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Development of a Prosthetic Coronary Artery Bypass Graft

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ABSTRACT

Background: The patient population undergoing repeat coronary revascularization is increasing, with estimates of approximately 15% of these patients in need of alternative conduits. Pre-existing conditions may limit the availability of suitable autogenous vessels for complete coronary revascularization. As an alternative, previous investigators have attempted to develop prosthetic conduits for coronary artery bypass grafting (CABG), but as yet without clinical success. To be of clinical benefit, a prosthetic graft would require demonstrated patency at least as good as a marginal quality autogenous vessel used in the same position, without unexpected adverse effects. The use of a prosthetic graft may also reduce surgical complications associated with conduit harvesting and thereby enhance the speed of patient recovery.

Methods: Our group has investigated the potential of a novel synthetic small diameter vascular graft (2.5- to 3.5-mm diameter), as an alternative conduit for CABG. The graft is designed with three distinct layers composed of Thoralon®, a proprietary polyetherurethaneurea with a silicone-based surface modifying additive. This biomaterial is the same material successfully used for the thromboresistant blood-contacting surfaces of an FDA approved and clinically successfull ventricular assist device.

Results: Aria™ grafts underwent extensive preclinical testing in sheep with results to over one year that demonstrate the graft's biocompatibility, biodurability, and ability to maintain patency in both peripheral access graft and coronary applications. Compassionate use human coronary implants have been performed in 27 patients in the coronary position in Canada and Europe. Although incomplete, the data demonstrate no device related serious injury and all surviving patients have remained symptom free.

Conclusions: A prosthetic coronary artery bypass graft has been developed and has undergone extensive pre-clinical testing and preliminary clinical use. Based upon the results, a prospective, randomized, controlled clinical study, the AEGIS/Canada (**A**lternativ**E** **G**raft **I**nvestigational **S**tudy) trial using the Aria™ graft in the coronary position in human patients is underway . Additionally, an IDE submission has been submitted to the FDA to expand the AEGIS clinical trial device to the United States.

INTRODUCTION

The patient population undergoing repeat coronary revascularization is increasing, with estimates of approximately 15% of these patients in need of alternative conduits [Canver 1995]. Recently the radial artery has been used more frequently for coronary bypass, and the gastroepiploic artery, inferior epigastric free artery graft and upper extremity vein conduits have also been used [Barner 1998, Eagle 1999]. However, pre-existing conditions such as severe diabetes, phlebitis, previous vein stripping, or previous vascular surgery, may limit the availability of suitable autogenous vessels for complete coronary revascularization. As an alternative, the development of prosthetic conduits for coronary artery bypass has been a long sought after goal. Grafts from biologic material have been proposed and tried, such as bovine heterografts [Mitchell 1993], cryopreserved allograft saphenous veins [Brockbank 1992], and autologous pericardium [Love 1998]. And although there have been some successes reported with ePTFE grafts of different designs [Emery 1996, McLarty 1998], there are still no clinically acceptable small diameter prosthetic grafts with internal diameters less than 5 mm.

To be of clinical benefit, a prosthetic graft would require demonstrated patency at least as good as a marginal quality autogenous vessel used in the same position, without unexpected adverse effects. The use of a prosthetic graft may also reduce surgical complications associated with conduit harvesting and thereby enhance the speed of

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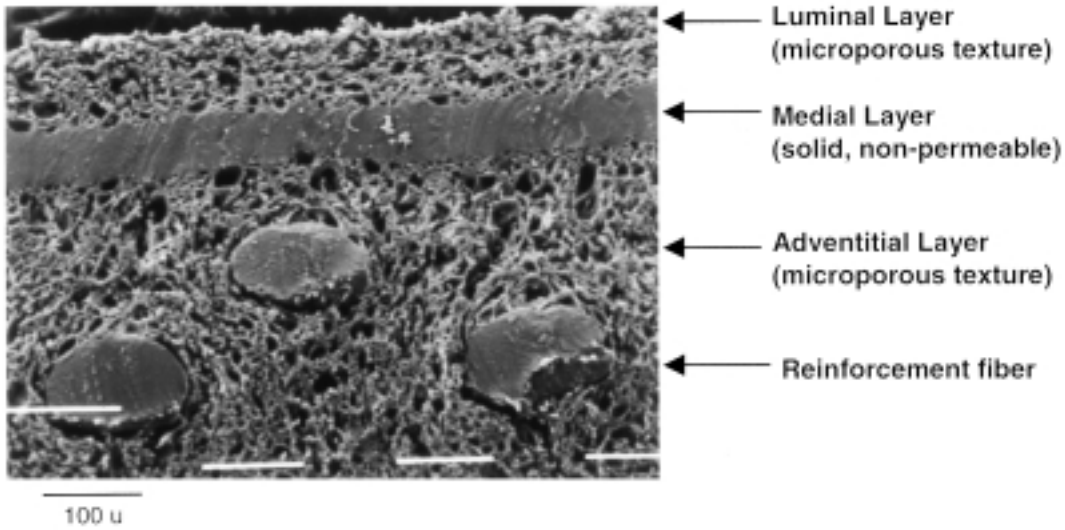

