Long-Term Outcomes of the Symmetry Vein Graft Anastomosis Device
A Matched Case-Control Analysis

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Background—The Symmetry Bypass Connector (St. Jude Medical) was developed to rapidly anastomose saphenous vein grafts to the aorta during coronary bypass surgery (CABG) without cross-clamping. Previous uncontrolled studies of this device observed vein graft closures at six months, possibly attributable to neointimal hyperplasia.

Methods and Results—To assess the long-term clinical outcomes of the Symmetry device, we performed a retrospective matched case–control analysis of patients who underwent CABG at Duke Medical Center between January 1, 2002 and December 31, 2003. In 121 patients, at least one proximal anastomosis used a Symmetry device. Traditional suture methods were used in 178 control patients, matched by age group, gender, use of cardiopulmonary bypass, and Hannan perioperative risk score. One-year outcomes were compared using the log-rank test and Cox proportional hazards regression models. Major adverse events were more frequent among cases compared with controls. By unadjusted Kaplan–Meier analysis for the composite end point of death, nonfatal myocardial infarction, repeat cardiac catheterization, or repeat CABG, there was a trend towards increased events in the Symmetry device group (P=0.053). No significant differences were detected for stroke, all cause mortality, or the combined end point of death or nonfatal myocardial infarction.

Conclusions—Use of the Symmetry Bypass Connector was associated with increased risk for major adverse events at 1 year, suggestive of early graft closure. The potential reductions in operative stroke risk (from the elimination of aortic cross-clamping) must be weighed against the potential risk for later adverse events. These findings encourage close follow-up of patients who received this device. (Circulation. 2006;114[suppl I]:I-425–I-429.)

Key Words: anastomosis ■ atherosclerosis ■ bypass ■ surgery ■ veins

More than 500,000 coronary artery bypass grafting (CABG) procedures are performed in the United States each year. Perioperative stroke is a devastating complication of CABG surgery, affecting between 1.6% and 6% of patients.1,2 This risk increases with age. Patients aged 75 years or older had postoperative neurologic events more than twice as frequently as patients aged 65 to 74, and 9-times more frequently than patients younger than 65.3 Cross-clamping and manipulation of the aorta contribute to the risk of perioperative stroke. CABG without cardiopulmonary bypass (off-pump CABG) is associated with lower stroke risk and mortality compared with the conventional cardiopulmonary bypass approach (on-pump CABG).4,5 The increasing number of off-pump CABG procedures inspired rapid methods for constructing proximal and distal graft anastomoses using sutureless vascular connectors.6 The Symmetry Bypass connector (St. Jude Medical) was a nitinol, star-shaped device designed to rapidly anastomose saphenous vein grafts to the aorta during CABG without use of side-biting or cross-clamping of the aorta. The Symmetry device was approved by the United States Food and Drug Administration in May 2001, and was the first such device marketed in the United States. More than 30,000 connector devices have since been implanted worldwide.

After the introduction of the Symmetry device, several case series reported early vein graft closures.7–12 Several of these were uncontrolled reports,7–9 whereas others used historical controls.10–12 It is often difficult to control for many factors that contribute to graft failure, including operator experience, vein quality, distal anastomotic technique, diabetes mellitus, and other patient characteristics. Consequently, we conducted a retrospective study using matched contemporaneous controls to assess the long-term outcome of patients receiving the St. Jude Medical symmetry aortic connector system for proximal vein graft anastomoses in coronary artery bypass grafting.
Methods

A retrospective matched case control analysis was performed using the Duke Cardiovascular Disease Databank. The null hypothesis was that no difference in graft patency existed between patients who received the Symmetry aortic connector system and patients who had proximal vein graft anastomoses created by traditional suturing methods. The study protocol was approved by the Duke Institutional Review Board before initiation of the study. The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Patient Population

The organization of the Duke computerized cardiovascular database and follow-up methods have been previously described in detail. Patients were included in the case group if they had undergone CABG surgery with placement of at least one St. Jude Medical symmetry aortic connector at Duke Medical Center between the dates of January 1, 2002 and December 31, 2003. Control patients who had undergone CABG by traditional hand suturing methods (saphenous vein grafts with or without internal mammary arteries) at Duke Medical Center between the dates of January 1, 2002 and December 31, 2003 were randomly identified from the Cardiovascular DataBank and matched according to age, gender, on-/off-pump and the Hannan model of perioperative risk (Table 1). Patients were excluded if they received only an internal mammary graft, or if they underwent valve replacement at the time of CABG.

