CLINICAL STUDY

A Prospective, Randomized Study of an Expanded Polytetrafluoroethylene Stent Graft versus Balloon Angioplasty for In-Stent Restenosis in Arteriovenous Grafts and Fistulae: Two-Year Results of the RESCUE Study

Abigail Falk, MD, Ivan D. Maya, MD, and Alexander S. Yevzlin, MD, for the RESCUE Investigators

ABSTRACT

Purpose: To assess the safety and efficacy of an expanded polytetrafluoroethylene stent graft versus balloon angioplasty for the treatment of in-stent restenosis in the venous outflow of hemodialysis access grafts and fistulae.

Materials and Methods: Two hundred seventy-five patients were randomized at 23 US sites to stent-graft placement or percutaneous transluminal angioplasty (PTA). Primary study endpoints were access circuit primary patency (ACPP) at 6 months and safety through 30 days; secondary endpoints were evaluated through 24 months.

Results: ACPP at 6 months was significantly higher in the stent-graft group (18.6%) versus the PTA group (4.5%; $P < .001$), and freedom from safety events (30 days) was comparable (stent graft, 96.9%; PTA, 96.4%; $P = .003$ for noninferiority). The separation in ACPP survival curves remained through 12 months (stent graft, 6.2%; PTA, 1.5%). Treatment area primary patency (TAPP) was superior for the stent-graft group (66.4%) versus the PTA group (12.3%) at 6 months ($P < .001$), with a survivorship difference in favor of stent-graft placement maintained through 24 months (stent graft, 15.6%; PTA, 2.2%). ACPP and TAPP for the stent-graft group were better than those for the PTA group when compared within central and peripheral vein subgroups ($P < .001$). In central veins, TAPP was 13.6% in the stent-graft group versus 4.3% in the PTA group at 24 months ($P < .001$).

Conclusions: Stent-graft use provided better ACPP and TAPP than PTA when treating in-stent restenosis in patients receiving dialysis with arteriovenous grafts and fistulae.

ABBREVIATIONS

ACPP = access circuit primary patency, AV = arteriovenous, CEC = clinical events committee, CI = confidence interval, ePTFE = expanded polytetrafluoroethylene, HR = hazard ratio, IPF = index of patency function, ITT = intent-to-treat, KDOQI = Kidney Disease Outcomes Quality Initiative, PTA = percutaneous transluminal angioplasty, TAPP = treatment area primary patency

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Vascular Access Guidelines (1) maintain that percutaneous balloon angioplasty (PTA) is the first-line treatment for stenosis in the access circuit. KDOQI guidelines suggest stent placement as a possible treatment option for acute

From Fresenius Vascular Care (A.F.), New York, New York; Nephrology Associates of Central Florida (I.D.M), Orlando, Florida; Department of Medicine (A.S.Y.), Division of Nephrology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin. Received September 11, 2015; final revision received June 8, 2016; accepted June 9, 2016. **Address correspondence to** A.F.; E-mail: abigail.falk@gmail.com

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elastic recoil after PTA, when a stenosis recurs within 3 months, in patients at increased risk with surgery, or following vessel rupture (1). In-stent restenosis accounts for as many as 73% of cases of restenosis in the hemodialysis access circuit resulting in reduced blood flow and loss of arteriovenous (AV) access patency in patients who require hemodialysis (2–4). The KDOQI guidelines do not provide recommendations for the treatment of in-stent restenosis, and, to date, we are aware of no clinical studies examining the best treatment options. Stent grafts may help reduce the recurrence of in-stent restenosis by providing a barrier to intimal hyperplasia. Preclinical work with a polytetrafluoroethylene-covered stent demonstrated that an inert barrier prevented mediators from leading to an accelerated proliferative response; the stent-graft group exhibited less neointimal hyperplasia ($P < .001$) and less luminal narrowing ($P < .01$) than the bare-metal stent group (5). Clinically, use of an expanded polytetrafluoroethylene (ePTFE) stent graft to treat venous anastomotic stenoses in patients with a prosthetic hemodialysis graft improved outcomes compared with balloon angioplasty alone; the 6-month primary patency rate at the site of treatment was 51% when using a stent graft, compared with 23% when treated with angioplasty ($P < .001$), whereas the primary patency rates of the overall access circuit were 38% versus 20%, respectively ($P = .008$) (6). The present study was designed to expand on these findings and evaluate the use of an ePTFE stent graft for the treatment of in-stent restenosis in the venous outflow circuit.

