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YEAR IN CARDIOLOGY SERIES

The Year in Cardiovascular Surgery

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The 2009 literature in cardiovascular surgery was characterized by several pivotal reports that will affect patient care and future trial design for years to come. The purpose of our annual review is to highlight key contributions in the field that focus on strategies and outcomes in cardiovascular surgery that practicing cardiovascular specialists will find both informative and useful in their daily practice. Particular emphasis this year was placed on articles that compare surgical with nonsurgical alternative treatment strategies or those that emphasize potential advances in specific surgical strategies. Our goal as always is to provide readers of the *Journal* with a succinct summary of specific studies organized around general categories, with pointed comments to highlight special significance or methodological limitations that cardiologists should consider in their pursuit of state-of-the-art care for their patients.

Surgery for Valvular Heart Disease

Surgery for asymptomatic severe mitral valve regurgitation. Long-term results in 161 patients who underwent early surgery were compared with 286 patients who received conventional medical follow-up for asymptomatic severe mitral valve regurgitation in the setting of preserved left ventricular function (1). The actuarial 7-year cardiac mortality was 0% in the surgery group and 5 ± 2% in the conventional treatment group ($p = 0.0008$), and actuarial 7-year event-free survival in 127 propensity score-matched patients was 99 ± 1% in the surgery group and 84 ± 4% in the conventional treatment group ($p = 0.007$) (Fig. 1). In the conventional treatment group, pulmonary hypertension (relative risk [RR]: 1.9, 95% confidence interval [CI]: 1.2 to 2.9, $p = 0.003$), age (RR: 1.0, 95% CI: 1.1 to 1.0, $p = 0.005$), and effective regurgitant orifice area (RR: 2.1, 95% CI: 1.1 to 3.8, $p = 0.02$) were independent predictors of the late development of surgical indications or congestive heart failure.

In another study of 192 patients with asymptomatic severe degenerative mitral valve regurgitation, overall, cardiovascular, and event-free survival were evaluated in 67 patients managed by a "conservative approach" of waiting for surgical indications to develop compared with 125 patients subjected to "early" surgery (2). Overall survival at 10 years was significantly better in patients undergoing early surgery for severe mitral regurgitation (86% vs. 50%, $p < 0.00001$, log-rank test) (Fig. 2), and this remained true in propensity subgroup analyses.

COMMENT. The timing of intervention on patients with severe asymptomatic mitral regurgitation in the absence of ventricular dysfunction or severe dilation remains controversial. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines (3) recommend early surgical intervention for patients with severe asymptomatic mitral valve regurgitation and a high probability of mitral valve repair. The results of these 2 studies reinforce the conclusions of an earlier prospective study by Enriquez-Sarano et al. (4) that had significant influence on the ACC/AHA recommendation for early surgery: there is a significant event rate (including mortality) in unoperated asymptomatic patients with severe mitral valve regurgitation subjected to conventional medical follow-up. An invited editorial to the Kang et al. (1) article reinforced the "unstated risk" of managing asymptomatic patients conservatively, noting that some patients will be lost to follow-up (occasionally because of death), whereas other patients will not return until complications, including heart failure, occur (5). Another invited editorial made the point that symptoms were the trigger for later surgery in 94% of patients who underwent conventional treatment in the Kang et al. (1) series, whereas none were noted to have ventricular dysfunction during follow-up (raising the question of how carefully echo follow-up actually was performed) (6). Both editorials emphasized the other key to early surgery in the Kang et al. (1) series: very low operative mortality (0%) and very high repair rates (94%), reinforcing the importance of "reference level" mitral surgery in asymptomatic patients.

Failure of guideline adherence in patients with severe mitral regurgitation. At the University of Michigan, all 300 patients with moderate-to-severe mitral valve regurgitation documented in the Echocardiographic Laboratory in 2005 were reviewed retrospectively to evaluate adherence to

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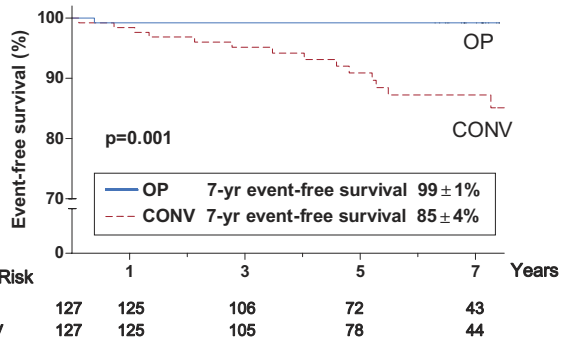

Figure 1 **Event-Free Survival in Asymptomatic Patients With Severe Degenerative Mitral Regurgitation and Preserved Ventricular Function**

Survival in patients with severe mitral regurgitation according to treatment strategy. CONV = conservatively treated patients; OP = operated patients. Modified and reprinted with permission from Kang et al. (1).

established ACC/AHA guideline recommendations for surgical intervention (7). Mitral surgery was performed in 59 (53%) of 112 patients with organic (nonischemic) moderate-to-severe mitral valve regurgitation, whereas 1 or more guideline indications for intervention were present in 39 (74%) of 53 unoperated patients. There were no significant differences in perioperative risks between operated and unoperated groups with organic mitral disease, and during follow-up, there were 12 cardiac and 2 unexplained deaths in the unoperated group (Table 1).

COMMENT. This study from a leading mitral valve surgery center documents a practice gap in terms of adherence to current guidelines for intervention in patients with mitral valve regurgitation. The findings re-enforce the need for continuing education regarding the adoption of valve guidelines in daily practice and promoting the use of routine risk assessment tools and multidisciplinary consultation in certain patient subgroups of patients with mitral valve regurgitation.

Implications of pre-operative ventricular variables on long-term outcome after mitral valve surgery. Recovery of left ventricular function after surgical correction of degenerative mitral valve regurgitation was evaluated in 1,063 patients who underwent surgery (mitral valve repair in 924 of 1,063 [87%]) between January 1980 and December 2000 (8). Patients had a greater likelihood of post-operative ejection fraction >60% if the pre-operative ejection fraction was >65% (RR: 1.8, $p < 0.001$) or if the left ventricular end systolic diameter (LVESD) was <36 mm (RR: 2.0, $p < 0.001$).

In another study, a multicenter registry was investigated to determine the effect of LVESD on survival in 739 patients with flail mitral leaflets (9). Under conservative management, 10-year risk-adjusted cardiac death-free survival was higher with an LVESD <40 mm versus one of 40 mm or more (73 ± 5% vs. 63 ± 10%, $p = 0.001$). There was a persistence of risk-adjusted excess cardiac mortality in patients with an LVESD of 40 mm of more who underwent surgery (RR: 1.8, 95% CI: 1.0 to 3.5, $p = 0.04$) (Fig. 3).

COMMENT. These studies emphasize the importance of careful assessment of left ventricular parameters in patients with degenerative mitral valve regurgitation. Current ACC/

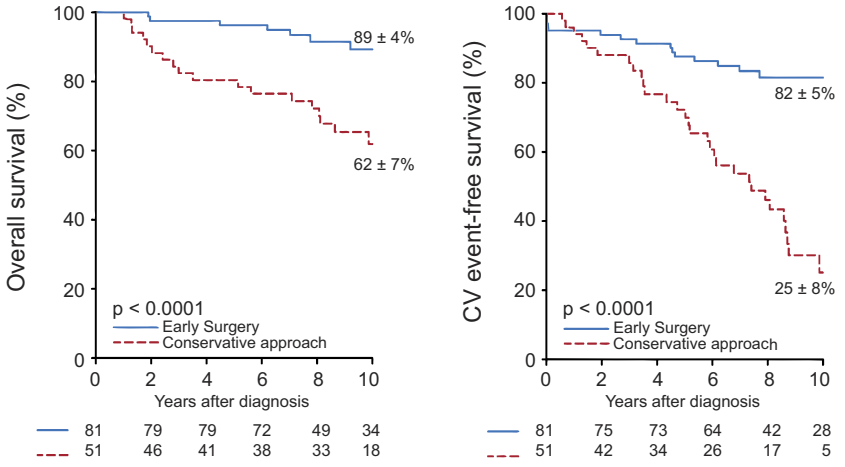

Figure 2 **Event-Free Survival in Asymptomatic Patients With Severe Degenerative Mitral Regurgitation and No Associated Complications**

Survival in patients with severe mitral regurgitation, but without left ventricular dysfunction or dilation, pulmonary hypertension, or atrial fibrillation according to treatment strategy. **(A)** Overall survival. **(B)** Cardiovascular (CV) event-free survival. The **solid line** represents patients who underwent early surgery. The **dashed line** represents patients treated conservatively. Modified and reprinted with permission from Montant et al. (2).

Table 1 Rationale for Not Permitting Mitral Surgery for Severe MR

Rationale	n (%)	Death	Cardiac Death	Interval to Cardiac Death (Days)
Asymptomatic	9 (17%)	1	0	—
Stable LVEF, stable chambers	17 (32%)	3	3	186, 839, 855
MR improved on subsequent echocardiogram	6 (11%)	1	1	213
Comorbidities/risk	10 (19%)	7*	4	3, 5, 26, 43
Patient refused	4 (%)	2	2	3, 32
Died before planned evaluation	1 (%)	1	1	5
MR unrecognized	4 (%)	1†	0	—
MR ignored	2 (%)	1	1	232

Includes 4 cardiac deaths, 2 noncardiac deaths, and 1 death resulting from an undocumented cause. Modified and reprinted with permission from Bach et al. (7). *There were 4 noncardiac deaths, 2 cardiac deaths, and 1 death of undocumented cause. †One death of undocumented cause.
LVEF = left ventricular ejection fraction; MR = mitral regurgitation.

AHA guidelines recommend a threshold for surgical referral of an LVESD of 40 mm or more or an ejection fraction of 60% or less in patients with chronic severe mitral valve regurgitation (3). European guidelines (10) agree with the ejection fraction threshold, but maintain the older ACC/AHA surgical threshold of an LVESD of 45 mm or more (11). Guidelines are likely to continue to move toward earlier surgery and more liberal ventricular thresholds for surgical intervention, before the onset of impairment of left ventricular function.

Management of moderate mitral valve regurgitation in patients undergoing aortic valve replacement. A retrospective review of 190 patients with moderate (grade 2) functional mitral regurgitation left alone at the time of aortic valve or root replacement found that in most instances, the mitral regurgitation improved with correction of the aortic valve pathological features alone (12) (Table 2). The long-term survival of 91 patients from this cohort was similar to that of case matched patients without mitral regurgitation undergoing aortic valve replacement ($p = 0.33$).