Statistical Analysis

Baseline characteristics were compiled for the 2 patient groups and compared using the Wilcoxon rank-sum test for continuous variables and the Pearson χ2 test for discrete variables. Time to the composite end point of major adverse cardiac events (death, nonfatal myocardial infarction, repeat cardiac catheterization, repeat CABG) was generated using Kaplan-Meier methodology and compared using the log-rank test. Secondary end points included the composite of death and nonfatal myocardial infarction, stroke, and all-cause mortality. Unadjusted Cox proportional hazards regression models estimated the unadjusted effect of each baseline characteristic on the primary end point. A multivariable Cox proportional hazards regression model estimated the hazard ratios for the Symmetry aortic connector adjusted for baseline patient characteristics. The regression model parameter estimates were validated internally using bootstrap estimation of the entire patient sample. Analyses were performed using SAS statistical software (SAS Institute, Cary, NC).

Results

In the Duke Cardiovascular Database, 121 patients received at least 1 proximal Symmetry aortic connector during the study period. There were 178 matched contemporaneous control patients who underwent CABG with vein grafts attached via traditional hand suturing techniques. There was no difference between the proportion of cases and controls.
with regards to diabetes, smoking, number of diseased coronary arteries, cerebrovascular disease, or renal failure (Table 2). Overall, 66% of the population was male, and 31% had diabetes. Eighty-six percent of the CABG procedures were performed off-pump.

Figure 1 displays the percent number of bypass grafts used for the cases and controls. In the control group, there was a higher percentage of patients who received 2 or 3 bypass grafts when compared with the case group. More patients in the case group received 4 bypass grafts. These differences achieved statistical significance by Wilcoxon 2-sample test ($P=0.0002$). In the case group, $>80\%$ of patients received 1 or 2 Symmetry devices during coronary artery bypass surgery (Figure 2). Additionally, 85.12\% of case patients received an internal mammary artery graft during bypass surgery, compared with 91.57\% of control patients ($P=0.08$).

At 30 days, 5 case patients and 3 control patients underwent repeat cardiac catheterization ($P=0.198$). Two case patients had repeat CABG at 30 days, but no control patients had repeat CABG in this time period ($P=0.085$).

Within 1 year of initial CABG, 7 patients in each group died (5.8\% cases versus 3.9\% controls), and 11 patients in each group had death or myocardial infarction (9.1\% cases versus 6.2\% controls). At 1 year, 26 patients (21.5\%) in the Symmetry connector group had sustained death, myocardial infarction, repeat catheterization, or repeat CABG, compared with 26 controls (13.5\%).

There was a trend toward an increased event rate in the cases when compared with the controls for the composite end point of death, nonfatal myocardial infarction, repeat cardiac catheterization, or repeat CABG ($P=0.053$), as seen in the Kaplan Meier estimates presented in Figure 3. No significant differences were seen for all-cause mortality ($P=0.44$), stroke ($P=0.19$), or the combined end point of death or nonfatal myocardial infarction ($P=0.33$).

Unadjusted hazard ratios for the Symmetry aortic connector were calculated for multiple end points and are shown in Table 3. The Symmetry aortic connector was not a significant independent predictor of any of the end points. Additionally, a multivariable Cox proportional hazards model for the

![Figure 2. Percent number of St. Jude connector devices used.](image-url)

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composite end point of death, nonfatal myocardial infarction, repeat cardiac catheterization, or repeat CABG was developed to assess the impact of the Symmetry aortic connector in an adjusted setting. Significant predictors of the composite end point included hyperlipidemia and peripheral vascular disease. When the Symmetry aortic connector variable was added to the model, it was not significant ($P=0.19$).

To assess the reliability of estimates from the Duke patient series, and to assess the possible influence of outliers on the model results, a bootstrap internal validation was performed. As expected, use of the St. Jude connector did not meet criteria ($\alpha=0.05$) for entry into bootstrap-resampled models for death or the composite end point of death or myocardial infarction. For the composite end point of death, myocardial infarction, repeat CABG, or repeat catheterization, use of the St. Jude connector met entry criteria in 66 of 200 bootstrapped samples, compared with 159 for hyperlipidemia, 115 for peripheral vascular disease, 84 for female gender, and 74 for diabetes.

### Discussion

The analysis of the results suggest that use of the Symmetry aortic connector system is associated with increased major adverse cardiac events at 1 year, suggestive of early graft closure. Although the determinants of postoperative vein graft patency are variable (including conduit quality, distal vessel run-off, progression of native vessel disease, and surgical technique), these results suggest that graft closure events occur with the Symmetry device more frequently than might be expected otherwise. The precise contribution of the device to early graft failure is unknown, but suspected to be intimal hyperplasia. These findings encourage close clinical follow-up of patients who have received this device. This may include more aggressive noninvasive testing postoperatively.

Despite initial promising reports, several other case series have also reported early vein graft closures with the Symmetry device. Cavendish et al reported a series of 121 CABG patients with Symmetry implants, of which 5 presented with an acute coronary syndrome 2 to 5 months after operation. In each patient all saphenous vein grafts were totally occluded or compromised with ostial stenoses. After percutaneous intervention of the occluded saphenous vein grafts, 2 patients presented again with near-occlusive ostial restenosis. Intravascular ultrasound showed severe neointimal hyperplasia only at the interface between the stent and the connector device.

