A Device for Proximal Anastomosis of Autologous Coronary Vein Grafts

Report from the Meeting of the Circulatory System Devices Panel of the Food and Drug Administration Center for Devices and Radiologic Health

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The Food and Drug Administration (FDA) Circulatory System Devices Advisory Panel was asked to make recommendations on the PAS-Port Proximal Anastomosis System (Cardica, Inc), a device intended to create an end-to-side anastomosis between the aorta and autologous vein graft during coronary artery bypass graft surgery. Advisory panels make nonbinding recommendations to the FDA.

Classically, coronary artery bypass graft surgery (CABG) has been performed with hypothermic cardiac arrest, aortic cross-clamping, and extracorporeal circulatory support to provide the “clean” field demanded by the challenge of suturing small vessels. These factors may contribute to the neurocognitive decline, strokes, and other adverse patient outcomes often observed after CABG. “Off-pump” and “beating-heart” bypass procedures have been developed in an effort to minimize the untoward effects of circulatory support and to permit faster postoperative recovery.

Facilitation of vascular anastomoses may permit faster and less invasive CABG. Anastomotic devices may not only simplify the procedural mechanics for the operator but also potentially obviate the need for many of the factors that contribute to poor patient outcomes, including extracorporeal circulatory support, induced hypothermic cardiac arrest, and aortic cross-clamping. Ultimately, these devices may simplify beating-heart surgery and reduce complications, although this remains to be proved.

In 2001, the Symmetry Bypass Aortic Connector (St Jude Medical, Inc) became the first automated vascular anastomotic device cleared for marketing in the United States by the Food and Drug Administration (FDA). After device clearance and marketing, and after tens of thousands of implantations in patients worldwide, a number of apparently device-related adverse events were reported to FDA. More than 180 injuries and 20 deaths were observed, apparently as a result of occlusion, thrombus, or stenosis at the connector site, aortic dissection associated with device deployment, graft kinking, and postoperative device detachment resulting in hemorrhagic shock and/or death. Ultimately, the Symmetry device was voluntarily withdrawn from the market in 2004.

It is on this backdrop that the FDA Circulatory System Devices Panel was asked to consider the PAS-Port Proximal Anastomosis system (Figure). The device consists of the implant (9 barbed tines that penetrate the vein to secure it to the aorta) and the delivery system. Importantly, several differences distinguish the PAS-Port from the Symmetry device. In contrast to the Symmetry device, the PAS-Port does not expose the endothelium of the implanted graft to metal, avoids contact with conduit intimal lining, has a lower profile, substantially reduces exposure of blood and subintimal tissue to metal, has an ≈150% larger orifice, and creates an aortotomy and deploys the implant in one action (by turning a knob at the end of the tool).

Ultimately, any vascular anastomosis device must be evaluated on clinical grounds. The Circulatory System Device Panel, at a March 2004 meeting on the topic of Vascular Anastomosis Devices for CABG, recommended quantitative angiography at a minimum of 6 months of follow-up as a surrogate for anastomotic device performance. Meta-analysis of studies conducted between 1979 and 2001 suggests hand-sewn vein graft patency rates at 12 months in excess of 80%. The FDA determined that for these anastomotic devices, clinical data should demonstrate a lower 95% confidence interval for 6-month vein graft patency >80%.

Many factors affect graft patency, including the technical quality of the anastomosis, graft quality and trauma during harvest, target vessel selection, effective orifice size, graft kinking, progression of underlying atherosclerotic disease, concurrently administered medications, and the presence of comorbidities (ie, diabetes, dyslipidemia, etc). As CABG is increasingly performed in patients who fail or are not good candidates for percutaneous revascularization, vein patency rates may be expected to decrease, as observed in the more recent PREVENT IV and PRAGUE trials, which had 12-month venous graft patency rates of ≈50% to 70%.
Study Design
Data from two separate European, multicenter, prospective, nonrandomized clinical trials involving 109 patients total were submitted to support device clearance. Neither study used a Data Safety and Monitoring Board or a Clinical Events Committee. The first study enrolled 55 patients during a 9-month period beginning in June 2002. When patency rates were deemed inadequate, a second data set was developed. This latter set was drawn from a prospective study of a non-FDA–cleared distal anastomosis system. A retrospective analysis was performed on 54 patients who, on the basis of surgeon preference, also received a PAS-Port device for a proximal anastomosis. Proximal and distal devices were not used on the same graft, although device use was potentially subject to significant selection bias. The use of two unapproved devices in individual patients during the same procedure significantly complicates interpretation of the results. Some panel members thought that the data sets were too different and too flawed to be combined, whereas others thought that the data were potentially poolable, albeit not adequately analyzed in the submitted format.