COMMENT. These data support potentially leaving grade 2+ or less mitral valve regurgitation untreated at the time of aortic valve surgery for aortic stenosis or regurgitation. The authors expressed an inclination to correct grade 3+ or more mitral valve regurgitation surgically at the time of aortic valve surgery, so we do not know from their study if it is prudent to leave more than moderate mitral regurgitation untreated in patients undergoing aortic valve surgery. It may well be that this question will be answered one day in a transcatheter aortic valve population with severe symptomatic aortic stenosis and grade 3+ or more mitral valve regurgitation deemed too high risk for surgical intervention (although current trials exclude such patients).

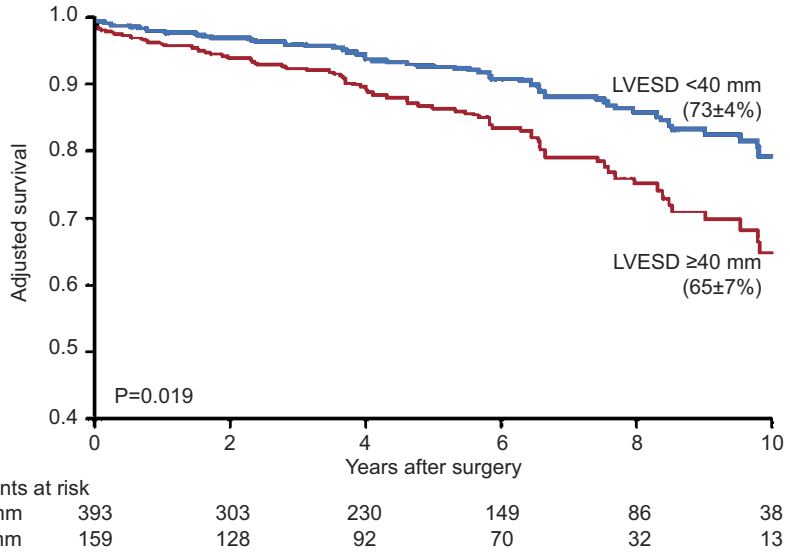

Figure 3 Adjusted Post-Operative Overall Survival According to LVESD in Operated Patients With Organic Mitral Regurgitation

Adjusted post-operative survival according to left ventricular end-systolic diameter (LVESD) in operated patients with organic mitral regurgitation. Modified and reprinted with permission from Tribouilloy et al. (9).

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Table 2 Mitral Regurgitation Grades After Isolated Aortic Valve Replacement in the Setting of Pre-Operative Aortic Stenosis and Grade 2 Mitral Regurgitation

Mitral Regurgitation Grade	n (%)
Discharge	
<1	23 (14%)
1	91 (57%)
2	42 (26%)
3	3 (2%)
4	0
Follow-up	
<1	16 (16%)
1	47 (47%)
2	34 (34%)
3	4 (4%)
4	0

Reprinted with permission from Wan et al. (12).

Ischemic mitral regurgitation: fate of unrepaired moderate regurgitation. Echocardiography was performed 12 months after surgery in 121 patients with moderate ischemic mitral regurgitation who had undergone isolated coronary artery bypass grafting (CABG): mitral regurgitation improved in 57 patients and was the same or worse in 64 patients (13). Pre-operative predictors of improvement in mitral regurgitation at 1 year of follow-up were greater area of viable myocardium (≥5 segments) and absence of dyssynchrony between papillary muscles ($p < 0.001$). There was clinical correlation with the degree of residual mitral valve regurgitation, because patients in whom regurgitation improved had better survival and functional status (Fig. 4).

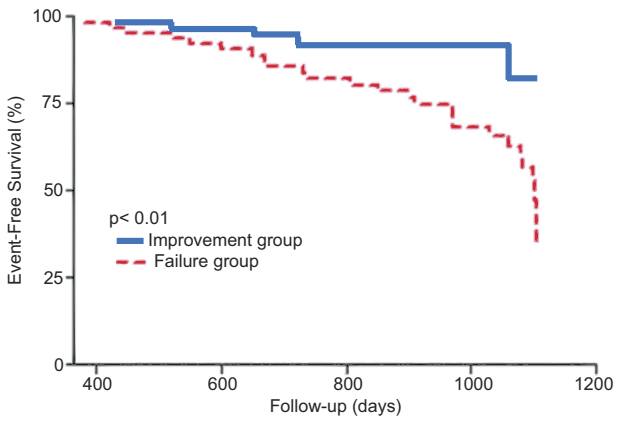

Figure 4 Event-Free Survival in Patients With Moderate MR Undergoing Coronary Artery Bypass Grafting

Kaplan-Meier event-free survival in patients with moderate mitral regurgitation (MR) undergoing isolated coronary artery bypass grafting. The **dashed red line** represents patients in whom MR was unchanged or worse at 12 months. The **solid blue line** represents patients in whom MR improved or resolved. Modified with permission from Penicka et al. (13).

COMMENT. This contemporary study shows that moderate mitral regurgitation often does not resolve after isolated CABG, confirming prior work (14). The present study provides clues into those patients in whom ischemic mitral regurgitation may improve without concurrent mitral valve surgery. An accompanying editorial emphasized that these data remind us that the ventricle, rather than the valve, should be our prime focus in targeting ischemic mitral regurgitation (15). Pre-operative assessment of patients with moderate ischemic mitral valve regurgitation probably should include more detailed study of ventricular viability and papillary muscle function, and results of these studies should factor into the decision of whether to intervene on the mitral valve in selected patients.

Outcome after aortic valve replacement in low-flow or low-gradient aortic stenosis without contractile reserve. Survival was examined in 81 consecutive patients with symptomatic calcific low-flow or low-gradient aortic stenosis (valve area ≤1 cm^2, left ventricular ejection fraction ≤40%, mean pressure gradient ≤40 mm Hg) without demonstrable contractile reserve on dobutamine stress echocardiography (16). Five-year survival was higher in patients undergoing aortic valve replacement versus medical management (54 ± 7% vs. 13 ± 7%, $p = 0.001$), including 42 propensity-matched patients (65 ± 11% vs. 11 ± 7%, $p = 0.02$) (Fig. 5). Concomitant bypass surgery ($p = 0.007$) and mean pressure gradient of 20 mm Hg or less ($p = 0.03$) were predictive independently of operative mortality, which was relatively high at 22% in the aortic valve replacement group.

In another prospective single-center study, outcomes were examined from 597 consecutive patients who underwent aortic valve replacement for aortic stenosis, including 12% (n = 73) with low ejection fraction low-gradient aortic stenosis (defined as a left ventricular ejection fraction of ≤30% and mean transvalvular gradient of <35 mm Hg).

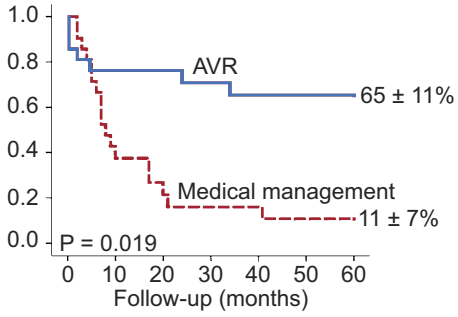

Figure 5 Prognostic Impact of AVR in Low-Flow or Low-Gradient Aortic Stenosis Without Contractile Reserve

Kaplan-Meier survival in propensity-matched patients with low-flow or low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography, according to whether they underwent aortic valve replacement (AVR). Modified and reprinted with permission from Tribouilloy et al. (16).

Low ejection fraction low-gradient aortic stenosis was not found to be an independent risk factor for mortality (17), although it was a strong predictor of major post-operative morbidity, including stroke (odds ratio [OR]: 4, 95% CI: 1 to 15, $p = 0.02$), deep sternal wound infection (OR: 10, 95% CI: 2 to 46, $p < 0.01$), and respiratory failure (OR: 4, 95% CI: 2 to 9, $p < 0.01$).

COMMENT. Approximately one-third of patients meeting current ACC/AHA Class I indications for aortic valve replacement are denied surgery, and severe left ventricular dysfunction is one of the most commonly cited reasons (18). This European multicenter study is the largest to date to examine the outcome of patients with low-flow or low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. Contractile reserve documented on dobutamine stress echocardiography is associated with lower operative risks in the setting of low-flow or low-gradient aortic stenosis (19). These studies emphasizes that aortic valve replacement still may represent the best option, even in the absence of documented contractile reserve, given the extremely poor survival with conservative management. Other alternatives, including heart transplantation or destination ventricular assist device therapy, remain options in highly selected patients with extensive coronary disease and myocardial scarring, or if the mean pressure gradient is 20 mm Hg or less.

Patient prosthesis mismatch after aortic valve replacement. Survival was analyzed in a retrospective review of 2,576 consecutive patients who survived to hospital discharge after aortic valve replacement (20). Moderate patient prosthesis mismatch, defined as an indexed effective orifice area between 0.85 and 0.65 cm^2/m^2, was identified in 31%; and severe patient prosthesis mismatch, defined as 0.65 cm^2/m^2 or less, was present in 2%. After adjusting for risk factors, severe patient prosthesis mismatch was found to predict decreased late survival in patients younger than 70 years of age, and moderate patient prosthesis mismatch was found to predict decreased late survival in patients with reduced pre-operative left ventricular ejection fraction <50%.

