ≥50%: 44–65.
Table 1. Patient and Disease Characteristics Among Patients Undergoing Aortic Valve Replacement

<table>
<thead>
<tr>
<th>Variable</th>
<th>AVR</th>
<th>AVR+CABG</th>
<th>AVR vs AVR+CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop EF</td>
<td>&lt;40</td>
<td>40–49</td>
<td>≥50</td>
</tr>
<tr>
<td>No. of procedures</td>
<td>318</td>
<td>261</td>
<td>2114</td>
</tr>
<tr>
<td>Median EF, %</td>
<td>30</td>
<td>45</td>
<td>63</td>
</tr>
</tbody>
</table>

Demographics

<table>
<thead>
<tr>
<th>Patient age, %</th>
<th>&lt;60</th>
<th>60–69</th>
<th>70–79</th>
<th>≥80</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of procedures</td>
<td>21.7</td>
<td>26.7</td>
<td>34.9</td>
<td>16.7</td>
</tr>
<tr>
<td>Median EF, %</td>
<td>30</td>
<td>45</td>
<td>63</td>
<td>30</td>
</tr>
</tbody>
</table>

| Women, %                      | 29.9| 38.3     | 47.8  | 27.4|
| Body mass index, kg/m²        | <31 | 31–36    | ≥37   | <31 |
| No. of procedures             | 87.4| 8.5      | 4.1   | 87.4|
| Median EF, %                  | 79.3| 13.3     | 7.4   | 79.3|

| Body surface area, m²         | <1.70| 1.70–1.99 | >2.00 | <1.70|
| No. of procedures             | 6.9 | 37.7      | 55.3  | 6.9 |
| Median EF, %                  | 9.3 | 44.5      | 46.2  | 9.3 |

| Comorbid disease              | Diabetes mellitus, % | Vascular disease, % | COPD, % | Dialysis or creatinine >2, % |
| CHF, %                        | 77.7 | 9.4 | 8.5 | 4.7 |
| NY Heart Association III–IV, %| 60.1 | 8.5 | 8.0 | 4.9 |

| Prior myocardial infarction (%)| No | <7 days preprocedure | >7 days preprocedure | No | <7 days preprocedure | >7 days preprocedure |
| CHF, %                        | 85.2 | 3.9 | 10.8 | 85.2 | 3.9 | 10.8 |
| NY Heart Association III–IV, %| 64.8 | 0.7 | 10.4 | 64.8 | 0.7 | 10.4 |

| Cardiac anatomy and function  | Left main stenosis ≥50%, % | Diseased vessels, n |
| CHF, %                        | 3.1 | 0.02 | 15.7 |
| NY Heart Association III–IV, %| 3.5 | 1.5  | 20.1 |

| Pulmonary hypertension, %     | 45.0 | 20.1 | 0.02 |
| Priority, %                   | 46.5 | 73.5 | 27.6 |
| Elective                      | 50.9 | 26.1 | 68.2 |
| Urgent                        | 2.8  | 0.4  | 3.9  |

| Preoperative valve characteristics | AV area (median) | AV gradient (median) | Symptoms, % |
| CHF, %                            | 0.60 | 0.70 | 86.70 |
| NY Heart Association III–IV, %    | 0.69 | 0.70 | 78.80 |

AVR indicates aortic valve replacement; CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; and NY, New York.
Baseline Characteristics
Demographic data of the study population are displayed in Table 1. Of note, the isolated AVR and AVR+CABG patients significantly differed on almost all studied variables with exceptions for CHF, pulmonary hypertension, and symptoms on presentation. In general, the AVR+CABG population was older, was less obese, and has a greater comorbidity burden. Specifically, the AVR+CABG population had a greater proportion of patients with diabetes mellitus, vascular disease, chronic obstructive pulmonary disease, renal failure, significant coronary artery disease, and nonelective surgery. Although statistical differences existed in preoperative valve characteristics (valve area and gradient) between the 2 procedures, the absolute differences were small.

Differences Across EF Atrata Among Isolated AVR
Among isolated AVR patients, 318 (12%) had preoperative EFs <40%. Patients with lower EF had lower median AV areas and AV gradients and were more likely to be symptomatic. Those with poorer EF were more likely to be men, be obese, and have CHF, recent MI, coronary artery disease, pulmonary hypertension, and higher levels of acuteness. Those having EF between 40% and 49% were more likely to be diabetic than those with poorer or normal EF. Age did not differ across EF strata.

Differences Across EF Strata Among AVR+CABG
There were 409 (16%) AVR+CABG patients with preoperative EF <40%. Patients with lower EF had smaller valve areas, had larger valve gradients, and were more likely to be symptomatic. Those with lower EF were more likely to be older, men, and diabetic and have peripheral vascular disease, renal failure, CHF, recent MI, coronary artery disease, pulmonary hypertension, and higher levels of acuteness. Patients with EF between 40% and 49% were more likely to have extensive left main disease than those with poorer or normal EF.