Figure 1. SEM of the Aria™ graft showing three-layer construction. The inner, or luminal, layer is a microporous textured Thoralon®, a polyetherurethaneurea layer designed for neointimal healing and thromboresistance. The middle, or medial, layer is made from solid Thoralon®, and is responsible for the strength of the graft and provides a non-permeable barrier and the self-sealing properties that prevent suture-hole bleeding. The outer, or adventitial layer, is a microporous textured layer designed to allow tissue incorporation. Reinforcement fibers are also embedded in the advential layer to reduce kinking.

patient recovery. If a conduit exists that does not have to harvested from the patient but is clinically equivalent in durability, the speed and complication profile of current and future CABG surgery will be vastly enhanced. Another promising quality of synthetic grafts is the potential of long term freedom from atherosclerotic degeneration. Endogenous saphenous vein typically undergoes accelerated atherosclerotic degeneration within 7 to 10 years after transfer to the coronary arterial circulation. The possibility of a synthetic graft includes the potential for an atherosclerotic free conduit with nearly infinite durability.

The purpose of this paper is to describe the development and pre-clinical results of a novel multilayer polyurethane coronary artery bypass graft developed from proven biocompatible and thromboresistant materials. Clinical trials are underway in Canada and are planned in the U.S.

MATERIALS AND METHODS

Our laboratory has extensive experience with research and delvelopment of thromboresistance surfaces in conjuction with development of a clinically approved ventricular assist device. The polymer which we have developed for the flexing blood contacting bladder and internal conduit surfaces is Thoralon®, which is a proprietary polyetherurethaneurea with a silicone-based surface modifying additive (SMA) designed for enhanced thromboresistance. A small diameter vascular graft (internal diameter 2.0 to 3.5 mm) called the Aria™ Coronary Artery Bypass Graft (CABG) has been developed from this material to mimic the trilaminar architecture of the natural arterial wall. The graft is an elastomeric tube designed with three distinct layers of Thoralon® (see Figure 1, ◉). The inner, or luminal, layer is a microporous textured layer, providing the blood surface with a SMA rich interface, with a structure designed for neoimtimal healing. The middle, or medial, layer is made from solid polymer, which is responsible for the strength of the graft and provides a non-permeable barrier that precludes cellular/fluid transport across the layer, and provides self sealing properties that prevent needle hole bleeding. The outer, or adventitial-like layer, is a microporous textured layer designed to allow tissue incorporation. To promote kink resistance, two reinforcement polyester monofilament fibers are embedded in the advential layer and wound circumferentially along the graft, with an unreinforced area at both ends for anastomosis. The Aria™ graft will be offered initially in 2.5, 3.0, and 3.5 mm internal diameters, with varying lengths ranging from 9 to 21 cm (reinforced region).

Aria™ grafts (3 mm) were implanted into adult sheep for aortic to left circumflex coronary artery bypass. Sheep were sedated with xylazine (0.3 mg/kg BW), followed by intravenous pentothal sodium. General anesthesia for thoracotomy and CABG implantation was maintained with inhalation anesthesia (isoflurane) with 100% oxygen gas as the carrier. Through the fourth intercostal space, the pericardial sac was incised and the proximal circumflex artery was identified. Standard techniques for establishing cardiopulmonary bypass were completed.