COMMENT. The impact of patient prosthesis mismatch on clinical outcomes after aortic valve replacement remains controversial. The group with patient prosthesis mismatch in this study had a significantly higher proportion of patients with almost all of the key baseline risk factors for decreased survival, including more advanced age, obesity, coronary artery disease, New York Heart Association functional class III or IV status, hypertension, diabetes, renal failure, and chronic lung disease, as well as significantly longer cardiopulmonary bypass times. Although the unadjusted survival curves suggest that a large decrease in survival is associated with patient prosthesis mismatch, after risk factors were controlled for, the only group in which moderate prosthesis mismatch was an independent predictor of decreased survival were patients with left ventricular dysfunction (Fig. 6), although the lower CI was close to 1.0. Selection of prostheses to minimize the risk of patient prosthesis mismatch in this scenario may have a role in further improving operative mortality, but as pointed out by Rahimtoola (21) in his later commentary, the very small numbers of patients in each group by latter stages of

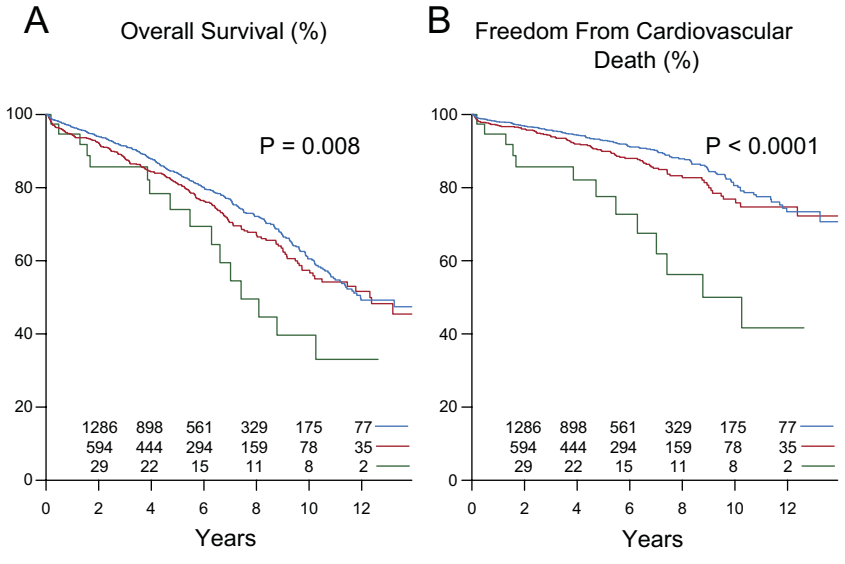

Figure 6 **Impact of PPM on Survival in Patients With Left Ventricular Dysfunction**

Survival after aortic valve replacement in patients with left ventricular ejection fraction <50%. **Blue line** = nonsignificant prosthesis-patient mismatch (PPM); **red line** = moderate PPM; **green line** = severe PPM. Modified and reprinted with permission from Mohty et al. (20).

follow-up indicate that these results must be interpreted with caution.

Overestimation of cardiac surgery risk by European System for Cardiac Operative Risk Evaluation (EuroSCORE). A single-center study examined operative mortality (observed vs. predicted by additive or logistic EuroSCORE) in 1,545 consecutive patients undergoing isolated aortic valve replacement over a 13-year period (22). The observed 30-day mortality was 2.2% and was overestimated substantially by additive (6.1%) and logistic (9.3%) EuroSCOREs. Higher-risk patients had 3.6% mortality, which also was overestimated by additive (8.3%) and logistic (14.3%) EuroSCOREs. Although EuroSCOREs successfully stratified patients into a higher risk category for 30-day mortality, particularly in more recently operated patients, it has become increasingly uncalibrated to absolute risk (Fig. 7).

Another single-center study examined outcomes in 282 octogenarians undergoing isolated aortic valve replacement for aortic stenosis to evaluate logistic EuroSCORE risk stratification for operative mortality (23). Patient groups were defined as low risk (logistic score <10%), moderate risk (logistic score ≥10% and <20%), and high risk (logistic score ≥20%); overall hospital mortality was 10.6% and was not significantly discriminated between groups using logistic EuroSCORE. Logistic EuroSCORE stratum, however, did significantly predict midterm 5-year survival (low risk: 70%, moderate risk: 53%, high risk: 38%, p = 0.05).

In a third study, a predictive risk stratification model limited to 3 independent factors (age, left ventricular ejection fraction, and creatinine level) was developed for elective cardiac surgical procedures at a single institution, based on analysis of 4,557 elective adult surgical patients (24). The predictive accuracy of the abbreviated risk score was compared with that of well-established more complex models, including the additive and logistic EuroSCOREs in a validation series of 4,091 patients, in which there were 105 deaths. The abbreviated risk score was shown to be accurate in all subsets of the population with an area under the receiver-operating characteristic curve always exceeding 0.8, and it was the most accurate score for predicting operative mortality (0.826) in elective patients undergoing isolated CABG. All risk scores demonstrated good negative predictive value (99%), but poor positive predictive value (<8%).

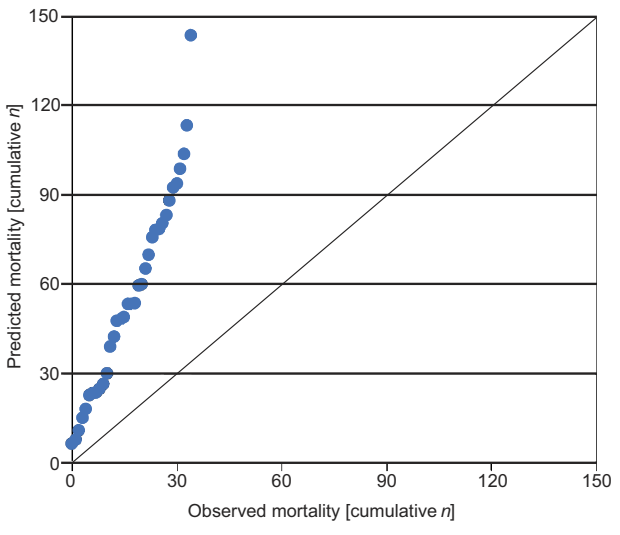

Figure 7 **Cumulative Sum Plot of Observed and Predicted 30-Day Mortality After Aortic Valve Replacement for the Logistic European System for Cardiac Operative Risk Evaluation**

Plot of the cumulative sums of observed and predicted mortality after aortic valve replacement. The **solid diagonal line** is the line of identity, representing perfect agreement between predicted and observed mortality. Modified and reprinted with permission from Osswald et al. (22).

COMMENT. EuroSCORE is a commonly used tool to assess operative risks in patients undergoing cardiac surgery. It is important to recognize that the data set supporting current additive or logistic EuroSCORE systems was generated in 1995 across a spectrum of cardiac surgery patients, with a vast majority of the study population undergoing coronary artery bypass surgery and relatively few undergoing isolated aortic valve replacement. Recognition of the limitations of the current EuroSCORE models to predict operative outcome in high-risk patients with aortic valve disease has led to the adoption of the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality model as the standard for current and future Food and Drug Administration transcatheter aortic valve replacement trials, which are intended at this point to target high-risk patient populations with severe symptomatic aortic valve stenosis. The STS Predicted Risk of Mortality model for isolated aortic valve replacement was generated from a study population of 67,292 patients undergoing surgery between 2002 and 2006 (25). Current efforts are underway to recalibrate the EuroSCORE with a new patient cohort, and it should be emphasized that although the STS Predicted Risk of Mortality model seems most accurately to predict mortality in high-risk patients undergoing aortic valve replacement, no current risk stratification system is calibrated to include all of the variables (such as extreme frailty) that may be present in a current candidate population for transcatheter valve therapy.

Despite sound methodology and calibration, the accuracy of large population risk prediction scores such as the STS score and EuroSCORE rarely exceeds an area under the receiver-operating characteristic curve of 0.75, and is particularly poor in patients at the extremes of risk. Intuitively, it may seem as though the greater the number of patients and variables included, the better calibrated each model will be. But including too many variables in a risk stratification model may cause overfitting resulting in a type I error, and a discrepancy in local practice such as referral patterns or patient selection may reduce the ability of an external model to discriminate within a local population. Furthermore, restricting the risk factors in a

model to readily quantified continuous variables reduces the degree of user interpretation inherent in broader models and also helps to reduce the chance of intercorrelation between supposedly independent variables. Internally developed risk stratification models, including a smaller number of variables and applied to homogenous patient sets, can be recalibrated annually to provide a more accurate risk stratification at an institutional level.

Aortic prosthesis choice in younger patients. Between 1995 and 2003, 310 patients between the age of 55 and 70 years undergoing primary aortic valve replacement were randomized to either a bileaflet mechanical valve versus a second-generation bioprosthesis at a single institution (26). There were no significant differences in baseline characteristics between the 2 groups, and mean follow-up was 9 ± 2 years. The study, which was powered to detect a 10% difference in late mortality between the 2 arms, showed no significant difference in operative mortality or morbidity, survival (Fig. 8), or cumulative late complications, including bleeding events, endocarditis, valve thrombosis, or nonstructural dysfunction according to whether patients had undergone valve replacement with a mechanical or bioprosthesis at 5, 10, or 13 years. The incidence of structural valve degeneration and reoperation was higher in the bioprosthetic group, with an escalating risk of valve failure starting at 10 years after surgery and showing no reduction in risk with time. The authors report linearized rates of valve failure of 2% per patient-year (95% CI: 1.4 to 3) and of reoperation of 2.3% per patient-year (95% CI: 1.5 to 3.1) for bioprosthetic valves, compared with 0% and 0.6% per year (95% CI: 0.2 to 1.1) for mechanical valves ($p < 0.001$).

COMMENT. In patients older than 65 years of age, who represent a steadily increasing proportion of patients undergoing valve surgery, reoperation rates with modern bioprostheses are particularly low, and current guidelines suggest bioprosthetic valves should be used routinely in these patients (3,10). Valve choice in younger patients is more controversial, and an accompanying editorial emphasizes how this study contributes to literature dominated by studies in older patients with valve models that since have been superseded (27). Patient and physician preference has shifted away from mechanical valves, even in patients younger than the age threshold of current guidelines; this may reflect increased awareness of the constant linearized risk of thrombotic or hemorrhagic stroke associated with mechanical valves, advances in surgical treatment of atrial fibrillation, which consequently is no longer a strong relative indication for a mechanical valve, and lifestyle choices. Current data suggest that there is little or no survival difference between mechanical and bioprosthetic valves. The findings in this study confirm that patients undergoing valve replacement with a mechanical valve can expect an annual risk of major hemorrhagic or embolic event, including stroke, of approximately 2% per year for life. Young patients undergoing bioprosthetic valve replacement can expect to start developing structural valve degeneration by approximately 10 years and eventually will need reoperation.

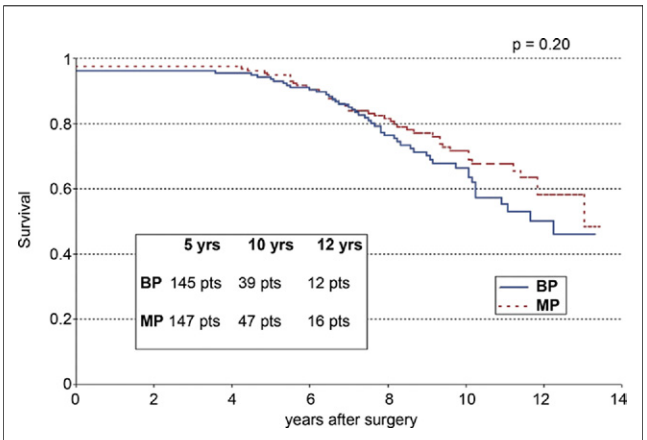

Figure 8 **Survival in Middle-Aged Patients After AVR According to Prosthesis Type**

Survival after aortic valve replacement (AVR) in patients 55 to 70 years or age, according to whether they received a mechanical AVR (**dashed red line**; MP) or bioprosthesis (**solid blue line**; BP). Modified and reprinted with permission from Stassano et al. (26).

