CLINICAL STUDY

The Pivotal Multicenter Trial of Ultrasound-Guided Percutaneous Arteriovenous Fistula Creation for Hemodialysis Access

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ABSTRACT

Purpose: To evaluate safety and efficacy of arteriovenous fistulas (AVFs) created with a thermal resistance anastomosis device.

Materials and Methods: A prospective single-arm trial at 5 sites enrolled 107 patients. Patients underwent ultrasound (US)-guided anastomosis creation between the proximal radial artery and perforating vein with the Ellipsys Vascular Access System (Avenu Medical, Inc, San Juan Capistrano, California) followed by separate maturation procedures. Primary endpoints were brachial artery flow volume $\geq$ 500 mL/min and target vein diameter $\geq$ 4 mm in $>$ 49% of patients and absence of device-related complications at 90 days.

Results: AVFs with fused anastomoses were created in 95% (102/107) of patients. Maturation procedures included anastomotic balloon dilation in 72% (77/107), brachial vein embolization in 32% (34/107), cubital vein ligation in 31% (33/107), and surgical transposition in 26% (28/107) of patients. Primary flow and diameter endpoints were achieved in 86.0% (92/107) of patients, exceeding performance goal of 49% ($P < .0001$). No major adverse events were attributed to the device. Cumulative patency was 91.6%, 89.3%, and 86.7% at 90 days, 180 days, and 360 days. Target dialysis veins were cephalic, basilic, and brachial veins in 74% (73/99), 24% (24/99), and 2% (2/99) of patients. Two-needle dialysis was achieved in 88% (71/81) of patients on hemodialysis at a mean 114.3 days $\pm$ 66.2. Functional patency was 98.4%, 98.4%, and 92.3% at 90 days, 180 days, and 360 days.

Conclusions: The Ellipsys® Vascular Access System met primary safety and efficacy endpoint goals in the US pivotal trial.

ABBREVIATIONS

AVF = arteriovenous fistula, ITT = intent-to-treat, SAE = serious adverse event, TRAD = thermal resistance anastomosis device

Over the 50 years since its inception, the arteriovenous fistula (AVF) remains widely acknowledged as the most effective access for hemodialysis in terms of morbidity and mortality (1–3). Despite this success, timely placement and development of functional fistulas for hemodialysis remains a difficult logistical problem (4–6). Percutaneous anastomosis devices have been developed as an alternative to surgical fistula creation (7,8). The Ellipsys Vascular Access System (Avenu Medical, Inc, San Juan Capistrano, California) is a thermal resistance anastomosis device (TRAD) that was developed to create percutaneous proximal radial artery–to–perforating vein fistulas with a side-to-side anastomosis. The TRAD uses tissue fusion to form an immediate and permanent bond between the anastomosed artery and vein (9). The minimally invasive TRAD fistula leaves the vessels in situ but otherwise mimics the anatomy and develops the functionality of the proximal radial artery fistula described by Toledo-Pereyra et al in 1977 (10). The present study was a prospective ultrasound (US) multicenter trial to evaluate the safety and efficacy of the TRAD in creating percutaneous AVFs in the office-based laboratory.

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J.E.H. is paid consultant for and has stock in Avenu Medical, Inc (San Juan Capistrano, California) and has a patent issued for systems and methods for creating arteriovenous fistulas. W.C.J., R.I.C., U.W., M.E.S., and R.N. have stock in Avenu Medical Inc.

Appendix A, Tables E1–E3, Figure E1, and Video 1 are available online at *www.jvir.org*.

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MATERIALS AND METHODS

The US pivotal trial of the Ellipsys Vascular Access System was a prospective, multicenter, single-arm comparison of the TRAD with a 90-day performance goal based on meta-analysis of surgical results obtained from the literature (**Appendix A**, **Tables E1–E3**, **Fig E1** [available online at *www.jvir.org*]) (11–18). The study complied with Declaration of Helsinki guidelines for research in human subjects. The initial study was performed under the US Food and Drug Administration Investigational Device Exemption (ClinicalTrials.gov identifier: NCT02363972) and an independent investigational review board approval (Western Institutional Review Board, Puyallup, Washington). All data related to endpoints and adverse events were collected at the sites with final adjudication by the medical monitor. Three contract research organizations were involved in electronic data capture (eClinicalOS; IBM Corp, Armonk, New York), monitoring and auditing (Headlands Consulting, San Juan Capistrano, California), and data management and analysis (Willes Consulting Group, Encinitas, California).

The primary efficacy endpoint were brachial artery flow volume $\geq$ 500 mL/min and target vein diameter $\geq$ 4 mm in $>$ 49% of patients at 90 days. The primary safety endpoint was absence of serious device-related complications, such as vessel perforation, vessel dissection, and electrical shock during index procedure and embolization in a previously uninvolved arterial territory within 90 days. Procedures were performed by 8 physicians, including 1 interventional radiologist and 7 interventional nephrologists, following device training and 2 proctored cases per site. Additional follow-up through 12 months included assessments of fistula patency, function, and comprehensive review of adverse events.

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
Age $>$ 18 y and $<$ 80 y
Chronic kidney disease classification stage IV or V
Adequate quality vein based on preoperative assessment
Adjacent vein diameter $\geq$ 2.0 mm at target anastomosis site
Confirmed adequate outflow vein $\geq$ 2.0 mm
Within 1 cm of surface
Adequate quality radial artery based on preoperative assessment
Arterial lumen diameter $\geq$ 2.0 mm at target anastomosis site
Adequate proximity of proximal radial artery and adjacent vein $\leq$ 1.5 mm vessel edge to vessel edge
Negative Allen test for ulnar artery insufficiency
Exclusion criteria
Pregnant or currently breastfeeding
Diagnosed hypercoagulable state
Recent surgery or other major illness within 6 weeks
Acute or active infection
Use of immunosuppressive medication
History of organ transplantation
Upper extremity arterial stenosis ($>$ 20 mm/Hg systolic blood pressure difference between arms)