MATERIALS AND METHODS

Study Design and Oversight

The RESCUE study (Randomized Study of the Fluency Plus Endovascular Stent Graft in the Treatment of In-Stent Restenosis in the AV Access Venous Outflow Circuit), a prospective, multicenter, randomized, concurrently controlled clinical trial, was designed to assess stent-graft use following balloon predilation compared with PTA alone in the treatment of in-stent restenosis in the access circuit of patients receiving hemodialysis with an AV graft or native fistula. The protocol was approved by the Food and Drug Administration and institutional review board at each study site. The RESCUE study was sponsored by Bard Peripheral Vascular (Tempe, Arizona) and was conducted under an investigational device exemption in accordance with the guidelines of good clinical practice and requirements of the Health Insurance Portability and Accountability Act. Patients were informed of the risks and benefits of participation in the study, and each provided written informed consent before being enrolled. Data were collected by on-site investigators, and Novella Clinical (Morrisville, North Carolina), a contract research organization, performed the statistical analyses. The Yale Angiographic Core Laboratory (New Haven, Connecticut) analyzed the angiographic films, an independent clinical events committee (CEC) adjudicated the clinical data, and a data safety monitoring board provided safety oversight. The RESCUE trial was registered on *clinicaltrials.gov* (ID code NCT01257438) before the start of patient enrollment.

Inclusion and exclusion criteria are listed in **Table 1**. Patients eligible for inclusion in the trial had an in-stent stenosis (> 50%) in the venous outflow circuit of a mature fistula (per KDOQI guidelines) (1) or an AV access graft (implanted > 30 d). Exclusion criteria included a concomitant thrombosis at the treatment site, stenosis crossing the elbow, or a stenosis in the cannulation zone, cephalic arch, or superior vena cava.

Study Endpoints and Definitions

Primary objectives were to evaluate whether the use of a stent graft was more effective in treating in-stent restenosis than PTA alone and whether stent-graft use was at least as safe as PTA (ie, noninferior). The primary efficacy endpoint was access circuit primary patency (ACPP) at 6 months, defined as the interval from treatment until the next thrombosis or repeat intervention anywhere in the access circuit. The primary safety endpoint was freedom from any localized or systemic safety event through 30 days that affected the AV access circuit and resulted in surgery, hospitalization, or death (excluding stenosis or thrombosis, which was captured in the calculation of ACPP). Secondary efficacy measures included binary restenosis (≥ 50% diameter stenosis; calculated by the angiographic core laboratory from a 90-d angiogram), ACPP, treatment area primary patency (TAPP; ie, the interval from treatment until repeat intervention at the original treatment site), and index of patency function (IPF; ie, the time from the study procedure to access abandonment divided by the number of repeat interventions performed on the access circuit to maintain vascular access) through 24 months. Secondary safety measures included freedom from any safety event through 24 months (adjudicated by the CEC) and patient deaths, as reviewed by the CEC and data safety monitoring board.

Patient Demographics, Access Data, and Baseline Characteristics

A total of 275 patients were prospectively enrolled at 23 sites between February 2, 2010, and October 7, 2013. Patients were randomly assigned at a 1:1 ratio to the stent-graft group (n = 132) and PTA group (n = 143). Baseline patient demographics, preexisting medical conditions, and clinical indicators were typical for patients