Valve sparing versus valve replacement. The 30-day outcomes of a multicenter registry of 151 patients undergoing surgery for aortic root dilation resulting from Marfan's disease were analyzed according to whether patients underwent aortic root replacement with a valved conduit (n = 46), including 39 mechanical and 7 bioprosthetic root replacements, or using an aortic valve-sparing procedure (n = 105), which were all, with one exception, remodeling rather than reimplantation procedures (28). Choice of procedure was entirely at the discretion of the surgeon. Patients who underwent valve-sparing surgery were significantly younger, had a lower incidence of acute type-A dissection, and were less likely to have severe aortic insufficiency on presentation than patients in the root replacement group; baseline characteristics otherwise were similar between the 2 surgical groups. There was no operative mortality in either group and no difference in the very low rates of major post-operative complications between groups. Grade of aortic insufficiency at discharge was mild or less in all patients.

Another study looked at long-term outcomes of valve-sparing root replacement in 103 patients with aortic dilation resulting from Marfan's disease, including 8 acute type-A dissections, reporting freedom from moderate or greater aortic insufficiency of 92 ± 4% at 10 years and 79 ± 8% at 15 years (29). Operative mortality was 2%, with 10% of patients requiring reoperation for bleeding.

COMMENT. Aortic root dilation is associated with significantly increased risk of death from aneurysm rupture, dissection, and aortic insufficiency, and it is an important

prognostic factor in Marfan's disease. These patients usually are young, and composite mechanical root replacement therefore is used frequently. As discussed above, in the section on prosthesis choice, this carries a linear 2% annual risk of major thromboembolic and hemorrhagic complications, including stroke. The analysis by Volguina et al. (28) suggests that early outcomes of both valve-sparing and valve-replacement techniques are comparable, although the study was underpowered to detect the study primary end point of a 20% difference in the composite end point of all valve-related complications and provides no information on late outcomes. The very low mortality rates reported in both valve-sparing series reflects the substantial experience of the surgeons in these single-surgeon series and has not been replicated in national registry data.

Ross procedure. A meta-analysis of 39 series published between 2000 and 2008, including more than 5,000 patients, was conducted to define better autograft durability, morbidity, and mortality after the Ross procedure (30). Mean follow-up in the 12 adult series, which contained 1479 patients, was 4 years (range: 1 to 7 years). Pooled early mortality was 3% in adults, (95% CI: 1% to 7%), and the rate of late mortality was 0.6% per year (95% CI: 0.3% to 1% per year). The most common complication was structural valve degeneration of the autograft, with a pooled rate of autograft dysfunction of 1% per year, ranging from 0.1% to 2% per year, with a similar rate of right ventricular outflow tract failure.

In a multicenter analysis of 1,335 patients who underwent a Ross procedure between 1988 and 2008 with mean follow-up of 6 years, pooled early mortality was 1%, and the incidence of any mortality during follow-up was 2.6%. Low rates of structural valve degeneration and reoperation rates were observed (31).

COMMENT. The main limitations of the meta-analysis are the inclusion of small series with relatively high mortality and failure rates, and the very short length of follow-up. As the accompanying editorial points out, the benchmark for operative mortality for aortic valve replacement in young adults is <1% (32), and other commentators have highlighted the authors' conclusions regarding "durability limitations" (21). The registry results, however, suggest that, in experienced hands, the Ross procedure offers a durable option for aortic valve replacement in adults with excellent midterm survival and freedom from structural valve degeneration and reoperation.

Isolated tricuspid valve surgery: outcomes. Investigators examined the midterm outcomes of 61 patients who underwent isolated tricuspid valve surgery for severe tricuspid regurgitation (33). Most patients had undergone prior mitral valve surgery, including 10 who had prior tricuspid valve repair. Eight patients underwent tricuspid valve repair, and the remaining 53 patients underwent valve replacement. Operative mortality was 10%, whereas median hospital stay was 26 days. Of survivors, 39% had no improvement in functional capacity at 6 months after surgery. In multivariate analysis, pre-operative hemoglobin and right ventricular end-systolic area were independent determinants of outcome.

COMMENT. Surgery for severe tricuspid regurgitation carries a high operative risk even in contemporary practice, and in many patients, correction may not result in improved symptoms or survival. Operating on patients before the right ventricle is severely dilated or before they are anemic may improve outcomes. Because most of these patients have undergone prior left-sided valve surgery, these data support an aggressive strategy toward tricuspid valve disease at the time of initial left-sided valve surgery.

Repair of incidental patent foramen ovale (PFO). Retrospectively reviewed intraoperative transesophageal echocardiogram data obtained from 13,093 patients undergoing various cardiac surgical operations identified 2,277 (17%) who had an incidental PFO diagnosed during surgery, of which 639 (28%) underwent surgical repair (34). Patients more likely to have their PFO repaired included females, younger patients, those undergoing mitral or tricuspid valve surgery, those with history of stroke or transient ischemic attack, and those with less comorbidity. Some surgeons also were more likely to repair incidental PFOs than others. Propensity matching was used to compare outcomes in patients in whom the PFO was repaired with those in whom the PFO was present but not repaired; other than perioperative stroke, which was more prevalent in the repaired group (odds ratio: 2.47, 95% CI: 1.02 to 6.00, $p = 0.04$), there was no difference in perioperative outcomes. There was no difference in long-term survival when they compared patients with PFO (regardless of whether repaired) with those without a PFO; however, for patients with a PFO, there was a tendency to better survival if the PFO was repaired ($p = 0.12$).

COMMENT. This study found no long-term survival benefit to repairing an incidentally diagnosed PFO during cardiac surgery and that there is a possibility that repair may increase the incidence of perioperative stroke. Long-term incidence of stroke was not reported; this would have been useful to know, especially considering the tendency to higher late mortality in the nonrepaired group and also that stroke prevention is the principal basis for closure of incidental PFOs. The study limitations include a long-study period (1995 through 2006), where surgical and diagnostic practices likely evolved, missing echocardiographic data on most patients operated in the period (41,578 operations were performed in the study period, but the authors could obtain transesophageal echocardiograms before and after surgery on only 34%), and low event rates, such that estimates of effect were imprecise with wide CIs. Interestingly, no biological explanation or hypothesis for their observations was offered by the authors.

Coronary Artery Disease (CAD)

Comparison of CABG and percutaneous coronary intervention (PCI). SYNTAX TRIAL: DES VERSUS CABG FOR LEFT MAIN OR 3-VESSEL CAD. A total of 1,800 patients with 3-vessel disease or left main CAD were assigned randomly to undergo CABG or PCI with drug-eluting stents (Taxus DES, Boston Scientific, Natick, Massachusetts) in a 1:1 ratio (35). A noninferiority comparison of the 2 groups was conducted with the primary end point of death from any cause, stroke, myocardial infarction, or repeat revascularization during the 12-month period after randomization. At 1 year, the rates of major adverse cardiac or cerebrovascular events were significantly higher in the PCI group (17.8% vs. 12.4% for CABG, $p = 0.002$) mostly because of an increased rate of repeat revascularization (13.5% vs. 5.9%, $p < 0.001$). The rates of death and myocardial infarction were similar between the 2 revascularization strategies at 12 months, whereas the stroke rate was significantly higher in the CABG group (2.2% vs. 0.6% with PCI, $p = 0.003$). The authors concluded that CABG remains the standard of care for patients with 3-vessel or left main CAD. A separate important feature of this study was the definition of a synergy between PCI with taxus and cardiac surgery (SYNTAX) score to predict outcomes based on the anatomical characteristics of coronary artery lesions (total occlusion, bifurcation lesion, length of lesion >20 mm, and presence of heavy calcifications). The rate of major adverse cardiovascular and cerebrovascular events was similar between the 2 groups in patients with low (0 to 22) and intermediate (23 to 32) SYNTAX scores; the rate of major adverse cardiac or cerebrovascular events and particularly the need for repeat revascularization after PCI, however, was significantly elevated in patients with high SYNTAX scores (>33), indicating very complex CAD (Fig. 9).

COMMENT. The SYNTAX trial is the first major randomized trial demonstrating that PCI with a drug-eluting stent is less effective than CABG for preventing the 1-year primary end point of major adverse cardiac or cerebrovas-

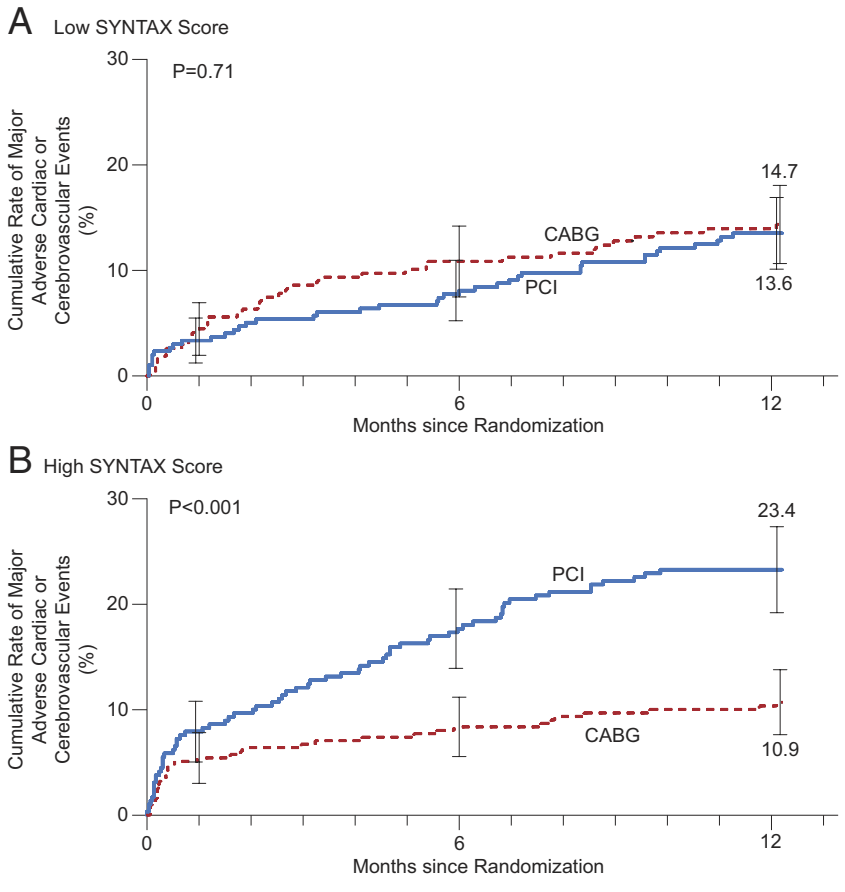

Figure 9 Rates of Major Adverse Cardiac or Cerebrovascular Events According to Synergy Between PCI With Taxus and Cardiac Surgery Score and Treatment

