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Survival Prognosis and Surgical Management of Ischemic Mitral Regurgitation

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Background. **Ischemic mitral regurgitation (IMR) has an adverse prognosis, but survival characteristics and management are controversial. This study reviewed a 20-year series of IMR patients managed with multiple approaches to assess and refine surgical strategies.**

Methods. **Patients having surgery for primary coronary disease from 1986 to 2006 were divided into group 1 (no IMR; bypass grafting only; n = 16,209), group 2a (IMR; bypass only; n = 3,181), group 2b (IMR; mitral repair; n = 416), and group 2c (IMR; mitral replacement; n = 106). Cox proportional hazards modeling adjusted for baseline differences, and therapeutic adequacy was quantified by area under each survival curve expressed as a percentage of group 1.**

Results. **Group 2 patients were older than group 1 patients and had worse baseline characteristics. Group 2a had less severe MR and group 2b had the most comorbidity. Assuming group 1 provided the best adjusted outcome at a given baseline risk, group 2a achieved 97.7%, 2b achieved 93.7%, and 2c achieved 79.1% of potential survival (hazard ratio 1.1, 1.4, and 1.6, respectively; $p < 0.003$). Most of the survival difference was perioperative.**

Conclusions. **Worse baseline risk is a major factor reducing long-term survival in IMR. Current algorithms in which mild to moderate IMR is managed with bypass only (group 2a) generally produced good late results. In patients with moderate and severe IMR, repair achieved 93.7% of full survival potential; valve replacement was less satisfactory, primarily owing to higher operative mortality. Future therapeutic refinement, emphasizing reparative procedures and better perioperative care, could enhance the surgical prognosis of IMR.**

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Ischemic mitral regurgitation (IMR) can be defined as mitral valve (MV) insufficiency precipitated by myocardial infarction, with normal leaflet and chordal morphology. Ischemic mitral regurgitation usually occurs with right or circumflex coronary infarction that involves the posterior ventricular wall, posterior papillary muscle, and adjacent mitral annulus [1]. Common anatomic features include annular dilatation, apical/lateral displacement of papillary muscles, and varying degrees of leaflet restriction or tethering [2]. It is clear that strong associations exist between IMR and increased late mortality, and that mild or moderate IMR, even after revascularization, reduces late survival [3–9]. The exact cause for limited IMR survival after valve surgery is controversial, but recent studies suggest that much is related to worse baseline characteristics, referencing outcomes to either mitral repair for prolapse or coronary artery bypass graft surgery (CABG) [10–15].

Current trends have favored valve repair for IMR, mainly utilizing ring annuloplasty [16–18]. Several studies emphasize increased perioperative mortality for valve replacement, but this subject remains controversial [19–25]. However, long-term survival data after repair versus replacement for IMR are not extensively available, and late outcomes after repair could be depressed because of durability, while replacement could be limited by valve-related complications [23, 26–28]. Therefore, this study identified factors influencing survival after surgical therapy for IMR, and compared long-term survival after valve repair versus prosthetic valve replacement. The goal was to define the effectiveness of treatment strategies, and to determine potential areas for future improvement.

Material and Methods

Institutional Review Board permission was obtained for this study and individual patient consent was waived. The Duke Cardiovascular Disease Databank identified all patients with coronary artery disease who underwent surgical therapy from January 1, 1986, through December

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31, 2006. Patients having procedures concomitant with CABG, but not related to IMR, were excluded (aortic valve, tricuspid valve, or MV operations for nonischemic etiologies, repair of postinfarct ventricular septal defect or papillary muscle rupture, ventricular aneurysm repair or restoration). Although patients having previous CABG were included, patients with prior MV procedures were excluded because they may not have been candidates for either repair or replacement. Three patients had operative conversion from repair to replacement, as identified by use of both a ring and valve intraoperatively, and were included in the study as replacement patients. This process produced 19,912 consecutive patients for analysis.

Preoperative baseline characteristics, intraoperative observations, and late outcome data for all patients were recorded prospectively over the entire 20 years, with a consistent variable set throughout the period. For the purpose of this study, patients were divided into two groups. Group 1 (n = 16,209) consisted of patients having no evidence of IMR based on preoperative and intraoperative studies. These patients underwent CABG alone. Group 2 consisted of patients prospectively defined to have some degree of IMR, based on either preoperative or intraoperative studies (including preoperative dye ventriculography, transthoracic echocardiography, or transesophageal echocardiography) or documented by the surgeon in the operative note. Group 2 patients in turn were divided into patients who received CABG only (group 2a; n = 3,181), MV repair with or without CABG (group 2b; n = 416), or MV replacement with or without CABG (group 2c; n = 106). The hospital charts of all 522 patients having MV procedures were audited to ensure proper categorization. Of the repairs, 24 patients received Kay annuloplasties and 11 transventricular repairs, and the remaining 381 were repaired with full annuloplasty