Patient Population

Patients requiring permanent access for hemodialysis were evaluated for study inclusion from February 2015 through June 2016 by 8 investigators at 5 sites. Of 261 patients evaluated, 117 met the inclusion and exclusion criteria (**Table 1**) and were enrolled in the study. All enrolled patients provided signed informed consent and had medical history and physical examination, laboratory studies, and Doppler ultrasound (US) examination data. Of 261 patients, the 144 who did not meet screening criteria included 73 (28%) who had unsuitable anatomy, 16 (6%) who declined to participate, 13 (5%) who were candidates for wrist fistula, 1 (0.4%) who failed Allen test, and 41 (16%) who were excluded for other medical reasons. Each of the 5 study sites completed 2 proctored percutaneous AVF procedures (n = 10 procedures) with 107 consecutive patients comprising the intent-to-treat (ITT) population (**Fig 1**). Access failure occurred in 4 patients, in whom wire access into the radial artery was not possible and the TRAD was not used, resulting in 103 patients treated with the TRAD. The demographics of the ITT population are summarized in **Table 2**. Mean patient age of 56.7 years (range, 30–80 y), mean body mass index was 31.2 kg/m^2 (range, 18.3–48.9 kg/m^2), and 73% of patients were men. All patients but 1 were treated with antiplatelet medications before the procedure. Suggested doses were 325 mg aspirin and 75 mg clopidogrel (Plavix; Bristol-Myers Squibb, New York, New York) orally, administered for up to 72 hours before the procedure and then daily through the 90-day follow-up period.

Procedure

The TRAD device and procedure are demonstrated in **Video 1** (available online at *www.jvir.org*). Briefly, the TRAD consists of a 6-F catheter and power controller that fuses and cuts an elliptical anastomosis between adjacent artery and vein using pressure and thermal resistance energy. Tissue fusion creates an immediate and permanent bond between artery and vein without the need for an indwelling implant. The tissue fused anastomosis tolerates balloon dilation, allowing increased blood flow without loss of anastomosis integrity. Balloon dilation and other maturation procedures were performed to adjust and direct the flow into an arm vein suitable for hemodialysis (7).

Procedures were performed in the office-based laboratory under locoregional anesthesia consisting of brachial plexus block (19) or local anesthesia with or without conscious sedation based on operator and patient preference. Initial venous access was retrograde through the cubital vein or brachial vein using a standard micropuncture needle and wire (Cook Medical, Bloomington, Indiana). The access needle was advanced intravenously under US guidance to the point of contact with the radial artery and then advanced

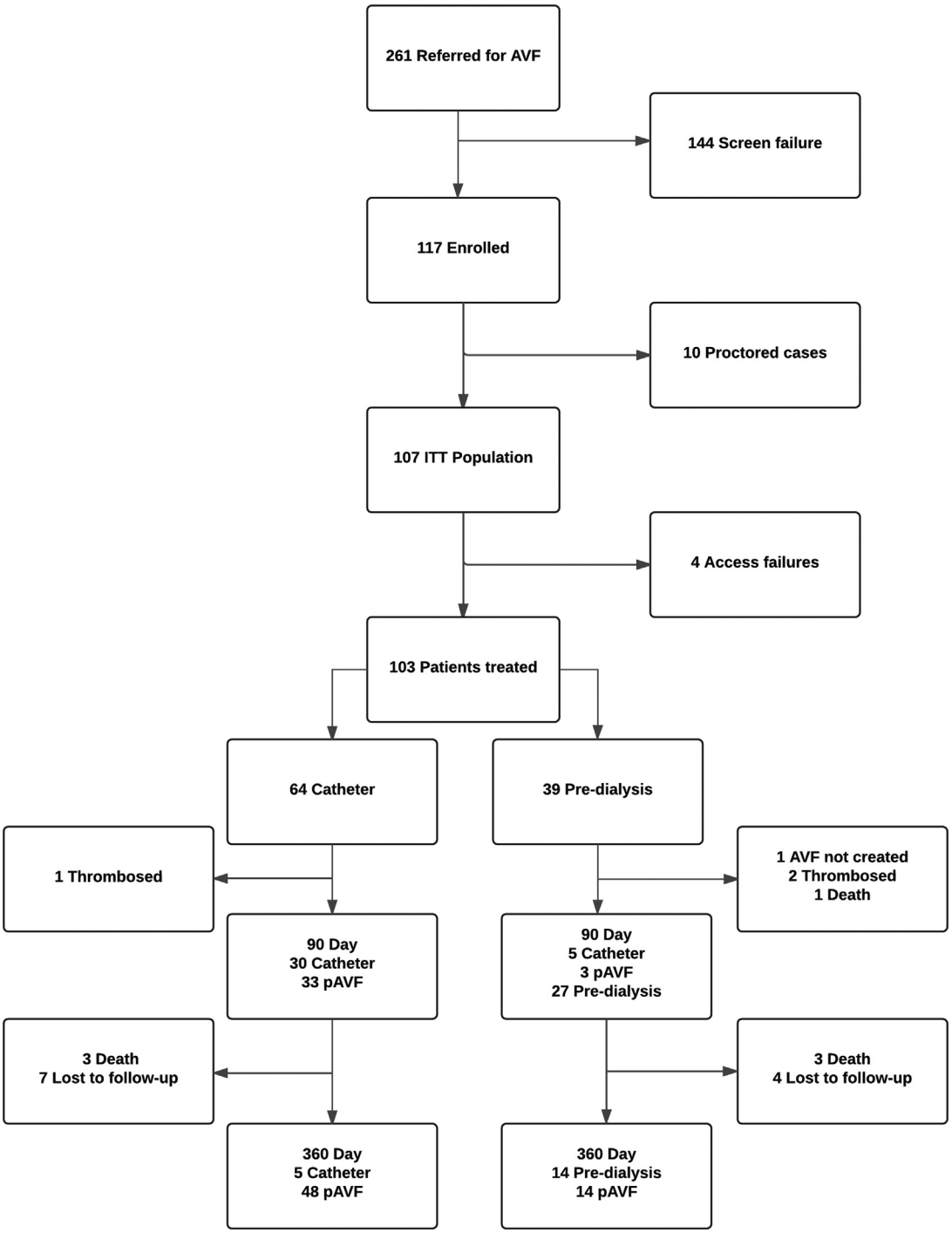

Figure 1. Flow diagram for study. pAVF = percutaneous arteriovenous fistula; Catheter = patient on catheter hemodialysis.

into the artery. A guide wire was positioned through the vein into the radial artery followed by a sheath (Glidesheath Slender 6; Terumo Medical Corp, Somerset, New Jersey) allowing the TRAD to be introduced into the radial artery. The artery and vein walls were then captured in the jaws of the device. The device was activated to fuse and cut an anastomosis and was then removed through the sheath. A completion Doppler US examination was performed to confirm fistula flow and measure brachial artery flow volume as shown in **Figure 2a–c**.