Kaplan-Meier event-free survival in patients randomized to coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) according to their synergy between PCI with Taxus and cardiac surgery (SYNTAX) score. Modified and reprinted with permission from Serruys et al. (35).

cular event in patients with left main or 3-vessel coronary disease, or both. This difference in outcomes mainly was the result of the inclusion of repeat revascularization in the primary end point. Perhaps the most significant finding of the trial was the demonstration of a CAD burden scoring system to define a high-risk subgroup (SYNTAX score: >33) in which CABG should be recommended strongly versus multivessel or left main PCI, or both. Another important finding of this study was the significantly higher stroke rate in the CABG arm at 12 months. Unfortunately, this study did not separate periprocedural from later stroke. No information regarding stroke prophylaxis during the CABG procedure was available. In addition, dual antiplatelet therapy was prescribed only in the PCI arm, whereas most CABG patients were treated with aspirin alone. Likewise, only 74.5% of patients in the CABG group received statin therapy, whereas in the PCI group, statin therapy was instituted in 86.7% of patients ($p < 0.001$). An accompanying editorial emphasized the importance of separating the diagnostic catheterization from the decision-making process in complex cases to ensure a time for a multidisciplinary heart team to review the data (36).

Sirolimus-eluting stent versus minimally invasive direct coronary artery bypass grafting (MIDCAB) for proximal left anterior descending artery (LAD) stenosis. A total of 130 patients were assigned randomly to either Sirolimus-eluting stent (n = 65) or MIDCAB (n = 65) with off-pump left internal mammary artery to LAD bypass surgery after a left anterolateral minithoracotomy (37). The incidence of major adverse cardiac events (MACE), such as cardiac death, myocardial infarction, and the need for target vessel revascularization, were compared at 1 year. Angiographic follow-up within 12 months was performed in almost 90% of patients in each group. The MACE rate was similar between the 2 approaches and occurred in 5 patients (7.7%) in each group (sirolimus-eluting stent: 1 myocardial infarction, 4 repeat revascularization procedures; MIDCAB: 5 myocardial infarctions). The improvement in clinical symptoms and freedom from angina was similar between the 2 groups.

COMMENT. Previous studies comparing bare-metal stenting and MIDCAB showed similar outcomes with respect to death and myocardial infarction, whereas the rate of repeat revascularization was significantly higher in the PCI group. This current trial showed that the need for repeat revascularization is not eliminated with drug-eluting stents in patients with isolated proximal LAD disease. The sirolimus-eluting stent, however, was not inferior to MIDCAB surgery at 12 months with respect to freedom from MACE and was performed with a lower rate of periprocedural complications (the rate of myocardial infarction in the MIDCAB group in this study was higher compared with that of previous reports). Although additional studies with longer-term follow-up are necessary, PCI with a drug-eluting stent seems to be a safe revascularization strategy for proximal LAD disease.

Comparison of off- and on-pump CABG: Veterans Affairs Randomized On/Off Bypass trial. A total of 2,203 patients were assigned randomly for coronary revascularization either to on- (n = 1,099) or off-pump (n = 1,104) CABG procedures (38). The primary short-term composite end point consisted of death or complications (reoperation, need for mechanical support, cardiac arrest, stroke, or renal failure) within 30 days after the operation. The primary 1-year composite end point was defined as death, repeat revascularization procedure, and nonfatal myocardial infarction. Secondary end points included completeness of revascularization, 1-year angiographic graft patency, neuropsychologic outcomes, and the use of major resources. The 30-day composite outcome was not significantly different between on- (5.6%) and off-pump (7%) CABG procedures ($p = 0.19$). The rate of composite outcome at 1 year was higher in the off-pump group compared with the on-pump group (9.9% vs. 7.4%, $p = 0.04$). The average number of grafts per patient was marginally higher in the on-pump group compared with the off-pump group (3.0 ± 1.0 vs. 2.9 ± 0.9, $p = 0.002$). The percentage of patients with fewer grafts performed than originally planned was significantly higher in the off-pump group compared with the on-pump group (17.8% vs. 11%, $p < 0.001$). The overall graft patency on angiography was lower in the off-pump group than in the on-pump group (82.6% vs. 87.8%, $p < 0.01$) (Table 3). The authors concluded that the off-pump surgical approach was

Table 3 Results of Post-Operative Coronary Angiography

Variable	Off-Pump Group	On-Pump Group	Absolute Percentage-Point Difference, Off-Pump vs. On-Pump (95% CI)	Relative Risk of Occlusion, Off-Pump vs. On-Pump (95% CI)	p Value
At least 1 occluded graft, n of patients/total n (%)	250/685 (36.5)	197/686 (28.7)	7.8 (2.8 to 12.7)	1.27 (1.09 to 1.48)	0.002
Graft patency, no. of grafts/total n (%)					
Overall	1,650/1,998 (82.6)	1,839/2,095 (87.8)	−5.2 (−7.4 to −3.0)	0.94 (0.92 to 0.97)	<0.001
Saphenous vein	967/1,262 (76.6)	1,122/1,339 (83.8)	−7.2 (−10.2 to −4.1)	0.91 (0.88 to 0.95)	<0.001
Left internal thoracic to left anterior descending artery, FitzGibbon grade A	550/618 (89.0)	592/635 (93.2)	−4.2 (−7.4 to −1.1)	0.95 (0.92 to 0.99)	0.01

A FitzGibbon grade A indicates excellent graft patency. Modified and reprinted with permission from Shroyer et al. (38).
CI = confidence interval.

associated with worse composite outcomes and graft patency. The neuropsychological outcomes and use of major resources were similar between on- and off-pump approaches.

COMMENT. The Veterans Affairs Randomized On/Off Bypass trial was a large randomized, controlled study comparing on- and off-pump CABG procedures. This study showed similar early mortality and morbidities between the 2 groups and confirmed the findings of previous randomized studies that have included smaller numbers of patients. A major finding of this trial was that the mean number of grafts per patient was significantly lower in the off-pump group compared with the on-pump group. Similarly, the angiographic graft patency rate was lower in the off-pump group. These 2 findings are in opposition with data from experienced centers in off-pump procedures, which have reported similar numbers of grafts and long-term patency between the 2 approaches. One potential explanation for these findings may be the limited experience of certain Veterans Affairs Randomized On/Off Bypass surgeons in off-pump procedures (experience with only 20 off-pump cases was required to qualify as a trial surgeon). Another limitation of this study is that participating patients were almost exclusively male without severe comorbidity. Additional studies are necessary to investigate the potential benefit of off-pump CABG in female patients and sicker patients. Similar neurocognitive outcomes between the 2 procedures is now well documented and further confirmed by this study. An accompanying editorial points out that off-pump techniques likely will remain reserved for selected patients and skilled surgeon advocates (39).

Comparison of endoscopic versus open vein graft harvesting in CABG. The outcomes of 3,000 patients undergoing CABG with either endoscopic vein harvesting (n = 1,753) or harvesting under direct vision (n = 1,247) was reviewed in a secondary analysis of the PREVENT IV (Project of Ex-Vivo Vein Graft Engineering via Transfection IV) trial (40). The technique of vein harvesting was not randomized and was left to surgeon discretion; baseline demographic characteristics were similar between the 2 groups. Late clinical outcomes, including death, myocardial infarction, and repeat revascularization, were reported. Angiographic studies at 12 to 18 months showed a higher rate of vein graft failure in the endoscopic group compared with the open group (46.7% vs. 38%, $p < 0.001$). At 3 years, endoscopic vein harvesting was associated with higher rates of death, myocardial infarction, or repeat revascularization (20.2% vs. 17.4%, $p = 0.04$) (Fig. 10).

COMMENT. Endoscopic vein harvesting in patients undergoing CABG has become popular during the last decade because of fewer wound complications, better cosmesis, decreased post-operative pain, and overall improved patient satisfaction. Previous studies comparing endoscopic versus open vein harvesting mainly have focused on early outcomes and have reported similar results between these 2 techniques. This secondary analysis from the PREVENT IV trial showed that endoscopic vein graft harvesting may be associated independently with vein graft failure at 1 year and major adverse clinical events at 3 years. Confounding factors that were not accounted for in this study include on- versus off-pump techniques, the quality of the vein grafts, the quality of the distal targets, or the experience of endoscopic

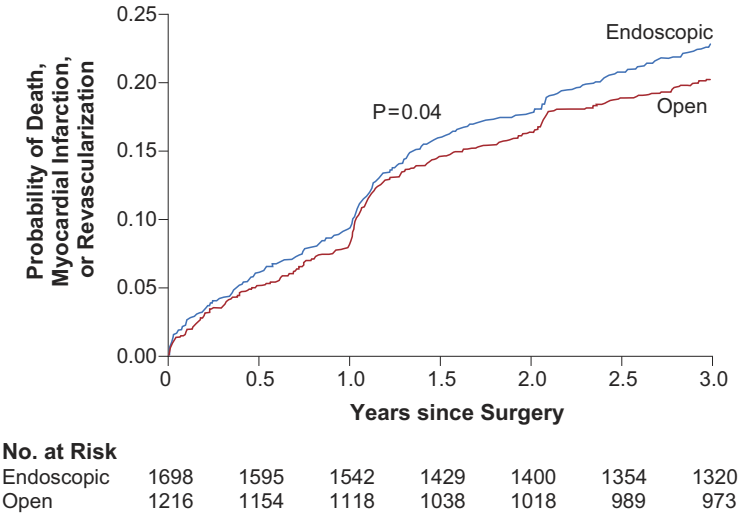

Figure 10 Event-Free Survival After Coronary Artery Bypass Grafting According to Technique Used to Harvest Conduit

Adjusted Kaplan-Meier event-free survival in patients after coronary artery bypass grafting who underwent saphenous vein conduit harvesting via either an endoscopic or open approach. Modified and reprinted with permission from Lopes et al. (40).

harvesters. The overall vein graft failure rate was higher in the PREVENT IV trial compared with most previous reports.