Table 1. Baseline Characteristics

		Group 1	Group 2			
			A	B	C	
	Total (n = 19,912)	CABG Only, No IMR (n = 16,209)	CABG Only, IMR (n = 3,181)	Mitral Repair (n = 416)	Mitral Replacement (n = 106)	Overall *p* Value
Age	64 (56, 71)	63 (55, 71)[b,c,d]	66 (59, 73)[a]	66 (59, 73)[a]	67 (61, 73)[a]	< 0.001
Sex						
Male	70.30%	72.1%[b,c,d]	63.40%[a,c,d]	55.50%[a,b]	47.20%[a,b]	<0.001
Female	29.70%	27.9%[b,c,d]	36.6%[a,c,d]	44.50%[a,b]	52.8%[a,b]	
History of diabetes mellitus	28.60%	27.7%[b,c]	32.10%[a,c]	39.2%[a,d]	25.5%[c]	<0.001
Hypertension	61.80%	59.9%[b,c]	69.90%[a,d]	73.8%[a,d]	60.4%[b,c]	<0.001
Hyperlipidemia	51.70%	50.3%[b,c]	57.90%[a,d]	62.7%[a,d]	45.3%[b,c]	<0.001
Body mass index	27.3 (24.5, 30.7)	27.4 (24.7, 30.8)[c,d]	26.7 (23.8, 30.2)[a,d]	26.9 (23.8, 30.3)[a,b,d]	25.6 (23, 29.4)[a,b,c]	<0.001
History of renal failure	2.60%	2.5%[b,c]	3.20%[a,c]	5.30%[a,b]	1.90%	0.001
NYHA class						
I	86.10%	89%[b,cd]	79.40%[a,c,d]	38.70%[a,b]	44.3%[a,b]	<0.001
II	4.20%	3.7%[b,c,d]	5.70%[a,c,d]	9.90%[a,b]	10.4%[a,b]	
III	5.30%	4.2%[b,c,d]	8.20%[a,c,d]	21.60%[#b]	21.7%[a,b]	
IV	4.40%	3.2%[b,c,d]	6.70%[a,c,d]	29.80%[a,b]	23.6%[a,b]	
Chronic lung disease	7.20%	7%[c]	7.00%[c]	15.10%[a,b]	8.50%	<0.001
History of CVA	11.20%	10.5%[b,c]	14.70%[a]	13.50%[a]	9.40%	<0.001
History of MI	54.10%	51.2%[b,c,d]	66.80%[a]	68.00%[a]	65.10%[a]	<0.001
Ejection fraction	52% (41, 62)	54% (44, 63)[b,c,d]	47% (36, 58)[a,c,d]	35% (27, 45)[a,b,d]	42.5% (35, 51)[a,b,c]	<0.001
Three-vessel disease	73.20%	72.1%[b,c,d]	79.50%[a,c,d]	73.8%[a,b,d]	56.6%[a,b,c]	<0.001
Left main disease ≥50%	19.50%	19.2%[c,d]	20.60%[d]	23.9%[a,d]	10.3%[a,b,c]	0.008
Reoperative CABG	4.70%	4.10%[b,c,d]	6.00%[a,c,d]	16.80%[a,b]	16.00%[a,b]	<0.001
Clinical status						
Elective	59.60%	61.6%[b,c]	51.2%[a,c]	45.7%[a,b,d]	60%[c]	<0.001
Nonelective	40.40%	38.4%[b,c]	48.8%[a,c]	54.3%[a,b,d]	40%[c]	
MR grade						
Moderate	4.60%	0%[b,c,d]	21.3%[a,c,d]	51.4%[a,b,d]	24.5%[a,b,c]	<0.001
Severe	1.50%	0%[b,c,d]	1.6%[a,c,d]	43.5%[a,b,d]	70.6%[a,b,c]	

[a] $p < 0.05$ compared with group 1. [b] $p < 0.05$ compared with group 2a. [c] $p < 0.05$ compared with group 2b. [d] $p < 0.05$ compared with group 2c.

CABG = coronary artery bypass graft surgery; CVA = cerebrovascular disease; IMR = ischemic mitral regurgitation; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association.

rings [11, 21]. The most common ring utilized was the St. Jude Seguin ring. In the replacement group, 28% of patients received a bioprosthesis, and 72% a mechanical valve. Partial or total chordal sparing valve replacement [22] was frequent, but this variable was not documented well, either in the databank or the charts, and could not be assessed in the analysis.

Survival outcomes and causes of mortality were obtained from mailed self-administered questionnaires or telephone follow-up, as well as review of hospital records. Mortality data were adjudicated by a multidisciplinary committee. Survival data were supplemented with information from the National Death Index. Follow-up for survival was 99.2% complete.