Secondary maturation procedures were performed to create functional fistulas and included balloon dilation, brachial vein embolization (**Fig 3a**, **b**), basilic vein ligation or embolization (**Fig 4a**, **b**), valvulotomy, and surgical transposition (7,8). These procedures developed accessible cannulation sites by directing flow from deep to superficial veins, isolating outflow into a specific target vein, and bringing matured veins closer to the skin surface.

Follow-up visits were scheduled at 24 hours, 1 week, 4 weeks, 3 months, and 12 months using the following

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Table 2. Demographic Characteristics of Intent to Treat Patients

Characteristics	Value
Race, white/black/Asian/other, n (%)	79 (73.8)/22 (20.6)/ 3 (2.8)/3 (2.8)
Ethnicity, Hispanic/not Hispanic, n (%)	38 (35.5)/68 (63.6)
Sex, male/female, n	78/29
Age, y, mean ± SD	56.7 ± 12.0
BMI, kg/m^2, mean ± SD	31.18 ± 7.13
Obesity*, n (%)	54 (50)
Type 1 diabetes, n (%)	5 (4.7)
Type 2 diabetes, n (%)	64 (59.8)
Hypertension, n (%)	105 (98.1)
Catheter dialysis at time of procedure, n (%)	66 (61.7)

BMI = body mass index.
*Defined as BMI > 30 kg/m^2.

standard-of-care assessments: vital signs, physical examination, Doppler US examination, and adverse event evaluation. Doppler US examinations were performed by registered vascular technologists at each site. Doppler US assessments of flow volume, anastomosis size, and vessel diameters of brachial artery and brachial, cephalic, and basilic veins were performed at the mid-distal upper arm (approximately 4 cm above antecubital fossa) during vein mapping and on all follow-up examinations (7,20).

Definition of Terms

Technical success was defined as successful creation of a fistula by the TRAD. Clinical success was defined as a clinically detectable fistula on discharge. Maturation procedures were secondary procedures performed before fistula achievement of primary endpoint of brachial artery flow volume ≥ 500 mL/min and target vein diameter ≥ 4 mm. Maintenance procedures were secondary procedures performed after the primary endpoint was reached or the patient underwent successful 2-needle fistula dialysis. Procedural success for secondary procedures was defined as described in the Society of Interventional Radiology (SIR) guidelines (21).

Data Analysis

Clinical data were recorded on source documents and entered into a validated electronic data capture system (eClinicalOS). All data were monitored by an independent study monitor, and adverse events were independently adjudicated by a medical monitor. Descriptive qualitative, quantitative, and statistical analyses were performed. Quantitative assessments were performed using SAS software (SAS Institute Inc, Cary, North Carolina) and included calculation of minimal, maximal, and mean values; SD; and 95% confidence intervals of variables. The primary effectiveness endpoint was tested for the ITT population using a 1-sample hypothesis comparing the Ellipsys Vascular Access System (test) with a performance goal based on previous studies of open surgery procedures to create an AVF. A meta-analysis of 8 previous studies was used to estimate a performance goal for the primary effectiveness endpoint (**Appendix A**, **Tables E1–E3**, **Fig E1** [available online at *www.jvir.org*]) (11–18). The weighted least squares mean success rate from the meta-analysis was 62% with the lower bound from a 2-sided 95% lower confidence interval of 49% (**Appendix A**, **Tables E1–E3**, **Fig E1** [available online at *www.jvir.org*]) (11–18). From this analysis, it was reasonable to use this lower limit as the performance goal for this study. The null and alternative statistical hypotheses are as follows:

$$H0: PTest \leq 49\% \text{ vs } HA: PTest > 49\%,$$

where PTest was the maturation success rate in the test group. This hypothesis was tested with a 1-sided binomial test. The null hypothesis was tested using a 1-sided significance level of .025. The effect of balloon size on percutaneous transluminal angioplasty success was modeled using a mixed effects model to account for repeated measurements within subjects. Kaplan-Meier analysis of cumulative and functional patency was performed as previously described (22,23).

RESULTS

Anastomosis Creation

Technical success for TRAD AVF creation was 95% (102 of 107). Needle access into the radial artery was unsuccessful in 4 patients, and a fistula was not created in 1 treated patient. Clinical success was achieved in 95% (98/103) of patients. The venous access site for the procedure was the cubital vein in 94% (97 of 103) of patients and the brachial vein in 6% (6 of 103). Artery access was into the proximal radial artery in all cases. The mean procedure time was 23.7 minutes ± 11.3 (range, 8–66 min). Spasm of the perforating vein was treated with balloon dilation under US guidance during the index procedure in 19% (20 of 107) of patients as shown in **Video 1** (available online at *www.jvir.org*). The mean time from end of procedure to discharge was 80.4 minutes ± 58.0 (range, 32–363 min). The mean proximal radial artery diameter before the procedure was 3.08 mm ± 0.62 (range, 2.0–4.6 mm), the mean perforating vein diameter was 3.48 mm ± 0.88 (range, 2.0–7.2 mm), and the mean distance between artery and vein was 0.65 mm ± 0.48 (range, 0.0–1.4 mm). The mean brachial artery flow volume was 330.4 mL/min ± 160.6 (range, 62–979 mL/min) postoperatively and increased 931.5 mL/min ± 369.8 (range, 42–2,281 mL/min) at 90 days and 1,089.7 mL/min ± 446.7 (range, 79–2,657 mL/min) at 360 days. The mean anastomosis cross-sectional area was 2.9 mm^2 ± 1.2 (range, 0.0–7.5 mm^2) and increased to 8.8 mm^2 ± 4.6 (range, 3.6–31.7 mm^2) at 360 days. The anastomosis cross-sectional area, diameter and flow volume of the brachial artery, and target vein diameters are summarized in **Table 3**.