Carrel et al reviewed 107 patients who had received at least 1 Symmetry connector device. At 6 months, 14 patients had routine angiography. Of the 24 vein grafts studied, 11 were anastomosed with a running suture and 13 with the proximal connector system. Five of the 13 patients had a 30% to 90% stenosis within the connector, and there was one complete occlusion. One hand-sewn anastomosis had occluded, but the remainder did not show any significant stenosis.

Reuthebuch et al reported a series of 61 patients who received a total of 77 Symmetry connectors. Eight patients with 12 implanted connectors developed ischemic symptoms within 8 months. Angiography revealed significant stenosis or occlusion within all connectors in these patients. Schoettle reported a retrospective review of two patient groups undergoing CABG. In group A, 323 patients underwent surgery from October 2000 through September 2001, with hand-sewn proximal anastomoses. In group B, 305 patients underwent surgery from October 2001 through September 2002, with proximal anastomoses constructed with the Symmetry device. Both groups received aspirin postoperatively and received clopidogrel daily for 2 months. Forty patients in group A underwent repeat cardiac catheterization, and of 71 venous grafts studied, 61 were widely patent. Forty-five patients in group B underwent repeat catheterization, and of 88 venous grafts studied, 39 were totally occluded. Seventeen had ≥90% stenosis, and 15 had ≥50% stenosis. These stenoses uniformly occurred at the connector site. Among the patients studied, this represented an 80% rate of occlusion or stenosis with the proximal venous graft connectors.

Dewey et al reported a series of 166 patients who underwent off-pump bypass grafting using at least 1 St. Jude symmetry aortic connector between May 2001 and December 2001. A control group of 159 patients was identified from a cohort of patients having beating heart surgery with 1 or more sutured proximal vein graft anastomosis in the preceding year. Patients with connectors showed an accelerated number of major adverse events beginning ~180 days from the time of surgery and stabilizing at ~300 days. Logistic regression analysis identified the presence of diabetes as a significant preoperative risk factor predisposing patients to earlier onset of adverse events ($P=0.03$).

Nishizaki et al reviewed 17 patients who received the aortic Symmetry connector with 19 patients who received saphenous vein grafts by traditional suture techniques. They...
observed that 4 of a total of 30 aortic symmetry connectors were occluded because of proximal vein graft kinking. They concluded that when using the aortic Symmetry connector, the proximal vein take-off is an important consideration to prevent early vein graft occlusion.

Although the St. Jude Symmetry aortic connector device was voluntarily withdrawn from the market in December 2004, these results have important implications for future aorto-saphenous vein graft connectors and their development. Before marketing a new medical device, manufacturers must provide the Food and Drug Administration (FDA) with “reasonable assurance” that the device is both safe and effective. There are 2 mechanisms for providing this assurance: the premarket notification (510(k)) process, and the premarket approval (PMA) process.

The FDA’s PMA process requires examination of detailed safety and effectiveness information for each device. The average PMA submission requires 1200 hours of rigorous review. The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (21 US C. § 360e et seq.) allows manufacturers to seek approval for a new device by showing that the new device is substantially equivalent to a device introduced to the market before May 28, 1976, when the amendments took effect. This 510(k) mechanism merely establishes whether a pre-1976 device and a post-1976 device are equivalent, regardless of how unsafe or ineffective the grandfathered device happens to be. The FDA completes the average 510(k) review within 20 hours. Not surprisingly, the PMA process represents a much more significant financial barrier to the market ($111 000 to $828 000 per device) than the 510(k) process ($50 to $2000 per device).18

The Symmetry device was approved through a 510(k) mechanism, intended to demonstrate similarity with a predicate device, the US Surgical AutoSuture VCS. In retrospect, the devices fundamentally differ in that the Symmetry connector is an intravascular device, whereas the AutoSuture VCS is an extravascular device. In its review of 510(k) premarket notications for aortic connector devices, the FDA required limited clinical studies, supported by extensive preclinical data. The clinical studies were designed to substantiate equivalence to historical data for conduit patency, using suture anastomosis as the gold standard control. The FDA accepted a relatively short follow-up period (6 to 9 months) to focus on the immediate adequacy of the anastomosis, rather than other factors contributing to graft failure. A 2004 meeting of the Circulatory System Devices Panel evaluated design parameters for future trials of anastomotic devices. The legacy of the Symmetry device will likely be more rigorous clinical evaluation of future connectors, with a continuing emphasis on long-term graft patency. Although more rigorous trial designs will increase research costs and lengthen development timelines, they will ultimately yield better clinical outcomes for patients receiving approved anastomotic devices.

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Disclosures

None.

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