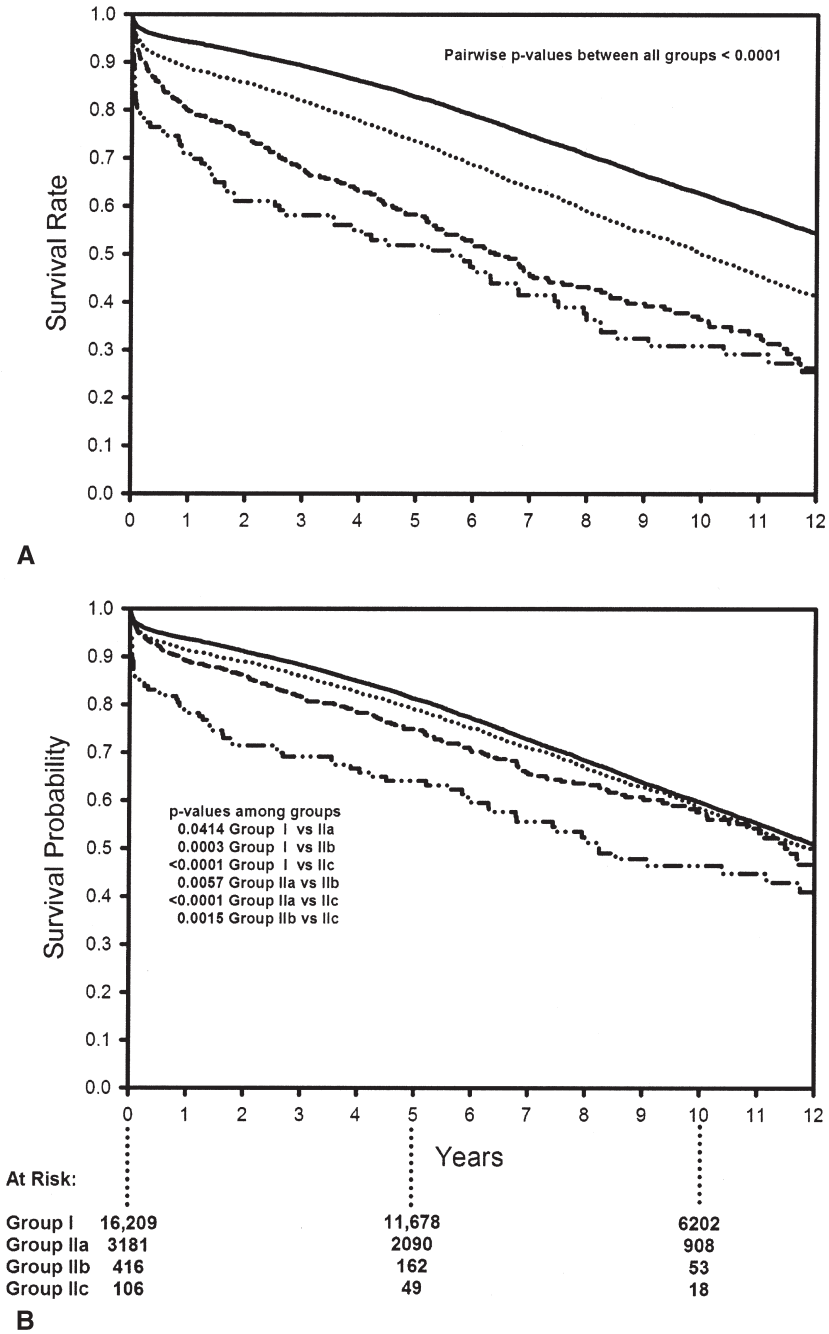

Fig 1. (A) Unadjusted Kaplan-Meier survival curves for group 1 (CABG only, no IMR), group 2a (CABG only, IMR), group 2b (MV repair), and group 2c (MV replacement). (B) Survival curves for groups 1 and 2, after Cox model statistical adjustment for differences in baseline characteristics. (CABG = coronary artery bypass graft surgery; IMR = ischemic mitral regurgitation; MR = mitral valve; solid line = group 1; dotted line = group 2a; dashed line = group 2b; dash-dotted line = group 2c.)

Baseline characteristics and clinical event rates were described using medians with 25th and 75th percentiles for continuous variables and frequencies and proportions for categorical variables. Descriptive data were compared using the Kruskal-Wallis or Wilcoxon rank-sum test for continuous and ordinal variables, and a Pearson χ^2 or Fisher's exact test for categorical variables, as appropriate. The general analysis strategy was to adjust for the impact of baseline characteristics on survival using multivariable Cox proportional hazards regression techniques [29]. To develop the risk-adjustment model, a pool of all covariates that have been shown to be important in previous analyses, and those that were clinically relevant and statistically important were chosen. The candidate variable list for baseline adjustment included the following factors: age, sex, race, history of diabetes mellitus, hypertension, hyperlipidemia, history of peripheral vascular disease, history of cerebrovascular disease, history of renal failure, body mass index, smoking history, chronic lung disease, history of myocardial infarction, history of CABG, history of percutaneous coronary intervention, New York Heart Association class, ejection fraction, number of diseased vessels, dementia, connective tissue disease, peptic ulcer, hemiplegia, any tumor, leukemia, lymphoma, moderate or severe liver disease, metastatic cancer, and human human immunodeficiency virus/acquired immune deficiency syndrome.

The preoperative presence and severity of mitral regurgitation (MR) was determined from ventriculograms performed at the time of preoperative catheterization, or from transthoracic or transesophageal echocardiograms. Because patients having valve procedures almost uniformly had moderate/severe MR, survival curves were not adjusted for severity of mitral insufficiency. Continuous and ordinal categorical variables were tested for linearity over the log hazard and were transformed as necessary to meet this modeling assumption. Stepwise Cox regression was used to select the covariates that were significant and independent predictors of mortality in the multivariable setting.