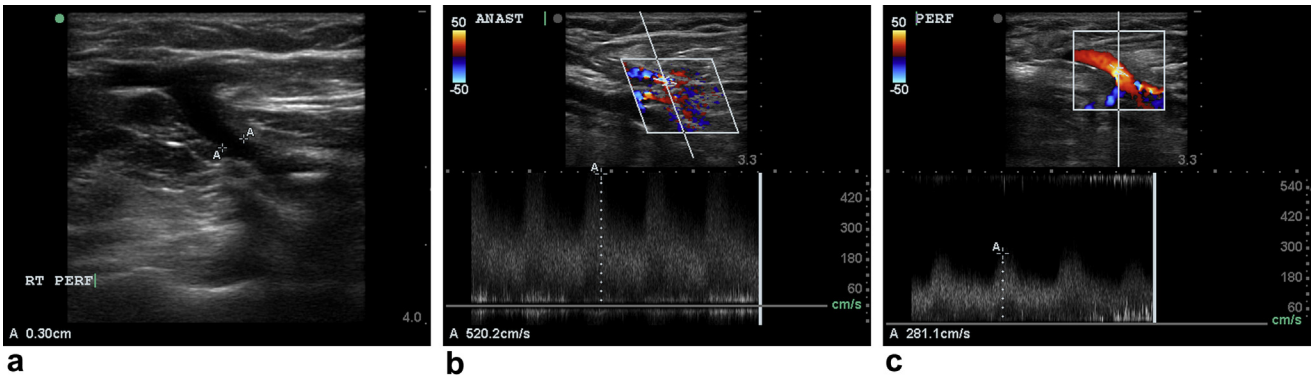

Figure 2. Sequential images demonstrate perforating vein before and after anastomosis creation and balloon dilation. **(a)** US image of proximal perforating vein (+) before procedure. **(b)** Perforating vein poorly distended. There was spasm in the proximal perforating vein (Doppler cursor) confirmed by elevated peak systolic velocity. **(c)** Color flow US image of perforating vein after balloon dilation with 5-mm balloon shows re-expansion of the perforating vein and decreased peak systolic velocity.

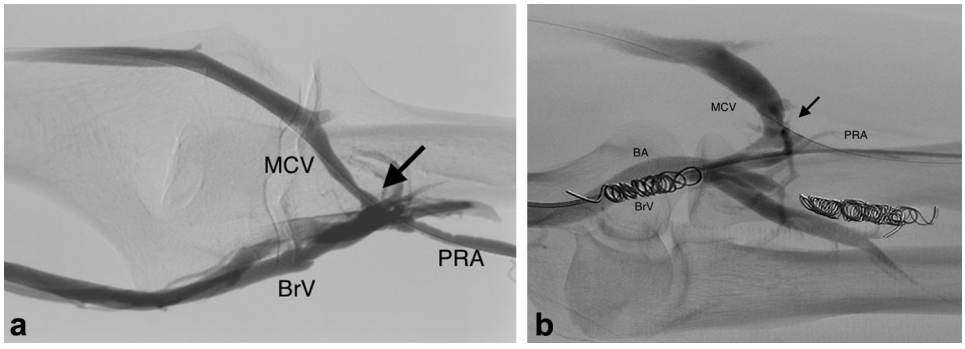

Figure 3. Radiographic images demonstrate the result of balloon dilation of the outflow followed by embolization of the brachial vein *(BrV)* directing flow into the cephalic vein. **(a)** Fistulogram of proximal radial artery *(PRA)* to perforating vein (arrow). Deep venous flow in the paired brachial veins *(BrV)* is noted medial to the elbow. In this patient, the median basilic vein is absent. **(b)** Contrast injection of the brachial artery *(BA)* after balloon dilation of perforating vein (arrow) and embolization of the BrV proximal and distal to the anastomosis. Final outflow was through the median cephalic vein *(MCV)* and cephalic vein.

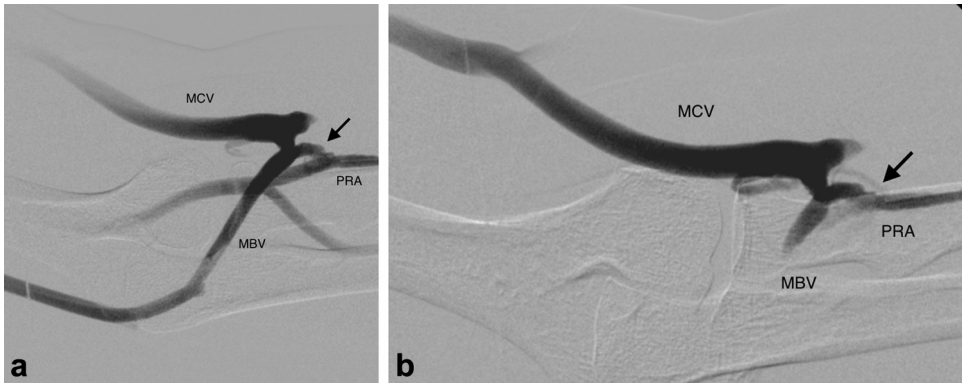

Figure 4. Fistulogram demonstrates successful modification in access outflow to targeted median cephalic vein *(MCV)* by ligation of the median basilic vein *(MBV)*. **(a)** The TRAD percutaneous AVF anastomosis between the perforating vein (arrow) and proximal radial artery is shown with substantial outflow into the competing MBV, hindering access maturation. **(b)** Image obtained after MBV ligation shows all AVF flow now into the MCV, with the targeted cephalic vein now palpable and easy to cannulate.

Fistula Maturation Procedures

Second-stage maturation procedures to increase and direct flow into the percutaneous AVF target outflow vein were performed in 99 patients at a mean 35.1 days ± 35.0 (range, 0–203 d) during 205 procedures. Maturation procedures included 113 balloon dilations of the anastomosis in 77 patients, 42 deep brachial vein embolizations in 34 patients, 34 cubital vein occlusions (17 ligation and 17 embolization) in 33 patients, 40 accessory (superficial) vein embolizations in 37 patients, and 28 surgical transpositions (Table 4).