In-Hospital Morbidity and 30-Day Mortality
In-hospital morbidity and 30-day mortality are displayed in Table 2. The AVR+CABG cohort universally experienced greater morbidity and 30-day mortality than isolated AVR patients. Although time to extubation was significantly longer in the reduced EF strata for both procedures, the absolute difference was small. Postoperative stroke and renal failure requiring dialysis were analyzed. However, the incidence of these morbidities was too small for meaningful analysis.

Isolated AVR In-Hospital Events and 30-Day Mortality
Among patients undergoing isolated AVR, patients with poorer EF were more likely to receive an intra-aortic balloon pump and have a slightly longer length of stay (Table 2). The 30-day mortality across EF strata did not differ.

AVR+CABG In-Hospital Events and 30-Day Mortality
Among patients undergoing AVR+CABG, reduced EF patients were more likely to receive an intra-aortic balloon pump, receive blood transfusion, return to the operating room for postoperative bleeding, and have longer lengths of stay. The 30-day survival improved with preserved EF.

Short-Term Survival
At 6 months the AVR+CABG patients had worse survival compared with isolated AVR patients (HR=1.41; 95% confidence interval [CI]=0.95–2.09, P=0.014) (Figure 1). Percent alive at 6 months in the isolated AVR cohort were 93% (EF ≥50%), 92% (EF 40%–49%), and 96% (EF ≥50%). Percent alive at 6 months in the AVR+CABG cohort were 87% (EF <40%), 88% (EF 40%–49%), and 93% (EF ≥50%). Regardless of procedure, the reduced EF (EF <40%) and moderately reduced EF (EF 40%–49%) cohorts had worse survival compared with their counterparts with preserved EF (EF ≥50%) (isolated AVR: reduced versus preserved, HR=1.7 [95% CI=1.0–2.8], P=0.05; moderately reduced versus preserved, HR=1.8 [95% CI=1.1–2.9]; P=0.02; AVR+CABG: reduced versus preserved, HR=2.0 [95% CI=1.3–3.1], P=0.001; moderately reduced versus preserved HR=1.7 [95% CI=1.2–2.5], P=0.004). For both isolated AVR and AVR+CABG cohorts, 6-month survival was statistically identical comparing reduced and moderately reduced EF strata (HR=0.93 [95% CI=0.50–1.76], P=0.834 [isolated AVR]; HR=1.2 [95% CI=0.72–1.90], P=0.53 [AVR+CABG]).
Long-Term Survival

At 8 years, the AVR+CABG population continued to demonstrate decreased survival compared with the isolated AVR population (HR=1.33; 95% CI=1.15–1.54; P<0.001). Regardless of procedure, preserved preoperative EF patients had better survival relative to their reduced EF counterparts (Figure 2). Percent alive at 8 years in the isolated AVR cohort were 64% (EF <40%), 61% (EF 40%–49%), and 75% (EF ≥50%). Percent alive at 8 years in the AVR+CABG cohort were 46% (EF <40%), 55% (EF 40%–49%), and 70% (EF ≥50%). Similar to the observations of short-term survival, at 8 years, survival was statistically equivalent for the EF <40% and the EF 40% to 49% groups (HR=0.93; 95% CI=0.64–1.36; P=0.72 [isolated AVR], HR=1.2; 95% CI=0.88–1.60; P=0.25 [AVR+CABG]) and reduced when compared with their preserved EF counterparts (isolated AVR: reduced versus preserved, HR=1.60; 95% CI=1.16–2.2; P=0.004; moderately reduced versus preserved, HR=1.7; 95% CI=1.30–2.25; P<0.001; AVR+CABG: reduced versus preserved, HR=2.0; 95% CI=1.60–2.60; P<0.001; moderately reduced versus preserved, HR=1.70; 95% CI=1.35–2.15; P<0.001).

Discussion

This study describes our large regional experience conducting AVR for severe AS in the setting of reduced preoperative EF. We analyzed 5277 patients (2693 AVR and 2584 AVR+CABG) of which there were 727 (318 [12%] AVR and 409 [16%] AVR+CABG) having preoperative EF <40%. There are several noteworthy findings in this study. First, the isolated AVR and AVR+CABG populations appreciably differ in preoperative characteristics, perioperative morbidity, and short- and long-term survival. Second, in the perioperative period, reduced EF did not confer a statistical increase in mortality risk among isolated AVR patients, whereas those who had AVR+CABG and preserved EF had improved survival. Third, independent of procedure, patients with preserved preoperative EF experienced better survival at 6 months and 8 years. Interestingly, the mildly reduced EF cohort had equivalent survival as those with reduced preoperative EF.