The adjusted survival curve for each group was calculated by applying its estimated baseline hazard function, along with covariate Cox model parameter estimates, to all patients in the cohort and then averaged over all patients at each time point. The resulting curves represent a survival estimate that would have been realized had all patients been in each treatment group. Areas under each survival curve were calculated, using the trapezoidal rule and presented for groups 2a, 2b, and 2c, as a percentage of group 1. These results were examined for all patients as well as conditioning on patients who survived the 90-day perioperative period. Causes of late mortality, after the first 90 days, were determined for each group and categorized broadly into cardiac versus noncardiac mortality. A logistic

Table 2. Cox Survival Model: Adjustment for Differences in Baseline Characteristics

Risk Factor	Wald χ^2	HR	95% CI		*p* Value
Age (HR per 10 year increase)	(2 d.f.) 1759.8				<0.0001
Age (linear piece below 55)		1.018	1.01	1.026	
Age (linear piece above 55)		1.058	1.055	1.061	
Ejection fraction (HR per 5% increase)	576.9	0.89	0.882	0.899	<0.0001
History of diabetes mellitus	273.5	1.493	1.423	1.565	<0.0001
History of peripheral vascular disease	168.6	1.449	1.37	1.532	<0.0001
History of renal failure	141.6	2.012	1.794	2.258	<0.0001
Hyperlipidemia	127.9	0.776	0.742	0.811	<0.0001
History of cerebrovascular disease	102	1.372	1.291	1.459	<0.0001
NYHA class	95.9	1.144	1.114	1.176	<0.0001
Number of diseased vessels (>50%)	55.3	1.161	1.116	1.207	<0.0001
Body mass index (HR per 1 unit increase)	50.1	0.964	0.954	0.974	<0.0001
Chronic lung disease	43.9	1.315	1.213	1.426	<0.0001
History of CABG	28.1	1.27	1.162	1.387	<0.0001
History of smoking	25.9	1.126	1.076	1.179	<0.0001
Number male	13.9	0.913	0.871	0.958	0.0002
Hypertension	11.8	1.084	1.035	1.136	0.0006
History of myocardial infarction	7.1	1.062	1.016	1.11	0.0078
Connective tissue disease	5.1	1.384	1.045	1.835	0.0236
Reference is group 1 (CABG, no IMR)					
Group 2a (CABG only, IMR)	4.2	1.059	1.002	1.118	
Group 2b (mitral repair, IMR)	13.3	1.296	1.128	1.49	
Group 2c (mitral replacement, IMR)	33.9	1.983	1.575	2.496	

CABG = coronary artery bypass graft surgery; CI = confidence interval; HR = hazard ratio; IMR = ischemic mitral regurgitation; NYHA = New York Heart Association.

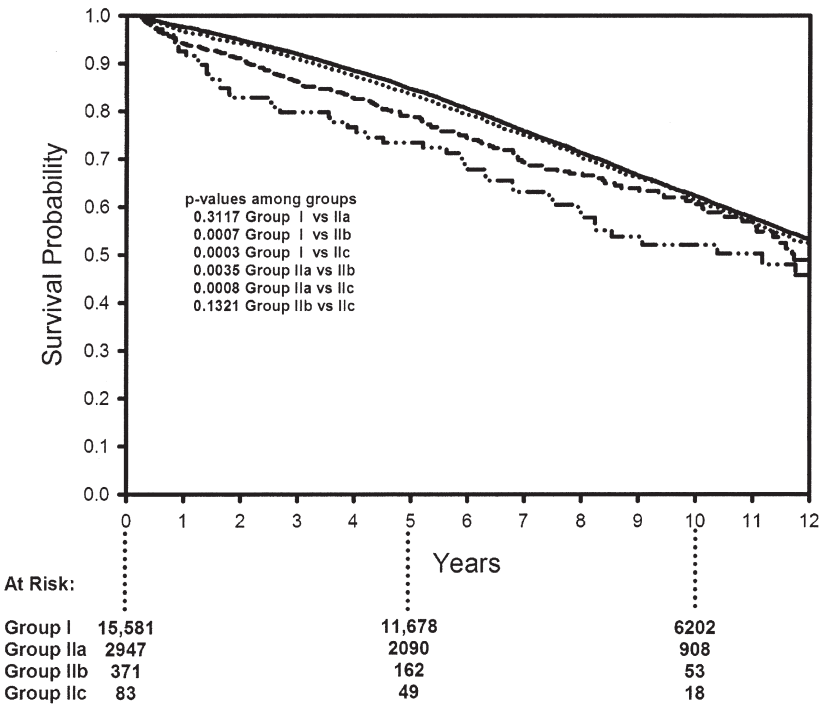

Fig 2. Survival curves for group 1 (CABG only, no IMR), group 2a (CABG only, IMR), group 2b (MV repair), and group 2c (MV replacement) after Cox model statistical adjustment for differences in baseline characteristics, and including only patients surviving 90 days after surgery. (CABG = coronary artery bypass graft surgery; IMR = ischemic mitral regurgitation; MR = mitral valve; solid line = group 1; dotted line = group 2a; dashed line = group 2b; dash-dotted line = group 2c.)

regression subanalysis was performed to evaluate the likelihood that a patient would receive valve repair versus replacement. All of the risk factors (above) were evaluated, adding surgeon performing the procedure as another candidate variable. Statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, North Carolina). A p value of 0.05 or less was considered statistically significant.