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Table 3. Diameter and Flow

Measurement	Procedure	1 d	7 d	28 d	90 d	360 d
Number of patients	98	98	97	97	96	77
BA diameter, mm	5.0	5.0	5.1	5.2	5.5	5.9
Cephalic diameter, mm	4.4	4.6	4.8	5.4	6.6	8.5
Basilic diameter, mm	4.9	4.9	5.4	5.3	6.3	7.7
CSA, mm^2	2.9	3.0	3.5	4.8	6.2	8.8
BA flow, mL/min	330.4	335.1	422.7	606.0	931.5	1,089.7
Cephalic vein flow*, mL/min	123.9	150.3	174.1	366.7	631.9	891.8
Basilic vein flow*, mL/min	182.4	187.1	262.7	345.4	860.8	1,084.8

BA = brachial artery; CSA = cross-sectional area.
*Flow when target vein. Diameter and flow are mean.

Table 4. Secondary Procedures

	Patients	Procedures	Days*
Total maturation	99	205	35.1 ± 35.0 (0–203)
PTA anastomosis	77	113	22.8 ± 21.2 (0–100)
Embolization deep	34	42	26.2 ± 21.9 (1–100)
Embolization branch	37	40	23.3 ± 16.9 (1–82)
Cubital	33	34	43.9 ± 46.3 (1–203)
Transposition	28	28	91.3 ± 45.4 (40–203)
Total maintenance	36	66	176.8 ± 97.6 (44–371)
PTA	28	51	182.6 ± 97.9 (44–369)
Embolization	10	10	97.0 ± 32.7 (50–154)
Stent	7	8	174.9 ± 111.5 (49–363)

PTA = percutaneous transluminal angioplasty.
*Days are reported as mean ± SD (range).

Anastomosis balloon dilation was successful (brachial artery flow > 500 mL/min) in 63% (71 of 113) of procedures using a mean balloon size of 5.6 mm ± 0.62 versus 5.1 mm ± 0.62 for unsuccessful percutaneous transluminal angioplasty (P = .0012). The initial target outflow vein after maturation was the cephalic vein in 74% (73 of 99), basilic vein in 24% (24 of 99), and other (brachial and forearm veins) in 2% (2 of 99).

Fistula Maintenance Procedures

An additional 66 procedures were performed in 36 patients at a mean of 177 days ± 97.6 (range, 44–371 d) to maintain functional fistulas after maturation and are summarized in Table 4. Overall, 271 procedures were performed during 12 months, for 2.7 procedures per patient per year. The target vein was altered in 4 patients based on unexpected maturation of the cephalic vein in 2 patients, and failure of the cephalic vein to mature in 2 patients.

Procedure Efficacy

The primary endpoint of brachial artery blood flow volume ≥ 500 mL/min and target vein diameter ≥ 4 mm was met by 86% (92 of 107, 97.5% lower confidence interval 77.9%) of the patients, well exceeding the 49% performance goal (P < .0001) at 90 days. In the ITT population, the cumulative patency by Kaplan-Meier analysis was 91.6%, 89.3%, and 86.7% at 90, 180, and 360 days, as shown in Figure 5. The mean time to reach the primary endpoint was 62.4 days ± 47.4 (range, 21–378 d). During the 12-month study, 2-needle dialysis was performed in 88% (71 of 81) of patients on hemodialysis at a mean 114.3 days ± 66.2 (range, 34–345 d). The 81 patients requiring hemodialysis during the study included 63 patients on dialysis at enrollment and 18 who initiated dialysis during the study. The mean time to 2-needle cannulation was 100.2 days ± 51.9 (range, 34–224 d) for patients on dialysis at the start of the study and 162.9 days ± 86.6 (range, 53–345 d) for predialysis patients initiating dialysis during the study. Functional fistula patency by Kaplan-Meier analysis was 98.4%, 98.4%, and 92.3% at 90, 180, and 360 days, as demonstrated in Figure 6 (23).

Procedure Safety

There were no major device complications in the prescribed primary endpoints of vessel perforation, vessel dissection, electric shock, or distal embolization. There were no device-related serious adverse events (SAEs) as adjudicated by the medical monitor. The patient with technical failure to create a fistula had a minor hematoma and underwent a successful

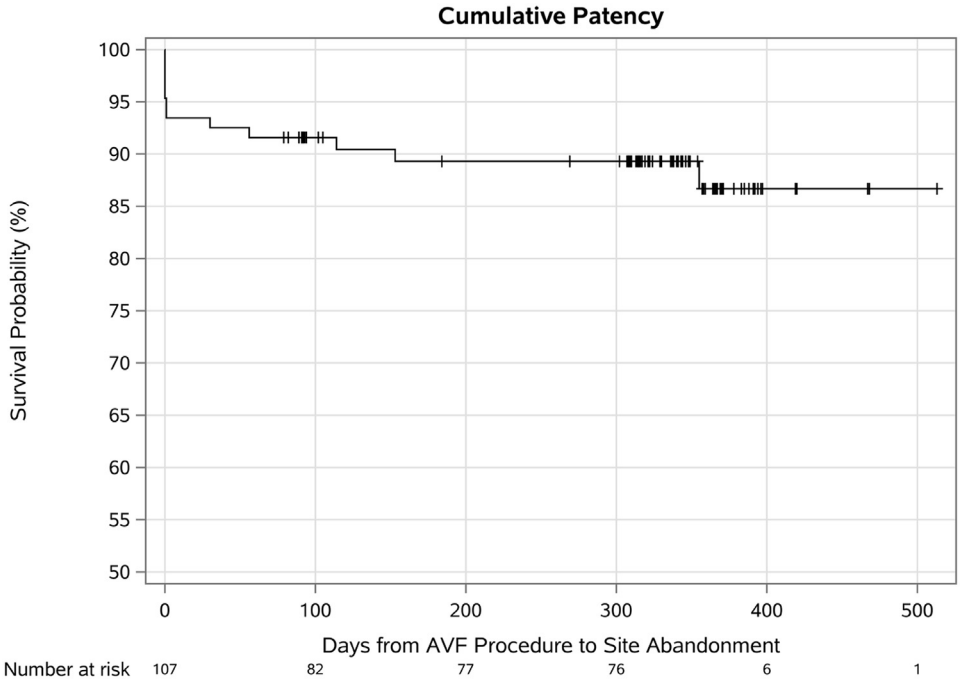

Figure 5. Cumulative patency of fistulas in the ITT population.