The Aria™ graft was prepared by beveling the coronary (distal) end of the non-reinforced portion of the graft at approximately 20–40 degrees through the non-reinforced region. The aortic end was cut at a 20–30 degree bevel. A 3.5- to 4.0-mm coronary arteriotomy was performed and the graft anastomosed to the coronary artery in an end-to-

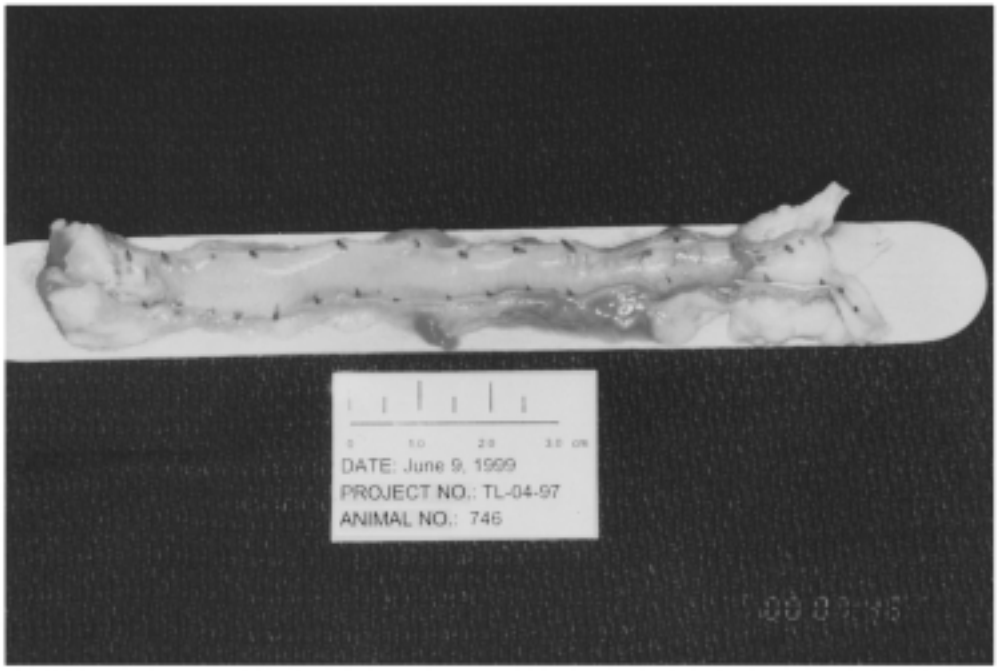

Figure 2. Photograph of Aria™ CABG after 426 days in vivo. The graft shows no thrombus formation and is clean of adherent tissue in the middle section. Proximal (left side) and distal (right side) anastomoses are widely patent with smooth, opaque neointima.

side fashion with a continuous pattern of 7-0 Prolene® suture. A 3.6-, 4.4-, or 5.6-mm Deknatel aortic punch was used to create a circular defect within the wall of the aorta. The proximal anastomosis was performed in a simple continuous pattern of 6-0 polypropylene. Cardiac/coronary circulation was resumed and both anastomosis sites were inspected and repaired as necessary. Blood flow through the graft was confirmed by surface Doppler of the distal graft/circumflex artery before, during, and after proximal ligation of the native vessel. The proximal left circumflex coronary artery was completely and singly ligated with a preplaced polypropylene suture approximately 5 mm proximal to the heel of the distal graft anastomoses. In most cases prior to completing the surgery, a 7x7-cm film of the same polymer was implanted subcutaneously for eventual biocompatibility and chemical characterization evaluations. Additional 2 year biocompatibility implants were performed in a separate series of experiments.

Animals were explanted at 30 days, 90 days, and at 12-14 months. Preliminary results of CABG explants at one year are described in this report, along with analysis of film samples after two years. Analysis of the remainder of the experiments are in progress.