Our survival data demonstrate that even with reduced preoperative EF patients do well out to 8 years. Prior research has demonstrated extremely poor survival of patients with severe AS who do not undergo valve replacement, with survival...
rates as low as 50% at 1 year and 2% at 10-year survival among the medically managed. \(^2,4\) Compared with the dismal natural history of medically managed severe AS, our 30-day (97% isolated AVR and 91% AVR+CABG), 6-month (92% isolated AVR and 87% AVR+CABG), and 8-year (64% isolated AVR and 45% AVR+CABG) survival rates in the reduced EF population support past (albeit potentially underpowered) studies, which demonstrate favorable survival after AVR in the setting of LV dysfunction. \(^5–9,19,20\)

The Cleveland Clinic published the largest series to date (3049 patients) exploring characteristics of the AVR population as part of an extensive and detailed study investigating the appropriate timing of valve replacement for AS. \(^3\) In their analysis, Mihaljevic et al \(^7\) analyzed all patients who underwent AVR, including those with moderate disease. Although differential outcomes between patients with AVR and AVR+CABG were not reported, subgroup analysis was performed on survival related to preoperative LV dysfunction, defined as an EF <50. Although it is difficult to precisely compare survival with our study owing to different entry criteria and referral patterns, short- and long-term survival are similar between Cleveland Clinic data and our data.

Our analysis of 5277 patients provides a more generalizable assessment of outcomes after AVR in the setting of reduced EF. First, the Cleveland Clinic is a quaternary care center, whereas our data are from multicenter practices. Second, we separately analyzed the isolated patients with AVR and AVR+CABG as we, along with others, have demonstrated increased mortality risk in the AVR+CABG cohort. \(^10–12\) Aggregate analysis of patients with AVR and AVR+CABG confounds survival estimates in these 2 disparate patient populations. Third, our analysis includes only those with severe AS to better provide outcome data on patients who are typically referred for AVR. Fourth, we modeled our EF cutpoint on the Cleveland Clinics 50% and further explored strata of LV dysfunction to provide more detailed information for clinical decision making.

The similarity in survival between the moderately reduced EF (40%–49%) and the reduced EF (<40%) strata provides further support to a growing body of literature, suggesting that optimal survival benefit from AVR occurs earlier in the disease process than the traditional criteria of symptomatic disease or criteria based on area or gradient. Subtle myocardial dysfunction (before hypertrophy) is measurable early in the pathogenesis of AS, including with mild disease. \(^2\) Such changes are potentially reversible with AVR. \(^2\) Furthermore, studies have shown that AVR patients experience compromised survival in the presence of decreased myocardial reserve. \(^17,23,24\)

With traditional operative referral practices, a large proportion of patients are referred for surgery after undergoing gross hypertrophy of their myocardium. Mihaljevic et al \(^7\) reported at the time of referral for surgery, 17% of patients have evidence of LV hypertrophy, which conferred increased mortality risk. \(^3\) Although earlier evidence attempted to reassure the cardiac care community that survival is not compromised waiting for AS to become symptomatic, \(^23\) our data and others suggest a significant proportion of the AVR population should be referred to surgery earlier in their disease to optimize the therapeutic and survival benefit of surgery. Thus, our findings of equivalent yet reduced survival among patients with reduced and mildly reduced EF further support this hypothesis that patients with AS should be treated before evidence of myocardial dysfunction. \(^2\)

We recognize some limitations to our present study. First, in this regional observational cohort study, we used multiple regression to adjust for potentially confounding factors. We acknowledge the inability to fully account for bias and confounding attributed to patient selection, we have selected our cohort based on the inclusion of severe aortic valve stenosis according to the American Heart Association and American College of Cardiology. However, we have attempted to address concerns related to unmeasured confounding, including age, sex, acuity, vascular disease, diabetes, prior MI, renal failure or creatinine >2 mg/dL, left main disease, chronic obstructive pulmonary disease, body mass index, medical center, and year. Furthermore, we lack data regarding postoperative valve gradient that would likely have an effect on survival, especially among those with reduced EF. Second, although we amassed a large regional series, we were limited in our ability to explore perhaps more meaningful EF strata (<20%, 20%–39%). However, we used EF cut points that have been reported by several investigators.

Traditionally thought of as high-risk surgical candidates, our analysis demonstrates favorable long-term survival in patients with reduced EF undergoing AVR for severe AS. Unfortunately, a significant proportion of these patients are not being referred for surgery because of the false assumption that they are poor surgical candidates. \(^3,27,28\) Our analysis fuels further optimism for favorable survival in patients with reduced EF. As a result, patients with reduced preoperative EFs should be referred for surgical evaluation because patients are likely to benefit in both the short and long term with aortic valve replacement. Such findings have importance, especially given the emergence of alternative treatment strategies for AS in patients who are at high risk. It remains to be seen whether a similar finding exists among many patients not being referred to surgery.

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Disclosures
None.

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Impact of Preoperative Left Ventricular Ejection Fraction on Long-Term Survival After Aortic Valve Replacement for Aortic Stenosis


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