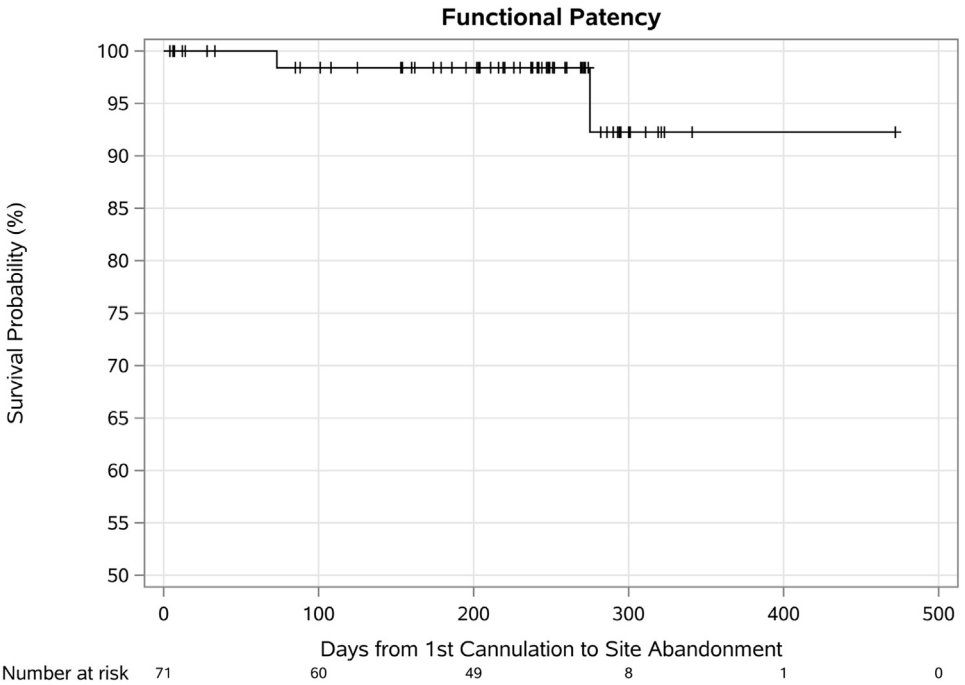

Figure 6. Functional patency of fistulas from 2-needle dialysis to abandonment (16)

surgical fistula in the same arm. One other patient had a minor hematoma at the access site treated with handheld pressure.

There were 2 SAEs that were adjudicated as possibly related or related to the study procedure by the medical monitor. One patient with a 3-month-old tunneled dialysis catheter who was treated for an exit site infection at the 24-hour follow-up visit with catheter replacement and antibiotics experienced methicillin-resistant *Staphylococcus aureus* sepsis at postoperative day 113 that was adjudicated as possibly related to the procedure. A second patient had cessation of respiration from conscious sedation before the procedure and was successfully treated with Ambu bag ventilatory assistance and reversal agents.

Throughout the study, 78 SAEs occurred in 42 patients. The most frequent SAEs were cardiac (8.7%); immune,

Table 5. Fistula Complications

Complication	Number (%)*	Treatment
Anastomosis related		
Early thrombosis (< 30 d)	12 (11.7)	Declot 9, abandoned 3
Late thrombosis	3 (3.9)	Declot 2, abandoned 1
Anastomosis stenosis	22 (21.4)	Balloon dilation
Fistula related		
Fistula stenosis	16 (15.5)	Balloon dilation
Central stenosis	4 (3.9)	Balloon dilation or stent
Cephalic arch stenosis	4 (3.9)	Balloon dilation or stent
Difficult cannulation	7 (6.8)	Balloon dilation or surgical elevation
Cannulation injury	13 (12.6)	Medical and endovascular management
Steal syndrome	1 (1.0)	Ligation of second anastomosis
Venous hypertension	3 (2.9)	2 endovascular, 1 ligation
Other		
Coil migration	1 (1.0)	Migrated to lung, asymptomatic
Vein rupture	1 (1.0)	During transposition treated with stent
Neuropathy	1 (1.0)	Transient day 7 to day 30
Epistaxis	1 (1.0)	Discontinued aspirin and clopidogrel
Infection	1 (1.0)	Jump graft and defibrillator lead removed

Note–Includes adverse events and maintenance procedures.
*% based on 103 treated patients.

infections, and infestations (5.8%); respiratory, thoracic, and mediastinal (5.8%); surgical and medical procedures and complications (4.9%); and vascular, blood, and lymphatic (8.7%) events. Several patients had multiple SAEs involving the same organ system, and several had events occurring in > 1 organ system. Nine SAEs in 9 patients were adjudicated as related to vascular, blood, or lymphatic systems. The 4 SAEs reported before 90 days included 1 case of peripheral arterial disease leading to transmetatarsal amputation and 3 cases of hemorrhage: 1 after a transposition surgery, 1 after a tunneled catheter exchange, and 1 after treatment of a complication of an elevation surgery. SAEs after 90 days included acute anemia requiring hospitalization, 2 cases of methicillin-resistant *S. aureus* septicemia, 1 steal syndrome, and 1 DeBakey type 1 aortic dissection. The steal syndrome developed after transposition with reanastomosis to the brachial artery with incomplete surgical ligation of study AVF.

Complications of Fistula

Early thrombosis (≤ 30 d) occurred in 12 fistulas; declotting was achieved in 75% (9 of 12) with balloon dilation alone in 6 patients and with additional aspiration thrombectomy in 3 patients. Thrombosis involved the anastomosis with minimal thrombus in the perforating vein. There was no separation or pseudoaneurysm formation at the anastomosis after balloon dilation. Late thrombosis occurred in 3 patients; 2 patients had successful thrombectomy, and 1 fistula was abandoned. Thrombosis was the cause for 4 of the 7 fistulas abandoned during the study. During the trial, 6.7% (7 of 103) of fistulas created were abandoned at a mean 101.4 days ± 125.5 (range, 1–355 d). Three were abandoned for early occlusion at the anastomosis, 1 was abandoned for failed thrombectomy of thrombosed access, and 3 were surgically ligated. There were 8 deaths in the ITT population; none were related to the device or the fistula. One patient reported a sensory paresthesia at day 7 that had resolved by day 30. There was 1 episode of epistaxis at day 30, which was treated by stopping antiplatelet therapy. Fistula complications are summarized in Table 5.