The authors emphasize the need for mechanistic studies to identify the potential injury mechanisms associated with endoscopic vein harvesting (40). One such study comparing endoscopic and open vein harvesting found that the endoscopic technique was associated with saphenous vein endothelial damage, reduced nitric oxide production, and decreased calcium mobilization in response to bradykinin (41). These alterations in saphenous vein structure and function associated with endoscopic harvesting potentially may explain the worse outcomes reported in this secondary analysis of the PREVENT IV trial. A randomized trial is warranted to clarify further the potential short-term benefits versus long-term risks of endoscopic vein harvesting in CABG patients.

Intraoperative completion angiography after CABG and hybrid revascularization. The outcomes of 366 consecutive patients who underwent CABG with (n = 112) or without (n = 254) concomitant PCI during the same procedure (hybrid) in a single institution were reviewed. All patients underwent a completion angiography before chest closure. The hybrid CABG and PCI procedure was planned in 67 patients (60%), whereas 45 patients (40%) underwent an unplanned hybrid procedure based on intraoperative findings. The indications for planned hybrid procedures were: minimizing surgical risk (n = 32), poor conduits (n = 3), ungraftable vessels (n = 29), or stenting of the left subclavian artery (n = 3). The indications for unplanned hybrid were: graft defects (n = 43), poor conduits (n = 1), or ungraftable vessels (n = 2).

Clinical outcomes were similar between the 2 groups. The operative mortality was 2.6% (n = 3) in the hybrid group versus 1.5% (n = 4) in the conventional CABG group (p = 0.33). The administration of higher dose clopidogrel in the hybrid group was not associated with increased post-operative chest tube output. In addition, the rate of reoperation for bleeding was not different between the groups. One patient in the hybrid group had acute post-operative in-stent thrombosis that was associated with a fatal outcome. Operating room time and costs were higher in the hybrid group. Completion angiography showed 12% of grafts (97 of 796) to have important defects. These defects were as follows: conduit defects (n = 54, 6.8%), anastomotic defects (n = 30, 3.7%), and target vessel errors (n = 13, 1.6%). Defects were repaired with minor adjustment of the graft (n = 22, 3%), with unplanned PCI (n = 48, 6%), or with surgical revision (n = 27, 3.4%).

COMMENT. An increasing number of surgeons use technologies such as the transit time flow meter to assess intraoperative graft patency, particularly in patients undergoing off-pump CABG procedures. This study suggests that intraoperative completion angiography may be a valuable tool that can provide significant information with major clinical implications. The Vanderbilt group pioneered the concept of hybrid operating strategies in which a CABG or valve operation is completed by a concomitant PCI procedure. Although this 1-stop hybrid concept may be useful in a select group of patients, additional studies are necessary to determine further its role in daily clinical practice.

Pre-operative clopidogrel administration in patients with acute coronary syndromes undergoing CABG. The outcome of 1,520 patients with non–ST-segment elevation acute coronary syndromes requiring CABG was reviewed in a subgroup analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial (42). Outcomes in clopidogrel-exposed patients (n = 773, 51%) were compared with those of patients not exposed to this agent before surgery (n = 747, 49%). Baseline patient characteristics were similar between the 2 groups. Of the 773 patients exposed to clopidogrel, 73 received it before hospitalization, 157 received it before hospitalization and in the hospital, and 543 patients received clopidogrel in the hospital only. Of these 773 patients, 524 (67.8%) patients underwent CABG fewer than 5 days after the last clopidogrel dose and 249 (32.2%) patients underwent CABG more than 5 days after the last clopidogrel dose. Clopidogrel-exposed patients had fewer composite ischemic events defined as death, myocardial infarction, or unplanned revascularization at 30 days (12.7% vs. 17.3%, p = 0.01). In multivariate analysis, pre-operative clopidogrel administration was an independent predictor of reduced 30-day composite ischemia (odds ratio: 0.67, p = 0.001). The rates of non–CABG-related major bleeding (3.4% vs. 3.2%, p = 0.87), blood transfusion (38.4% vs. 38.4%, p = 1), and reoperation for bleeding (1.3% vs. 1.3%, p = 0.94) were similar in those patients who did and did not receive clopidogrel before CABG. In the cohort of clopidogrel-exposed patients, the rate of ischemia and bleeding was slightly higher in the group of patients who underwent CABG within 5 days after the discontinuation of the treatment.

COMMENT. This subgroup analysis from the ACUITY trial showed that upstream administration of clopidogrel in patients with non–ST-segment elevation acute coronary syndromes requiring urgent cardiac catheterization and referred for CABG is beneficial and is associated with a significant reduction in post-operative ischemic events. Moreover, this clinical benefit was not compromised by an increased rate of major bleeding or blood transfusion in the clopidogrel-exposed group of patients. The latter events occurred, however, at a modestly higher rate in the group of patients who underwent CABG fewer than 5 days after the discontinuation of this medication. An accompanying editorial emphasized that these findings support the current ACC/AHA guidelines for upstream clopidogrel administration in all non–ST-segment elevation acute coronary syndromes patients and ACC/AHA and Society of Tho-

racic Surgeons guidelines for a 5-day waiting period after the termination of clopidogrel before proceeding with CABG unless there is an urgent or emergent indication for the procedure (43). Additional studies are required to understand better this protective effect of pre-operative clopidogrel administration.

Effect of prior PCI on the outcome of CABG. The outcomes of 29,928 patients undergoing primary CABG between 2000 and 2005 in 8 cardiac centers were reviewed (44). Patients were divided into 3 groups: no previous PCI (n = 25,752, 86%), 1 previous PCI (n = 3,078, 10.3%), and 2 or more previous PCIs (n = 1,098, 3.7%). Risk-adjusted multivariate analysis showed that 2 or more previous PCIs were associated with a significant increase in hospital mortality (OR: 2.0, p = 0.0005) and major adverse cardiac events (OR: 1.5, p = 0.01).

In another retrospective study, the outcomes of 1,758 diabetic patients who underwent primary CABG between 2001 and 2006 were analyzed (no previous PCI: n = 1,537, 87.5%; previous PCI: n = 221, 12.5%) (45). After risk adjustment, patients with a history of PCI had an increased operative mortality (OR: 4.0), rate of perioperative MACE (OR: 2.7), and decreased age-adjusted survival at 2 years (93.4% vs. 87.4%, p < 0.01).

COMMENT. There has long been a feeling among surgeons that previous PCI may complicate CABG procedures. The results of these studies are in agreement with some earlier smaller studies. Multiple attempts at reintervention with PCI, particularly in diabetic patients, probably should be avoided in patients who are reasonable CABG candidates. Although there are several possible hypotheses to explain the observations, such as the existence of a more progressive form of the atherosclerotic disease in patients with prior PCI undergoing CABG, post-stenting inflammatory response with endothelial dysfunction, or distal implantation of a bypass graft forced by the presence of multiple proximal stents, the mechanism(s) by which prior PCI compromises the outcomes of CABG remain undetermined. An invited editorial questioned if these results should dampen enthusiasm toward hybrid approaches and reinforced that patients requiring complex revascularization may be better served by primary CABG (46).

Surgery for Advanced Heart Failure

Left ventricular assist devices (LVADs): extended support. As a follow-up study to the 2007 report that presented 6-month outcomes of patients bridged to cardiac transplantation with the HeartMate II (Thoratec Corporation, Pleasanton, California) continuous LVAD (47), the HeartMate II investigators report on the 18-month follow-up of the 281 patients enlisted in this multicenter, prospective study (48). All patients received a HeartMate II LVAD, which is a second-generation axial flow pump, as part of a Food and Drug Administration pre-approval study. The investigators found that at 18 months, 56% of patients had been transplanted and 21% remained alive and on device support, whereas 20% had died while on LVAD support (in the remainder, the heart had recovered and the LVAD had been explanted). Considering only patients who remained on LVAD support (censoring patients at transplantation or explantation), the actuarial patient survival at 18 months was 72%, whereas the freedom from major device malfunction was 92%.

COMMENT. Because two-thirds of the patients underwent transplantation or died within 9 months of device implantation, a minority of patients actually required extended support. In this subgroup, excellent device durability associated with reasonable morbidity and good survival was demonstrated.

LVADs: continuous-flow versus pulsatile-flow devices. Another study published by the HeartMate II investigators provides better insight into longer-term efficacy of continuous flow LVADs. In this study started in 2005 (49), the investigators evaluated the role of the HeartMate II LVAD as definitive or "destination" therapy for advanced heart failure in patients ineligible for transplantation. They randomized 200 patients to receive the then approved pulsatile-flow device for destination therapy (HeartMate XVE, Thoratec Corporation, Pleasanton, California) (n = 66) or the investigational continuous-flow HeartMate II device (n = 134). The primary composite end point of survival without disabling stroke and reoperation for device malfunction at 2 years was reached by 46% of patients in the continuous-flow LVAD group compared with 11% in the pulsatile-flow group (p < 0.001). The actuarial 2-year patient survival was substantially better in those who received continuous flow LVADs (58% vs. 24% in the pulsatile group, p = 0.008) (Fig. 11).

COMMENT. This rare randomized trial of 2 surgical therapies demonstrates the superiority of the second-generation continuous-flow LVADs over pulsatile-flow LVADs, with substantial reduction in risk of death and device failure at 2 years. Secondary analysis also showed a reduction in risk of device failure, device infection, right ventricular failure, and renal failure—all major limitations to extended use of mechanical circulatory support. An accompanying editorial highlighted some limitations of the study, including absence of information on screened but not enrolled patients and the possibility of bias in patient care and study reporting because of lack of blinding (50). Also, this cohort represented a low- to medium-risk cohort of patients requiring destination therapy that may not be typical of those seen in routine practice. Nevertheless, this study has opened a new era in the use of continuous flow LVADs as permanent destination therapy for patients with advanced heart failure; the results of this study have rendered obsolete the use of pulsatile LVADs for long-term support. The particularly poor results in the pulsatile group raise questions as to

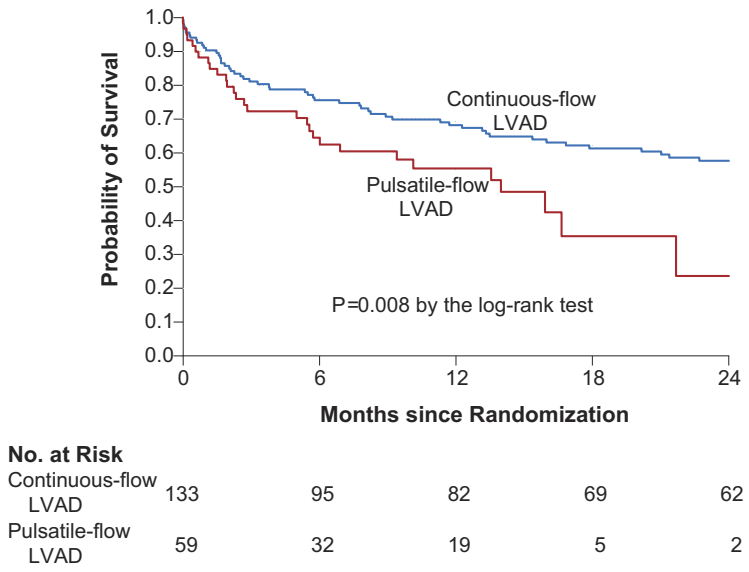

Figure 11 **Survival After LVAD Implantation According to Device Type**

Kaplan-Meier survival of patients who received either a continuous- or pulsatile-flow left ventricular assist device (LVAD). Pulsatile-flow LVADs were replaced with continuous-flow LVADs in 31% of patients. Modified and reprinted with permission from Slaughter et al. (49).

whether randomization is a necessary approach to evaluate new ventricular assist device technology.