Table 3. Cox Survival Model: Adjustment for Baseline Characteristics in 90-Day Survivors

Risk Factor	Wald χ^2	HR	95% CI		p Value
Age (HR per 10-year increase)	1568.3				<0.0001
Age (linear piece below 55)		1.019	1.011	1.028	
Age (linear piece above 55)		1.058	1.054	1.061	
Ejection fraction (HR per 5% increase)	572.1	0.887	0.879	0.896	<0.0001
History of diabetes mellitus	283.2	1.537	1.462	1.616	<0.0001
History of peripheral vascular disease	172.2	1.487	1.401	1.577	<0.0001
History of renal failure	157.1	2.206	1.949	2.496	<0.0001
Hyperlipidemia	113.3	0.778	0.742	0.814	<0.0001
History of cerebrovascular disease	79.4	1.35	1.264	1.442	<0.0001
Chronic lung disease	53.1	1.38	1.266	1.505	<0.0001
Number of diseased vessels (>50%)	50.6	1.161	1.114	1.21	<0.0001
NYHA class	74.4	1.137	1.105	1.171	<0.0001
Body mass index (HR per 1 unit increase)	40.1	0.965	0.955	0.976	<0.0001
History of smoking	28.1	1.138	1.085	1.194	<0.0001
Hypertension	10.9	1.085	1.034	1.139	0.0009
History of CABG	10.8	1.175	1.067	1.294	0.0010
Connective tissue disease	4.7	1.393	1.031	1.881	0.0306
Male	3.9	0.95	0.903	0.999	0.0477
Reference is group 1 (CABG, no IMR)					
Group 2a (CABG only, IMR)		1.031	0.972	1.093	0.3117
Group 2b (mitral repair, IMR)		1.306	1.119	1.524	0.0007
Group 2c (mitral replacement, IMR)		1.655	1.257	2.177	0.0003

CABG = coronary artery bypass graft surgery; CI = confidence interval; HR = hazard ratio; IMR = ischemic mitral regurgitation; NYHA = New York Heart Association.

Table 4. Causes of Early Mortality (Less than 90 Days) and Late Mortality (More Than 90 Days)

		Group 1	Group 2		
			A	B	C
	Total (n = 19,912)	CABG Only, No IMR (n = 16,209)	CABG Only, IMR (n = 3,181)	Mitral Repair (n = 416)	Mitral Replacement (n = 106)
Early mortality					
Procedure-related death	62.2% (552/887)	60.7% (357/588)	62.7% (146/233)	9.8% (30/43)	82.6% (19/23)
Cardiac death	24.6% (218/887)	25.2% (148/588)	24.5% (57/233)	20.9% (9/43)	17.4% (4/23)
Noncardiac death	13.2% (117/887)	14.1% (83/588)	12.9% (30/233)	9.3% (4/43)	0.0% (0/23)
Late mortality					
Procedure-related death	0.9% (71/7,667)	0.8% (48/6,045)	1.1% (16/1,406)	3.7% (6/164)	1.9% (1/52)
Cardiac death	49.4% (3,785/7,667)	48.1% (2,908/6,045)	54.2% (762/1,406)	53.0% (87/164)	53.8% (28/52)
Noncardiac death	49.7% (3,811/7,667)	51.1% (3,089/6,045)	44.7% (628/1,406)	43.3% (71/164)	44.2% (23/52)

CABG = coronary artery bypass graft surgery; IMR = ischemic mitral regurgitation.

Results

Baseline characteristics for the 19,912 patients in group 1 and group 2 are shown in Table 1. Patients with IMR (group 2) demonstrated worse preoperative risk factor profiles than group 1. Specific adverse factors in group 2 included greater age, hyperlipidemia, diabetes, hypertension and renal insufficiency, as well as higher heart failure class, EF reduction, and myocardial infarction history. More female patients existed in group 2, suggesting that IMR disproportionately affected women. Comparing groups 2b and 2c, 2b patients displayed more class IV heart failure symptoms, worse EF, greater myocardial infarction history, as well as more diabetes mellitus, hypertension, and hyperlipidemia. The incidence of prior CABG was higher for group 2 relative to group 1, but was similar between groups 2b and 2c (16.8% versus 16.0%, respectively). Median follow-up was 7.7 years (4.1, 12.0).