DISCUSSION

This pivotal trial of the Ellipsys Percutaneous Vascular Access System demonstrated that the TRAD used in a 2-stage procedure met the prescribed safety and efficacy endpoints for AVF performance goals derived from the literature. Vascular access benchmarks, such as technical and clinical success, early fistula failure, maturation rate, functional fistula development, and cumulative patency of TRAD fistulas, were consistent with reports in the surgical literature (3).

The proximal radial artery anastomosis site evaluated in this study had the same features of surgical fistulas using proximal radial artery inflow and the perforating vein outflow (24,25). The proximal radial artery and anastomosis size effectively controlled fistula flow and helped limit complications compared with brachial artery fistulas (26). The TRAD perforating vein fistula left the entire superficial venous system intact for use in the initial or subsequent fistulas as has been described for surgical perforating vein fistulas (25). The proximal radial artery site was particularly

useful, as fewer patients were good candidates for a radiocephalic fistula at the wrist, and up to 67% of new surgical AVFs are appropriately constructed with proximal radial artery inflow (27).

The 2-step process of fistula creation and maturation provided high cumulative and functional patency rates (22,28). The time to 2-needle dialysis has been reported to be 360 days, with 31 days for the first access appointment, 154 days for the access surgery, and the remaining time for maturation (29). In the present study, mean time to 2-needle dialysis was 100 days, improving on the mean 136 days reported in the 2016 United States Renal Data System report (30). The prompt placement of the TRAD fistulas in the office-based laboratory achieved 2-needle cannulation in 34 days, demonstrating additional potential to further improve time to dialysis access. Factors that reduced time to 2-needle dialysis access included consolidation of vein mapping, anastomosis creation, fistula maturation, and follow-up to a single clinic. The TRAD fistula should reduce use of medical resources, such as multiple consultations and operating room time and restrictions, in addition to prompt performance of maturation procedures.

Fistula blood flow volume increased incrementally with increased balloon size and could be monitored during the procedure with Doppler US and palpitation of the target dialysis vein. This allowed the blood flow volume to be increased for individual factors affecting cannulation. For example, a fistula close to the skin could be successfully cannulated with lower blood flow volume than a deep fistula. The redirection of venous blood flow was based on initial target vein response to flow, which minimized the need for deep brachial vein embolization, transpositions, and cubital vein ligations, while preserving veins for future use. The resultant fistulas had low to moderate flow, avoiding the complications of high-flow fistulas, such as steal syndrome, aneurysm formation, central stenosis, arm swelling, and cardiac damage (26,31–33).

Vascular spasm of the perforating vein immediately after the procedure has not been previously reported in TRAD fistula creation (7). In this study, vascular spasm was easily treated with vasodilators and balloon dilation as a matter of routine care and was not specifically evaluated. The recognition and treatment of spasm occurring after the procedure may have improved the maturation rate in this study, as has been described for vessel dilation after surgical fistula creation (34).

No SAEs were attributed to the TRAD. In 1 patient, the TRAD failed to create a fistula resulting in a minor hematoma. The anastomoses remained intact throughout the study with artery and vein directly connected without separation or pseudoaneurysm. Early thrombosis of the TRAD fistulas was similar to the 12% thrombosis in the clopidogrel arm of the study reported by Dember et al (35). The absence of a surgical incision enabled immediate physical and Doppler US examinations and treatment of thrombosis with a high success rate, whereas surgical fistulas with this complication were often abandoned.

Limitations of the present study included the single-arm design without direct comparison of TRAD fistulas with surgical fistulas. This was mitigated by the existence of a comparable surgical experience with proximal radial artery fistulas. The TRAD percutaneous AVF was novel in how it was created and matured into a functional fistula. There was no defined protocol for maturation, and there was a tendency to underdilate the anastomosis during maturation and not achieve brachial artery flow volume $>$ 500 mL/min. The results of TRAD fistulas are likely to improve with increased operator experience, as was shown in surgical fistulas (6). Finally, the patient population was 73% male, which is higher than the approximately 57.8% of patients with end-stage renal disease in the United States (30). The higher number of male patients was attributed to a higher screen failure rate among female patients failing to have a vein diameter $\geq$ 2 mm diameter.

In conclusion, TRAD fistulas were created with US guidance in the office-based laboratory with good clinical outcomes and minimal complications meeting the safety and efficacy thresholds of the US pivotal trial. The TRAD fistulas demonstrated AVF characteristics similar to surgically created fistulas at the favored proximal radial artery site using a minimally invasive approach performed in the office-based laboratory.

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APPENDIX A. AVF META-ANALYSIS

A meta-analysis was undertaken in support of developing a performance goal for the primary effectiveness endpoint analysis in Avenu Medical's clinical trial of the Ellipsys Vascular Access Catheter System (Protocol 01-0014-01). The methods used for choosing the studies for the meta-analysis are outlined in this Appendix; 8 studies were chosen.

The primary effectiveness endpoint in the Avenu study is maturation percentage rate at 90 days, where maturation is defined as an access site intended for dialysis needle cannulation that achieves a venous diameter of $\geq$ 4 mm and blood flow $\geq$ 500 mL/min as measured via duplex US. In most studies chosen for the meta-analysis, effectiveness/success (AVF success rate) was based on AVF patency and successful cannulation for hemodialysis. It is the opinion of Avenu Medical that these study endpoints are representative of the anticipated endpoint in the present study.

Several of the studies chosen for the meta-analysis included AVFs in various extremity locations. The present study focuses on AVFs created in the forearm, specifically radiocephalic fistulas. Where possible, results for radiocephalic fistulas were extracted from the studies chosen for the meta-analysis.

Where available, results for an ITT population were used rather than study success based on completed cases only. When success rates were not presented for an ITT population, success rates were recalculated for the ITT population where possible. Patency/success rates incorporating use of maturation assistance procedures were used where available. These rates are more conservative (higher) than success rates excluding assistance procedures following the initial procedure and are more representative of the present study endpoint.

In several articles, to obtain estimates of AVF success rates at 3 months following the initial AVF procedure, the results had to be extracted from Kaplan-Meier analyses. These rates may be optimistic, as they are not based on an ITT analysis. However, because dropout rates were low in most studies, these rates were deemed representative of expected results based on proportions. A summary of the 8 studies used in the meta-analysis is provided in **Table E1**. Based on the results provided in the publications, AVF success rates were calculated as presented in **Table E2**.