RESULTS

Four sheep have survived for a minimum of one year. Gross observations and histologic evaluation of the Aria™ graft have been made on two explants after 368 and 426 days of use. One animal is still ongoing after more than 1.5 years. There were no any unanticipated reactions to the graft. The grafts were encased in a thin fibrous material characteristic of implant encapsulation. Figure 2 (◎) shows a photo of a graft removed at 426 days demonstrating the entire lumen of the graft including the aortic and coronary anastomoses. The lumen of the graft was fully patent and had a glassy, opaque coating throughout the middle of the lumen. In both cases analyzed, the middle of the graft is free of cellular deposition. The aortic and coronary anastomoses are covered circumferentially and about 1.5 cm lengthwise into the graft with a white, smooth, and continuous neointima. For each anastomosis, the size of the ostium was measured grossly. All measurement of aortic and coronary anastomoses ranged from 3 mm to 3.5 mm. No measurable signs of anastomotic stenosis or hyperplasia were identified.

The histology presented in Figure 3 (◎) shows a nicely conformed layer of neointima with few macrophages in a graft after 368 days in vivo. Furthermore, histology shows the tissue on the adventitia is firmly adhered with penetration into the pores of the foam. There are mild numbers of macrophages on the adventitial surface at one year. The solid medial layer of the graft shows no cellularity and appears to be unaffected throughout the study. The gaps in the solid black medial layer are the result of histological sectioning.

Evaluation of Thoralon® films after one and two years of subcutaneous implantation in sheep demonstrated no adverse biological or healing responses. Chemical analysis for molecular weight and polydispersity show that no bulk degradation of the film occurred through two years (see Table 1 (◎). Mechanical testing of the films also showed no decrease in the tensile strength or percentage elongation of the films explanted at two years.

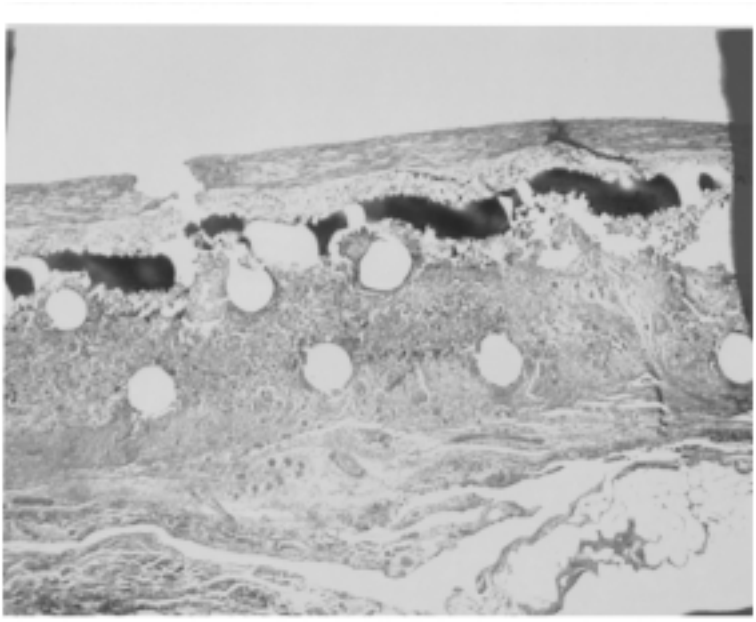

Figure 3. Histological (EVG stain) cross section of Aria™ CABG at the proximal anastomosis at 368 days in vivo. The three-layer structure is completely intact with tissue incorporation into the adventitial foam and a thin neointima formed on the luminal foam coat. The breaks in the middle layer and neointima are sectioning artifact.

There is also some limited clinical experience with a previous model of the Aria coronary artery bypass graft in 27 patients at two centers from 1993–1996. This graft had a single reinforcement winding and the graft was trimmed by the surgeon to length, and was successfully implanted for compassionate use to allow complete revascularization in patients who did not have adequate autologous vessels. Five patients died early from causes unrelated to the graft and 22 are alive and were asymptomatic at one year. Although there is limited information from these patients, the results support the safety of the design and materials with grafts implanted in humans for over six years without serious injury or death related to the device. The graft design was subsequently modified to provide grafts of pre-set lengths and double reinforcement. The effects of these improvements will allow trimming limited to beveling the non-reinforced ends for anastomosis to the vessel, and the added reinforcement promotes ease of handling and greater kink resistance. This design was used for animal studies presented in this study.