LVADs: use in less sick heart failure patients. LVADs generally have been reserved as a bridge to cardiac transplantation and for use as destination therapy in patients with stage D heart failure not suitable for transplantation. LVADs are used as cardiac replacement therapy in this context. A novel approach is to use LVADs to provide partial ventricular support in severely symptomatic heart failure patients who do not yet meet hemodynamic criteria for complete cardiac replacement therapy. In a prospective feasibility study, the Synergy Pocket Micro-pump device (CircuLite, Inc., Saddle Brook, New Jersey) was implanted in 17 patients with advanced heart failure, of whom 15 required repeated hospitalizations for decompensations but were not receiving intravenous inotropic therapy (51). The Synergy device is a new-generation micropump, approximately the size of an AA battery, that is implanted minimally invasively in the right infraclavicular fossa with an outflow connected to the subclavian artery and an inflow placed into the left atrium through a small right thoracotomy without cardiopulmonary bypass. The pump generates an output of only 2.5 to 3 l/min (as opposed to conventional LVADs, which can provide up to 10 l flow/min), but the theory is that this would supplement, rather than replace, the native heart output and that the cumulative output would be sufficient to reverse symptoms. The authors indeed found an increase in the mean cardiac output from 3.8 l/min before surgery to 6.3 l/min ($p < 0.0001$) daily after surgery, and in 9 patients who had cardiac catheterization (4 to 19 weeks after implantation), there remained evidence of hemodynamic improvement (Fig. 12). Of the 17 patients, there were 3 deaths, 1 reoperation to place a biventricular assist device, and 8 pump exchanges for pump thrombus.

COMMENT. This study demonstrates that in less sick heart failure patients, it is possible to improve hemodynamics by placing a micropump that flows only 2.5 to 3 l/min. Although hemodynamics were enhanced, the adverse event rate was high, and patients were not supported long enough to evaluate for sustained improvement in quality of life with this approach (median duration of support was 81 days; all but 4 of the 13 survivors on device had undergone transplantation by the time of the report). Pump thrombosis is a concern, but authors report that modifications to device design and higher-target international normalized ratio have reduced its frequency. Future study in New York Heart Association functional class III patients not requiring cardiac transplantation should allow longer periods of support to determine the clinical outcomes of partial ventricular support compared with medical therapy.

Surgical ventricular reconstruction: the STICH (Surgical Treatment for Ischemic Heart Failure) trial. The STICH investigators published the results of their hypothesis 2 arm, which included 1,000 patients with left ventricular ejection fraction <35% and anterior wall left ventricular dysfunction randomized to CABG alone or CABG with surgical ventricular reconstruction (SVR) (52). No difference was found between the 2 groups in terms of the primary outcome (death from any cause or hospitalization for cardiac cause) or mortality from any cause at any point during follow-up of

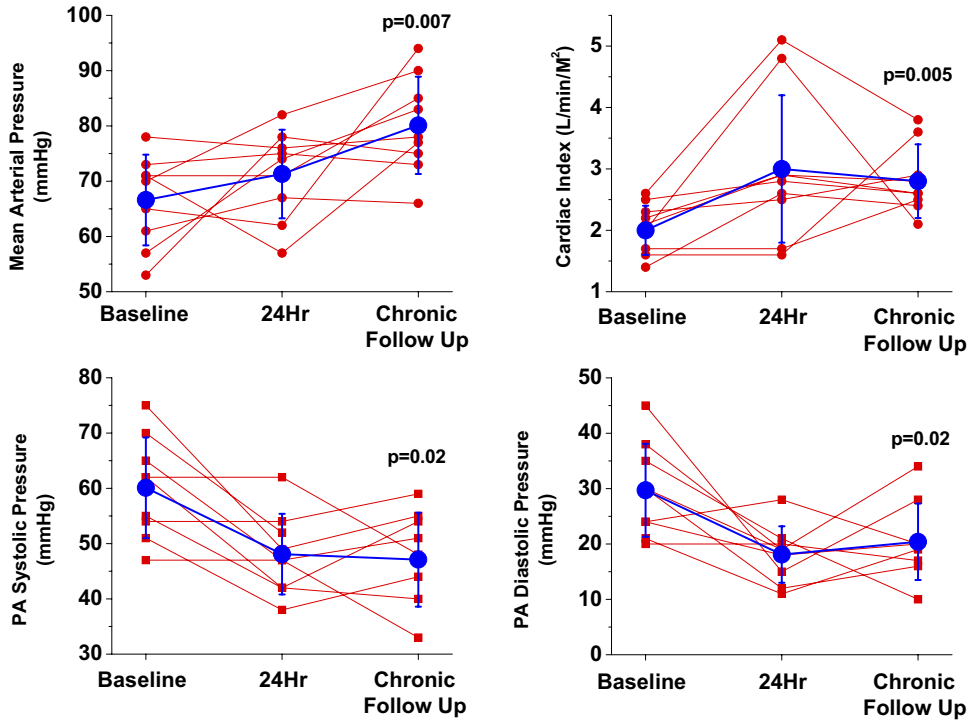

Figure 12 **Hemodynamic Changes Associated With Partial Ventricular Support Device**

Pulmonary artery (PA) systolic pressure and cardiac index before insertion of a micro left ventricular support device, compared with 24 h (Hr) and 10 ± 6 weeks after insertion. **Red lines** represent individual patients. **Blue lines** are the mean values. Modified and reprinted with permission from Meyns et al. (51).

up to 5 years (Fig. 13). An economic analysis of the same cohort published separately did not show any difference in health-related quality of life using both disease-specific and generic tools and also found that the hospital costs were $14,500 more in the SVR group (53).

COMMENT. This study, which suggested that SVR does not lead to improvement in survival or reduction in hospitalizations or symptoms compared with CABG alone, has had a divided response among surgeons and cardiologists. An accompanying editorial concluded that the routine use of SVR cannot be justified (54), whereas another editorial suggested the lack of efficacy of SVR may be the result of the disturbance of the 3-dimensional architecture of the ventricle with deleterious effect on both systolic and diastolic function (55). Some experts in the surgical community, however, are very critical of the trial design and question the robustness of the study conclusions. Most of these limitations are detailed in a commentary by Buckberg and Athanasuleas (56). The strongest criticism arises from the quality of the surgical procedures performed in the study. The STICH investigators, based on prior data, stipulated that SVR should achieve at least a 30% reduction in ventricular volume, but actual measurement of volumes in the 161 SVR patients who underwent post-operative imaging showed that the mean volume reduction was 19%, implying that many patients did not have adequate ventricular repair. Furthermore, although SVR is reserved for patients with prior myocardial infarction with regional scar, 13% of patients in the trial had no prior myocardial infarction. Imaging data requirements on enrollment and follow-up also were not met for most patients, making it impossible to define with certainty the pre- and post-operative ventricular geometry and volumes, such that patients who did not need SVR (because they had ventricular volumes below the required threshold for SVR) may have been included in the trial. Two-thirds of patients did not undergo a volume measurement after surgery. The reality, therefore, is that the patients included in the trial may not necessarily reflect the true target for SVR therapy, and a substantial proportion of patients in the SVR group did not receive the trial-defined intervention (ventricular repair to achieve at least 30% volume reduction). Buckberg and Athanasuleas argue that "the wrong operation, using the wrong volume measurements, was done on the wrong patients resulting in the wrong conclusions" and called for retraction of the study.

Surgical ventricular reconstruction: superior results with mitral annuloplasty versus replacement. Long-term outcomes were reported for 76 patients with ischemic cardiomyopathy who underwent SVR with concurrent mitral valve

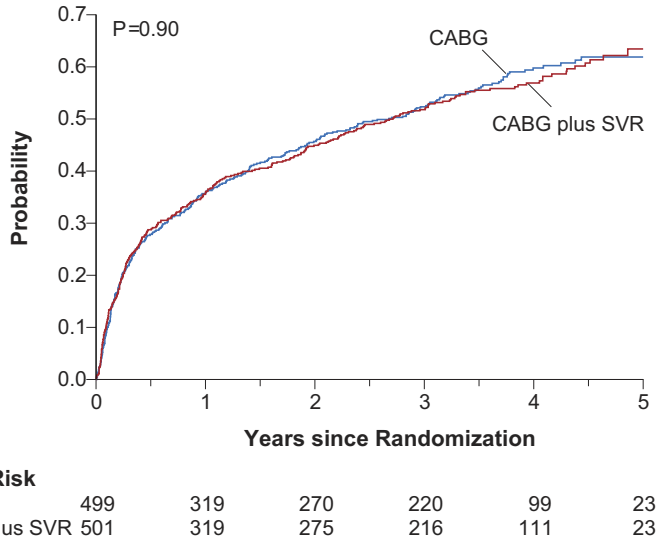

Figure 13 **Probability of Adverse Event After CABG Compared With CABG and SVR in Patients With Left Ventricular Ejection Fraction <35%**

Kaplan-Meier estimates of the probability of major adverse cardiac events or death. Modified and reprinted with permission from Jones et al. (52). CABG = coronary artery bypass grafting; SVR = surgical ventricular reconstruction.

repair (n = 61) or replacement (n = 15) for coexisting mitral valve regurgitation (57). Of note (see STICH trial in the previous text), a mean ventricular volume reduction of 40% was achieved in these patients. The 5-year survival of the cohort was 68% and was superior in the subgroup undergoing valve repair (Fig. 14).