A random effects model was used to generate an estimate of the average AVF success rate across the 8 studies. The random effects estimate was calculated using the Metafor (Meta-Analysis Package for R) package (11). The AVF success rates and confidence intervals for each of the 8 studies as well as the random effects summary results are shown in **Figure E1**. The random effects model estimates an average success rate of 62% with a 95% confidence interval of 49%–75%. From this analysis, it is reasonable to use the lower limit of 49% as the performance goal for the primary effectiveness endpoint analysis in the present study.

AVF Meta-analysis Literature Search Protocol

A literature search protocol was designed to specifically identify all publications relevant to the outcomes of autogenous surgical radiocephalic AVF creation and clinical use (eg, maturation, hemodialysis use). As the surgical technique has been in clinical use for the last 50 years and the literature was known to be extraordinarily large, the search was designed specifically to extract all known meta-analyses and systematic reviews for the technology. The following key words were used in the search: radiocephalic, fistula, autogenous, arteriovenous (AV).

A database limit of meta-analysis was set. No date limits were imposed. The results of the search are shown in **Table E3**.

Articles that analyzed fistula grafts, indwelling catheters, stents, and other implants were excluded as nonequivalent technologies. Systematic reviews and meta-analyses whose sole focus was AVF site other than radiocephalic vein were also excluded. Articles reporting on radiocephalic AVFs in conjunction with other fistula sites, such as brachiocephalic vein, were included where the results and analysis were reported separately. Analyses that focused on imaging techniques, patient disease state, medicinal substance use, surgical transposition and/or hemodialysis puncture sites, and other such evaluations and did not report or analyze fistula-related outcomes were also excluded. Unrelated medical areas, such as dural AVFs, were logically excluded. Articles whose focus was assisted maturation only were included only if de novo primary patency rates were reported for autogenous radiocephalic fistulas. Duplication of trials within each meta-analysis and systematic review was considered.

Individual articles cited by this meta-analysis were reviewed to identify details from the trials that may pertain to the quantification of outcomes associated with autogenous radiocephalic AVFs. Articles chosen reported results at 3 months ($\pm$ 30 d) on average.

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Table E1. Summary of AVF Studies

First Author, Publication Date	Study Cohort*	Results Based on ITT or CC	Results Based on Proportion Successful or KM Estimate	Results Include Maturation Assistance Procedures	Time Point for Endpoint
Huber, 2002 (12)	RC	ITT	Proportion	Not specified	3.4 months (mean for entire study cohort)
Huijbregts, 2008 (13)	All (upper arm, forearm)	ITT	Proportion calculated from KM results	Assisted	3 months
Pflederer, 2008 (14)	Nontransposed forearm RC	CC	KM	Assisted	3 months
Lockhart, 2004 (15)	All	ITT calculated from available data†	Proportion	Not specified	Adequacy for dialysis (with cutoff at 6 months)
Rodriguez-Niedenfuhr, 2000 (16)	RC	CC	KM	Not specified	3 months
Wong, 2011 (18)	All	ITT	Proportion (calculated from results provided)	Unassisted	3 months
Yildrim, 2006 (17)	RC control group	ITT	Proportion	Unassisted	77.1 d (mean maturation, unspecified for failures)
Dember, 2008 (35)	Placebo group (forearm, upper arm)	CC	Proportion	Not specified	120–150 d, or at the initiation of dialysis

AVF = arteriovenous fistula; CC = completed cases; ITT = intention-to-treat; KM = Kaplan-Meier; RC = radiocephalic.
*If subset of study patients used; otherwise all specified.
†Excluding 11 patients not ready for dialysis at time of analysis.

Table E2. Summary of AVF Success Rates

First Author, Publication Date	No. Patients	No. AVFs	No. Successful AVFs	Proportion Successful
Huber, 2002 (12)	28	28	21	75.0%
Huijbregts, 2008 (13)	395	491	349*	71.1%
Pflederer, 2008 (14)	Not specified	203	173 (calculated†)	85% (KM)
Lockhart, 2004 (15)	101	101	36	35.6%
Rodriguez-Niedenfuhr, 2000 (16)	Not specified	631	486 (calculated†)	77% (KM)
Wong, 2011 (18)	60	60	38	63.3%
Yildrim, 2006 (17)	25	25	12	48.0%
Dember, 2008 (35)	373	373	151	40.5%

AVF = arteriovenous fistula; KM = Kaplan-Meier.
*Number available at end of 3 months.
†Denotes numbers that were not specified in the literature but were calculated based on the proportion successful.

Table E3. Search Results

Key Words	Limits	Returned Results
Radiocephalic fistula	Date: none Language: English Literature type: meta-analysis	1
	Date: none Language: English Literature type: systematic Review	2
Autogenous AVF	Date: none Language: English Literature type: meta-analysis	1
	Date: none Language: English Literature type: systematic review	4
AVF	Date: none Language: English Literature type: meta-analysis	29
	Date: none Language: English Literature type: systematic review	97

AVF = arteriovenous fistula.

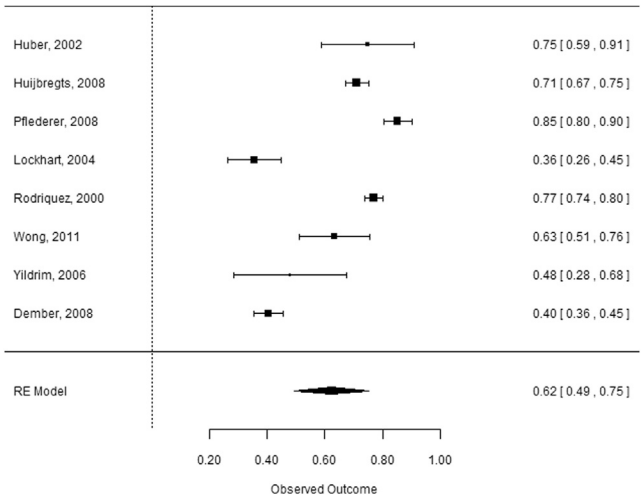

Figure E1. Success rates for each study and 95% confidence intervals. RE = random effects.