DISCUSSION

The Aria™ coronary artery bypass graft and its biomaterials have undergone extensive preclinical in vitro testing and in vivo implant evaluation. Although the biostability of certain polyurethanes has come into question, especially evident when placed under enormous strain (for example as high as 400% in certain experiments) [Zhao 1990], many of these experiments do not address the relevance of high strain to the intended use of the device. The results from our preclinical and clinical studies, under normal physiologic conditions establish the biocompatibility, durability, and safety of the graft and materials for the intended application. The preliminary results in sheep in the left circumflex arterial bypass model corroborate the biocompatibility of the graft, and demonstrate its thromboresistant properties with 3-mm grafts patent to well over one year after implant in the sheep model. One interesting observation is the apparent limited extent of anastomotic

Table 1. Molecular weight (number average M_n and weight average M_w), polydispersity, and physical properties of explanted Thoralon® polyurethane films show no bulk degradation after subcutaneous implant in sheep for up to two years (mean ± standard deviation).

	Implant Duration (years)			
Parameter	0.0 (baseline)	0.5	1.0	2.0
M_n (g/mole)	51,180 ± 9,940	54,210 ± 9,850	57,900 ± 9,630	62,400 ± 16,500
M_w (g/mole)	116,300 ± 6,640	136,700 ± 6,850	143,200 ± 4,340	148,700 ± 3,817
Polydispersity	2.32 ± 0.35	2.62 ± 0.62	2.52 ± 0.37	2.50 ± 0.56
Tensile strength (psi)	6132 ± 224	5998 ± 214	6109 ± 168	7304 ± 230
Elongation at break (%)	907 ± 27	789 ± 18	849 ± 26	862 ± 26
Stress at 300% strain (psi)	1331 ± 18	1555 ± 56	1535 ± 23	1677 ± 95

intimal hyperplasia. The explanted grafts were noted to have a pre-implant appearance in the body of the graft with smooth, thin neointima at the anastomoses extending a short distance toward the graft body. This is encouraging since anastomotic neointimal hyperplasia is a major cause of failure of vascular grafts. These results in sheep obviously should be interpreted cautiously, as they may be different in human subjects.

There also is extensive clinical experience with using the same biocompatible polymer in other cardiovascular applications. The same material has been successfully used for the thromboresistant blood-contacting surfaces in an FDA approved ventricular assist device blood pumping sac and cannulae [Farrar 1988], which is being used extensively for bridge to transplantation and for postcardiotomy support [Farrar 1997, Körfer 1999, McBride 1999], with clinical use as long as 515 days in humans.

An analogous graft, the Vectra™ Vascular Access Graft, has undergone extensive human clinical use, with approximately 5,000 implants worldwide. This is also a three layer polyetherurethaneurea graft available in 5- and 6-mm internal diameters that has been used for patients hemodialysis access. Clinical results from Australia [Allen 1996] and Japan [Amano 1996] have been published. Several patients from these series have been undergoing repeated punctures for dialysis access over a five year period while maintianing fully functioning grafts, which further provides evidence of the biodurability and safety of the biomaterials and graft design. The results from these studies also indicate that the graft has rapid self-sealing properties allowing early hemodialysis access. The Vectra™ graft is currently under investigational study in the United States and preliminary results have been presented [Glickman 1999] with similar findings as in Australia and Japan.

Based on the results from the animal studies as well as the low early and late mortality, lack of complications or reoperations, and high rate of asymptomatic patients at one year in the compassionate use of the device, plans for a prospective, randomized, controlled clinical study of the Aria™ CABG in the coronary position are in progress. There are two clinical trials, the AEGIS/Canada (**A**lternativ**E** **G**raft **I**nvestigational **S**tudy) trial which is underway, and an IDE submission has been made to begin the AEGIS/U.S. clinical trial for the Aria™ CABG device in the United States. Subjects will be identified that have marginal quality autologous vessels to be used for bypass. Marginal quality vessel are defined as vessels with variable segmental changes, evidence of clot or fibrosis, evidence of varicosities or rigid segments, or thin-walled friable tissue. Subjects will be randomized to Aria™ or marginal autologous vessels. The primary objective of these studies will be to evaluate whether the Aria™ CABG is at least statistically equivalent to marginal quality autologous vessels with respect to patency, with one year arteriograms, and/or complication rates.

Disclosure

David J. Farrar, PhD, is an employee of Thoratec Laboratories Corporation, the developer and manufacturer of the Aria™ vascular graft.

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