Unadjusted Kaplan-Meier survival was best for patients undergoing CABG without evidence of preoperative IMR (Fig 1, top panel). The presence of IMR (group 2) was associated with reduced unadjusted survival, regardless of treatment. Survival curves risk-adjusted with a Cox model for differences in baseline characteristics are shown in Figure 1 (bottom panel), and the details of the multivariable model are provided in Table 2. Much of the reduced survival for group 2 was related to worse risk

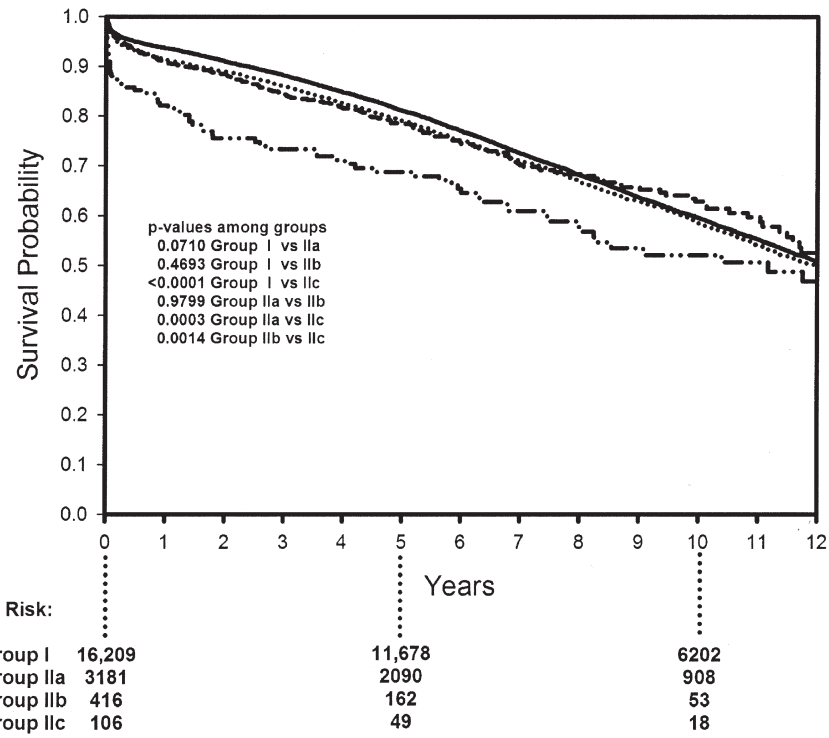

Fig 3. Survival curves for group 1 (CABG only, no IMR), group 2a (CABG only, IMR), group 2b (MV repair), and group 2c (MV replacement) after risk adjustment for differences in baseline characteristics and also adjustment for artificially elevated preoperative ejection fraction (EF) in IMR patients. (CABG = coronary artery bypass graft surgery; IMR = ischemic mitral regurgitation; MR = mitral valve; solid line = group 1; dotted line = group 2a; dashed line = group 2b; dash-dotted line = group 2c.)

Table 5. Cox Survival Model: Adjustment for Differences in Baseline Characteristics and Preoperative Ejection Fraction Augmentation

Risk Factor	Wald χ^2	HR	95% CI		*p* Value
Age (HR per 10 year increase)	(2 d.f) 1752.7				<0.0001
Age (linear piece below 55)		1.018	1.009	1.026	
Age (linear piece above 55)		1.058	1.055	1.061	
Ejection fraction (HR per 5% increase)	573.4	0.89	0.882	0.899	<0.0001
History of diabetes mellitus	273.1	1.492	1.423	1.565	<0.0001
History of peripheral vascular disease	166.9	1.446	1.367	1.529	<0.0001
History of renal failure	142.6	2.018	1.798	2.264	<0.0001
Hyperlipidemia	130.6	0.774	0.741	0.809	<0.0001
History of cerebrovascular disease	103	1.374	1.293	1.461	<0.0001
NYHA class	100	1.147	1.117	1.179	<0.0001
Number of diseased vessels (>50%)	53.1	1.157	1.113	1.204	<0.0001
Body mass index (HR per 1 unit increase)	51.9	0.963	0.953	0.973	<0.0001
Chronic lung disease	44.1	1.316	1.213	1.427	<0.0001
History of CABG	28.9	1.274	1.166	1.391	<0.0001
History of smoking	23.6	1.12	1.07	1.173	<0.0001
Male	14	0.913	0.87	0.958	0.0002
Hypertension	10.8	1.08	1.032	1.131	0.0010
History of myocardial infarction	6.2	1.058	1.012	1.106	0.0127
Connective tissue disease	4.9	1.373	1.036	1.82	0.0273
Reference group 1 (CABG, no IMR)					
Group 2a (CABG only, IMR)	3.3	1.052	0.996	1.111	0.0710
Group 2b (mitral repair, IMR)	0.5	1.054	0.914	1.215	0.4689
Group 2c (mitral replacement, IMR)	16.5	1.615	1.282	2.035	<0.0001

CABG = coronary artery bypass graft surgery; CI = confidence interval; HR = hazard ratio; IMR = ischemic mitral regurgitation; NYHA = New York Heart Association.

factors, and adjusted group 2a and 2b curves were more similar to group 1. After risk adjustment, however, 2b patients continued to demonstrate statistically and clinically superior survival relative to 2c. In the area under the curve analysis, 2a patients achieved 97.7% of group 1 survival and 2b patients, 93.7%, but group 2c patients achieved only 79.1%.