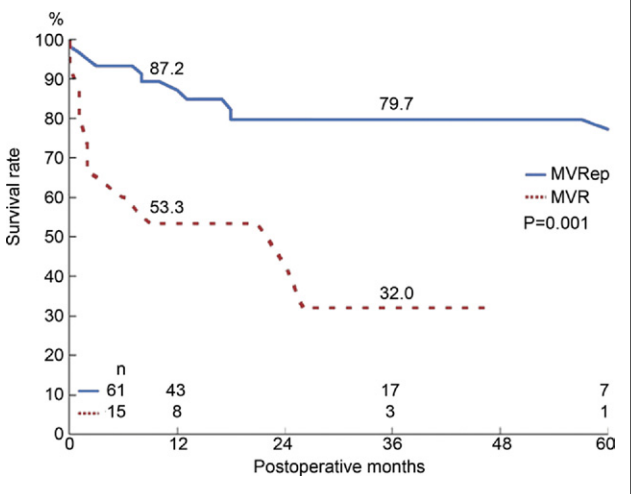

Figure 14 **Survival in Patients With End-Stage Ischemic Cardiomyopathy and Mitral Regurgitation Treated by MVRep or MVR**

Five-year survival following mitral valve repair (MVRep) or mitral valve replacement (MVR) for mitral regurgitation in patients undergoing surgical ventricular restoration for end-stage ischemic cardiomyopathy. Modified and reprinted with permission from Suma et al. (57).

COMMENT. Excellent long-term outcomes are achievable with SVR, where 40% volume reduction was achieved. With mitral insufficiency, valve annuloplasty has substantially better results than replacement. This may reflect a higher risk associated with replacement, bias introduced by more advanced ventricular disease in the replacement cohort, or both.

Heart transplantation: results with alternate heart listing. Alternate heart lists increasingly are prevalent. In this strategy, high-risk patients who ordinarily are not candidates for transplantation, such as elderly patients, are listed for transplantation, but undergo transplantation only with marginal donor organs, which usually would not meet criteria for use for transplantation. This study explored the degree to which matching marginal donors with high-risk recipients compromises post-transplant outcomes by analyzing 13,024 transplants performed in the United States between 1999 and 2005 (58). They found that the results of transplantation were substantially worse when high-risk recipients were paired with marginal donors (5-year survival: 51.4%) compared with standard donors receiving standard hearts (5-year survival, 75%) (Fig. 15).

COMMENT. Expectedly worse survival is seen when marginal donor hearts are used on alternate list recipients. However, a median survival of 5 years is a substantial improvement on a median survival of 6 to 12 months that many of these patients otherwise would face without transplantation. The higher 1-year mortality may lead to reluctance in centers offering alternate list transplantation be-

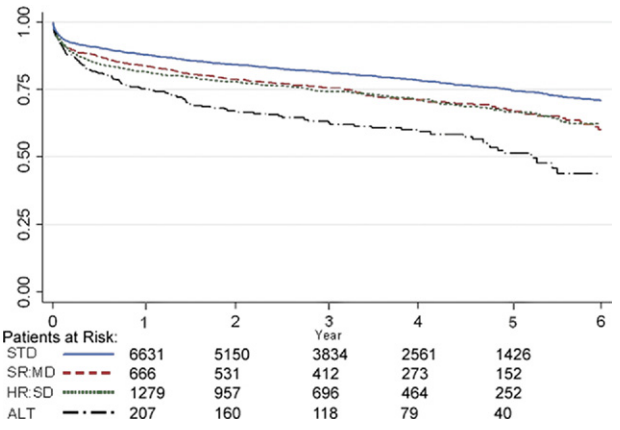

Figure 15 **Survival After Cardiac Transplantation**

ALT = alternate list transplant (high-risk recipient and marginal donor; **black line**); HR:SD = high-risk recipient and standard donor **(green line)**; SR:MD = standard recipient and marginal donor **(red line)**; STD = standard recipient and standard donor **(blue line)**. Modified and reprinted with permission from Russo et al. (58).

cause this statistic often is used as an index of surgical quality, unless outcomes in this subgroup are considered separately in the future.

Miscellaneous

Atrial fibrillation (AF). Continuous heart rhythm surveillance was carried out for 2 years after surgical atrial ablation in 45 cardiac surgery patients with a pre-operative history of AF using an implantable cardiac rhythm monitor (Reveal XT 9529, Medtronic, Inc., Minneapolis, Minnesota) (59). Two patients underwent lone atrial ablation, and 43 underwent ablation concomitantly with other cardiac surgical procedures: high-intensity ultrasound was used in 33 patients, and cryothermy was used in 12 patients. All patients had pulmonary vein isolation, and in patients with persistent AF, an additional ablation line to the left atrial isthmus was created. Complete sinus rhythm with no AF burden was achieved in 43% of patients, whereas approximately one-third of patients were in AF on average for between 1 to 8 h/day, and 31% had an average daily burden of AF of more than 8 h. In comparison, the sensitivity of conventional interval Holter monitoring performed at 3-month intervals was just 60%, only identifying recurrence of AF when it was present for more than 17 ± 8 h/day. All except 4 patients were asymptomatic.

COMMENT. "Snapshot" assessment of cardiac rhythm using interval electrocardiograms, 24-h Holter recording, or symptom-driven monitoring overestimates the success rates of conversion from AF. Implantable wireless devices programmed automatically to store data quantifying AF burden provide continuous rhythm surveillance and seem to document significantly more episodes of recurrent AF, particularly in a minority of patients who have late recurrent AF.

Cardiopulmonary bypass (CPB), vasoplegia, and microvascular dysfunction. The association between hypotension immediately after institution of CPB and the incidence of post-bypass vasoplegia was analyzed retrospectively in 2,823 patients undergoing adult cardiac surgery (60). The incidence of vasoplegia after starting CPB (defined as a requirement for near maximal vasopressor support) was 20% and was closely correlated with a decline in mean arterial pressure of >20% from baseline lasting for more than 2 min within the first 5 min of CPB. Three main hemodynamic patterns were observed after starting bypass: an early, dramatic fall in mean arterial pressure responsive to vasoconstrictors; a more gradual decline that persisted despite pharmacological intervention; and an intermediate group with gradual decline that responded well to pharmacotherapy. Vasoplegia after starting CPB was found to be a strong, independent predictor of prolonged hospital stay and operative mortality (OR: 2.62, 95% CI: 2.05 to 3.36, $p < 0.001$). Independent risk factors for vasoplegia identified in this study included pre-operative beta-blocker and angiotensin-converting enzyme-inhibitor use, valve surgery, reoperation, increasing EuroSCORE, pre-bypass aprotinin, and hypotension.

In another study, the deleterious effects of bypass on tissue perfusion were examined at the microvascular level by quantifying sublingual capillary blood flow in patients during on- and off-pump cardiac surgery, and the results were compared with those of patients undergoing general anesthesia for noncardiac surgery (61). In all 3 patient groups, microvascular dysfunction resulted in marked heterogeneity of perfusion after induction, which was significantly worse in patients undergoing cardiac surgery compared with major noncardiac surgery, persisted for more than 24 h after surgery, and was only slighted exacerbated by cardiopulmonary bypass compared with off-pump cardiac surgery.

COMMENT. Cardiopulmonary bypass likely causes vasoplegia through 3 interrelated mechanisms (61). First, patients may exhibit a hypersensitivity response causing a persistent proinflammatory state: in these patients, the resultant hypotension may be addressed partially by use of vasoconstrictors. Second, bypass may result in widespread endothelial dysfunction in some patients, causing hypotension that is refractory to vasopressors. Third, the institution of bypass may contribute to mechanical dysfunction of the vascular system resulting from loss of pulsatile flow and hemodilution: the resultant hypotension may be compensated for to some extent by use of vasopressors and resolves on cessation of bypass.

Most centers already routinely withhold angiotensin converting enzyme-inhibitors for 24 h before cardiac surgery to reduce the risk of post-bypass vasoplegia, and there may be a case for assessing the risks and benefits of a similar strategy

for pre-operative beta-blockade. These studies illustrate the major impact of endothelial dysfunction on outcomes after cardiac surgery and the multifactorial cause and pathogenesis of post-operative malperfusion states. The finding that significant endothelial dysfunction and tissue malperfusion is associated with off-pump cardiac surgery, with a relatively small increment resulting from cardiopulmonary bypass, may partly explain the similarity in morbidity and mortality observed between the 2 techniques in randomized studies.

Pre-operative anemia and bleeding. The role of pre-operative anemia (defined as hemoglobin <12 g/dl in men and <11 g/dl in women) as a predictor of early and late mortality after CABG was analyzed by comparing outcomes in 10,025 patients who underwent CABG at a single center between 1998 and 2007 with a matched population cohort (62). The incidence of pre-operative anemia was 16% (n = 1,608): lower hemoglobin was associated with diabetes mellitus, chronic obstructive airways disease, peripheral vascular disease, low left ventricular ejection fraction, renal dysfunction, prior cardiac surgery, emergency surgery, intraoperative transfusion, and need for intra-aortic balloon support. Patients with normal hemoglobin levels were more likely to be younger men. Multivariate logistic regression analysis showed that low hemoglobin was an independent risk factor for late mortality (hazard ratio: 1.61, 95% CI: 1.4 to 1.8, $p < 0.0001$), both as a continuous variable and as a dichotomous variable (anemia), along with age and re-exploration for any reason. Post-operative survival of patients with normal pre-operative hemoglobin levels was found to be better than that of an age-matched population.

Recombinant factor VIIa is approved by the Food and Drug Administration for the treatment of perioperative bleeding in patients with coagulopathies such as hemophilia, although concern about thrombotic complications limits the liberal use of the drug in the setting of cardiac surgery. In a multicenter trial, 179 patients who met a prespecified bleeding rate after cardiac surgery were randomized to placebo, low-dose factor VIIa (40 μg/kg), or high-dose factor VIIa (80 μg/kg) (63). Significantly fewer patients in the 2 groups receiving factor VIIa underwent reoperation or required allogeneic transfusions, and the increase observed in a composite end point of adverse events (including death, myocardial infarction, stroke, and graft occlusion) between the placebo and treatment groups did not reach statistical significance. The study was underpowered to determine the safety of factor VIIa.

COMMENT. Although the negative impact of perioperative transfusion on mortality after cardiac surgery is well recognized, the association between pre-operative anemia and survival after cardiac surgery is less well characterized. The current findings may reflect chronic or occult morbidity not accounted for in the risk model, as well as the reduced ability of anemic patients to compensate for perioperative blood loss and consequent tissue hypoxia. It is not certain whether the anemia is itself a cause of excess mortality (and therefore potentially reversible by pre-operative hematinics or blood transfusions) or a surrogate for severity of disease or comorbidity. A larger randomized study powered to detect a difference in major adverse clinical events would be required to demonstrate the safety of factor VIIa in the management of post-operative bleeding.

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