Effectiveness
The primary study end point was graft patency (<50% stenosis at angiography) at 6 months. The observed patency rate for the subset of 77 patients who underwent 6-month angiography was 91% (81 of 89 grafts), although more than 20% of the patients did not undergo 6-month angiography and had patency imputed from other modalities, including MRI, CT, and stress ECG. In 3 patients, the absence of symptoms was considered evidence of patency. The majority of the panel agreed that patency should be angiographically determined and that the accuracy of other modalities, particularly in imaging the orifice of a vein graft at the site of a metal anastomosis device, is uncertain. No data were presented to demonstrate the reliability of other imaging modalities compared with angiography under these circumstances. Physiological or clinical end points (ischemia evaluation, symptoms) in lieu of anatomic end points (angiography) are insufficient.

Although the panel recognized that complete angiographic follow-up is unrealistic, the lost-to-follow-up problem would be less concerning in a randomized trial or a larger cohort. In this case, the relatively small number of patients and the poor study design magnify the problem. Because of the large amount of missing angiographic data, the generalizability of the observed patency rate to a larger population (potentially tens or hundreds of thousands of patients) was questioned.

Safety
Several device failures were noted during the studies. Failure to successfully deploy the device and complete an anastomosis occurred in 12 patients (11%), although each patient was successfully converted to a hand-sewn anastomosis and had good clinical results. Implant dislodgement, leakage around the implant, and damage to the device were also rarely observed. The device and delivery tool were slightly modified between the first and second study to address some of these events.

Other observations, such as hypokinesia or ischemia in the vascular territory of the device but with angiographically confirmed graft patency, are more difficult to interpret because of the potential for transient thromboemboli. Although some events are obviously device-related, the panel discussed the challenge of distinguishing device-related safety issues from procedure (CABG)-related safety issues, a classification that would be simplified by a randomized trial design.

Other Issues
The panel discussed some aspects of the device that may potentially affect both effectiveness and safety. Because anastomotic devices have many similarities to endovascular stenting, including blood and subintima exposure to bare metal, well-defined antithrombotic regimens would facilitate study interpretation. Two episodes of conduit thrombosis and distal anastomotic obstruction occurred and may have represented embolic events. A predefined antithrombotic regimen was not used, although virtually all patients received some antiplatelet or anticoagulant therapy (aspirin, warfarin, etc). Future studies should prespecify the antithrombotic regimen to permit systematic evaluation.

The Panel also discussed the applicability of “outside the United States” (OUS) data to support device clearance for the US market. The use of foreign data are permitted as long as
they meet US standards and are applicable to the US population. Although there is no absolute requirement for these OUS studies to be conducted under an FDA-issued Investigational Device Exemption, the applicability of the data to the US market and the likelihood that the clinical trial design and data will be acceptable to the FDA increases significantly if the device sponsor discusses these issues with the FDA before initiating a trial.

Conclusions
The panel concurred that vascular anastomotic devices have great potential and that the data regarding the PAS-Port Proximal Anastomosis System look promising. The majority, however, believed that more robust data were required, particularly because of thousands of potential device implants annually. Although well-conducted observational studies with additional patients may be satisfactory, a randomized, controlled study would be easiest to interpret and may ultimately prove “least burdensome.” Future studies should also consider collecting additional data on the factors cited as the rationale for the development of this technology, such as reduction in operative times and reduction in neurocognitive decline after CABG.

Disclaimer
Dr Maisel is the chairperson of the Circulatory System Devices Advisory Panel. The opinions expressed here are the personal views of the author and do not necessarily represent the policies, practices, positions, or opinions of the FDA.

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