The most prominent difference between group 1 and group 2 was observed in the immediate postoperative period. Thirty-day operative mortality for each of the cohorts was: group 1, 2.5%; group 2a, 4.6%; group 2b, 6.3%; and group 2c, 18.9% ($p < 0.01$ for all pair-wise comparisons except for group 2a versus group 2b, where $p = 0.144$). To assess long-term survival, adjusted survival curves for patients surviving 90 days after the procedure were generated (Fig 2). The associated statistical model is given in Table 3. Even when perioperative mortality was eliminated from the analysis, a trend existed toward improved late mortality in the repair versus replacement group ($p = 0.13$). Although this difference did not reach statistical significance, the analysis was likely underpowered, due to small sample size. Late cardiac-related mortality (Table 4) was similar in each of the groups (group 1, 48.1%; group 2a, 54.2%; group 2b, 53.0%; group 2c, 53.8%), supporting the durability of the IMR treatment strategies, including MV repair.

An important predictor of post-CABG outcome is baseline EF; in fact, this variable was the second most important factor in the survival model. It is understood that EF is artificially augmented by the reduced afterload of MR, in which a significant portion of the total stroke volume is directed into the low-resistance left atrial circuit [30]. To account for this load-related augmentation in preoperative ejection fraction, survival curves for 2b and 2c patients, with predominantly moderate to severe MR,

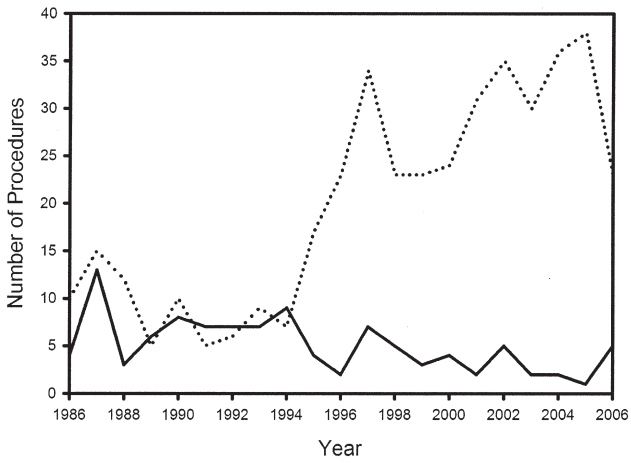

Fig 4. Number of mitral valve (MV) repairs (group 2b [dotted line]) and mitral valve replacements (group 2c [solid line]) performed for ischemic mitral regurgitation per year during the study period.

were further adjusted assuming an 8.8 point artificial augmentation of true EF preoperatively (Fig 3, Table 5). This adjustment is based on the work of Suri and colleagues [31] who showed an 8.8% reduction in EF after successful valve repair or replacement for MR. After EF adjustment, group 2b patients achieved an even better survival, 98.9% of group 1 survival by the area under the curve method ($p = 0.47$), whereas group 2c patients only achieved 85.6% ($p < 0.01$). In general, survival after valve replacement in every analysis was almost 15% lower than repair over the follow-up period.

Finally, trends in numbers of repair versus replacement procedures over the 20-year period are shown in Figure 4. Repairs predominated in later years, but a consistent incidence of valve replacement occurred over the entire period. The year of surgery was evaluated as a predictor of mortality by dividing the 20 years into three periods. No consistent time trend was identified. Outcomes were slightly worse in era 1 (hazard ratio = 1.027), and then improved in era 2 (hazard ratio = 0.910), and again were worse in era 3 (hazard ratio = 1.030). Therefore, year of surgery was not included in the final model.

In the subanalyses, propensity for performing repair versus replacement seemed to be related to surgeon (18 different surgeons contributed patients). In the logistic regression, the surgeon variable was by far the most important factor determining selection of repair versus replacement (Wald $\chi^2 = 58.9$, $p < 0.0001$). However, the severity of MR (Wald $\chi^2 = 19.9$, odds ratio = 3.377 [1.977, 5.766], $p < 0.0001$) was a factor in this analysis, with replacement patients having a higher percentage of severe versus moderate MR, as compared with repair. Additionally, patients selected for replacement tended to have better ejection fractions (Wald $\chi^2 = 11.4$, odds ratio = 1.277 [1.108, 1.472], $p = 0.0007$).

Comment

A high incidence of preoperative risk factors is characteristic of IMR, and these factors influence survival significantly. When differences in baseline characteristics were adjusted statistically, the adverse risk profile of IMR seemed be a major factor limiting survival in IMR, accounting for much of the 58% 5-year survival of IMR patients after repair. Thus, CABG-only patients with the same risk profiles as IMR would have similarly reduced survival, because advanced age and adverse cardiac characteristics have such major effects on outcome. This phenomenon has been demonstrated now in studies from at least four different centers, and with reference patients having either mitral repair for prolapse, or CABG [10–13, 15]. The present analysis confirms this principle in a large cohort undergoing simultaneous and consecutive procedures in the same institution over a 20-year period. An additional strength of this report is the highly complete long-term follow-up available in the Duke Databank.

Patients with mild to moderate IMR usually were managed with CABG only (group 2a). This strategy generally produced good results, achieving 97.7% of standard CABG (group 1; no IMR) survival. It should be emphasized, however, that group 2a is probably very heterogeneous, and certain subgroups may have reduced survival outcomes or greater symptoms of heart failure [3]. Alternatively, some group 2a patients may have had active ischemia with reversible left ventricular dysfunction and mitral insufficiency, and CABG alone can reduce MR in this situation (although not commonly).

Mitral valve repair plus CABG (group 2b) achieved 93.7% of adjusted survival relative to standard CABG (group 1). This finding speaks to the effectiveness of surgical repair with full ring annuloplasty for moderate to severe IMR, and supports current trends toward increasing valve repair [32]. Repair did average a 6.3% lower survival than the reference group (group 1) over 12 years, with most of the increased mortality occurring early after the procedure. Interestingly, late cardiac mortality was not increased for group 2b relative to group 1, again suggesting that valve repair generally is durable and effective. In previous studies from this and other institutions, only a 9% to 10% incidence of recurrent moderate or worse echocardiographic MR was observed after full ring annuloplasty [11, 17], and the late reoperation rate has been low [10]. Finally, if artificially augmented EF in MR is taken into account, survival prognosis after repair becomes even better, achieving 98.9% of group 1 adjusted survival (Fig 3), again supporting the application of repair strategies to this disorder.

Mitral valve replacement for IMR (group 2c) produced less favorable results. This finding was observed for both unadjusted and risk-adjusted analyses, and replacement survival was consistently 10% to 15% less than repair over the follow-up period. This difference was due largely to a higher operative mortality after replacement, consistent with other studies, perhaps because of prolonged ischemic times, destruction of the submitral apparatus, or other factors [23]. However, a difference (although not statistically significant) in late survival also was observed among the 90-day survivors, suggesting a greater ongoing risk with replacement. While utilization of valve replacement procedures declined drastically within the last decade, a small but consistent subgroup continued to have replacement. This cohort may have had specific mitral features that caused the surgeon to avoid repair and choose replacement. Extensive tethering of the posterior leaflet may be difficult to overcome with full annuloplasty rings, and in these instances, surgeons may have selected the replacement strategy. Consistent with this possibility is the observation of more severe MR for the replacement group. Techniques that enable successful repair of these types of valves could further reduce prosthetic replacement and avoid the associated increased mortality. Efforts in this regard include posterior leaflet pericardial patch augmentation in combination with annuloplasty, asymmetric ring design, or submitral approaches to compensate for leaflet tethering or papillary muscle displacement [16, 17, 33–37]. This study does not address the potential efficacy of these approaches, but it does highlight the fact that patients who were chosen for replacement failed to achieve a great

deal of their survival potential. New adjunctive repair strategies could increase applicability and long-term stability of repair, and improve overall patient outcomes further.

The primary discrepancy in adjusted outcomes for all groups occurred during the perioperative period. This finding emphasizes the continued need for improvement in operative and perioperative management of IMR patients, who appear to be at higher risk for early complications and mortality relative to the CABG-alone cohort. Potential areas for improvement include preoperative optimization, better intraoperative myocardial protection, improved neurologic protective strategies, and better management of postoperative immune dysfunction and infection [38].

This observational study should be qualified by describing the possibility of undefined treatment selection biases or treatment deficiencies. Additionally, important factors associated with heart failure may not have been available for assessment. For example, left ventricle volume was not recorded as a variable in this data set, but has been shown to have important predictive value for ischemic cardiomyopathy [39]. Had other such variables been included, the MV repair versus replacement survivals may have changed, but the dramatic differences observed in this analysis make this possibility less likely. Furthermore, the determination by Suri and colleagues [31] of change in EF after resolution of mitral regurgitation is based on data in mitral prolapse patients. This may be different than the pathophysiology of IMR; therefore, an 8.8% reduction in EF may not be accurate for IMR patients. Another limitation relates to techniques for valve replacement. Many of the replacement patients were accrued early during the 1980s and 1990s, and complete chordal sparing may not have been universally applied in this era. Because chordal preservation may maintain postoperative ventricular function and positively impact perioperative outcomes [40], the inability to evaluate this technical factor is a drawback of this analysis. Moreover, a common modality for determination of MR grade was ventriculography. This limitation reflects the broad time span covered by this review. While the majority of patients who were treated after 1986 received intraoperative transesophageal echocardiography, some early patients did not. Finally, a variety of medical and device therapies (namely, automated implantable cardiac defibrillator) affecting survival outcomes could not be documented in this study, and could have been applied differently to group 2b and 2c patients, who had advanced heart failure profiles.

In conclusion, worse baseline risk is a major factor reducing long-term survival in IMR. Current algorithms in which mild to moderate IMR is treated with bypass only generally produced good late results. Mitral repair appeared to restore patients to a survival curve very similar to that of CABG patients without IMR, thus reducing the adverse mortality effects of moderate and severe IMR. Mitral valve replacement was less satisfactory, achieving an almost 15% lower survival over follow-up. The major differences were seen in the early postoperative period, emphasizing the need for better perioperative management strategies. The results of this study support the current trend of increasing use of valve repair relative to replacement for significant IMR.

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