Patency of ePTFE Arteriovenous Graft Placements in Hemodialysis Patients: Systematic Literature Review and Meta-analysis

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ABSTRACT

Arteriovenous grafts (AVGs) are an appropriate option for vascular access in certain hemodialysis patients. Expanded polytetrafluoroethylene (PTFE) has become the dominant material for such grafts, due in part to innovations in graft design and surgical interventions to reduce complications and improve patency rates. Comprehensive evidence syntheses have not been conducted to update AVG performance in an era in which both access choice and PTFE graft functioning may have changed. We conducted a systematic review and meta-analysis summarizing outcomes from recent studies of PTFE AVGs in hemodialysis. A systematic review and meta-analysis of studies evaluated PTFE AVG outcomes and followed PRISMA standards. Literature searches were conducted in multiple databases to identify observational and interventional studies of AVG patency and infection risk. Primary, primary assisted, and secondary patency rates were analyzed at 6, 12, 18, and 24 months post-placement. Kaplan-Meier graft survival plots were digitized to re-create individual patient level data. Patency rates were pooled using a random-effects model. We identified 32 studies meeting our selection criteria that were published from 2004 through 2019. A total of 38 study arms of ePTFE grafts were included, representing 3,381 AVG accesses placed. The mean primary, primary assisted, and secondary patency rates at one year were 41% (95% CI: 35%-47%), 46% (95% CI: 41%-51%), and 70% (95% CI: 64%-75%), respectively. Mean 24-month patency rates were 28% (95% CI: 22%-33%), 34% (95% CI: 27%-41%), and 54% (95% CI: 47%-61%), respectively. A high degree of heterogeneity across studies was observed. Overall risk of infection was not consistently reported, but among available studies the pooled estimate was 9% per patient-year (95% CI: 6%-12%). This meta-analysis provides an up-to-date estimate of the performance of
PTFE AVGs, within the context of improved graft designs and improved interventional techniques.

**INTRODUCTION**

Current National Kidney Foundation guidelines recommend an arteriovenous fistula (AVF) as the first access for hemodialysis. However, primary failure rates for AVF remain high (over 20%) and for many patients AVF is not a viable option due to vascular anatomy or to other factors. In these cases, an arteriovenous graft (AVG) is recommended for vascular access in the upper extremity. One of the most widely used graft materials is expanded polytetrafluoroethylene (PTFE).

The use of AVGs has historically been hampered by low patency rates, with reported secondary patency of 76% at 6 months and 55% at 18 months. In addition, PTFE grafts can suffer from high rates of complications, including infections, thrombosis, and steal syndrome. Recent advances in prosthetic graft material engineering may have contributed to an increase in the durability of PTFE, as may recent advances in coating technology such as covalent heparin modifications. However, there has been no recent comprehensive evaluation of PTFE AVG functional patency rates when used for hemodialysis access. Furthermore the “Fistula First” initiative has changed patient selection criteria for placement of an AVG rather than an AVF. We therefore considered it important for present day hemodialysis access practice to conduct a systematic review and meta-analysis in order to summarize key outcomes in recent studies of PTFE vascular access grafts.

**MATERIALS AND METHODS**

*Study design*
This systematic review and meta-analysis was conducted in accordance with PRISMA guidance. Methods of the analysis, inclusion and exclusion criteria were specified in advance and documented in a protocol, with search terms identified a priori.

The study population consisted of patients with chronic kidney disease or end-stage kidney disease who were either preparing for, or currently on, chronic hemodialysis treatment using a PTFE graft. Inclusion criteria for studies to be considered in this meta-analysis were: 1) at least one study arm included a PTFE graft; 2) study described newly-created AVGs (incident grafts), as opposed to only graft revisions; and 3) studies published in English. Clinical trials, observational study designs and systematic reviews were included. Studies were excluded if: 1) study arms had fewer than 30 patients receiving PTFE grafts; 2) patients were treated prior to the year 2000; 3) no patency results were reported at 6, 12, 18, or 24 months; 4) study was exclusively pediatric; and 5) the study only included lower extremity dialysis access grafts, which are known to have substantially different patency and infection outcomes than upper extremity grafts. Studies using only Hemodialysis Reliable Outflow (HeRO) grafts with no PTFE study arm were excluded.

_Literature search_

Literature searches were conducted in November 2019 in Medline, Embase, Cochrane Library, and Clinicaltrials.gov databases. A flow diagram of the study selection and inclusion process is shown in Figure 1. The search terms used in each database are found in Supplemental Table S1. Additional studies were identified through searching the reference lists of included systematic reviews.
Studies were screened for eligibility by two reviewers at the levels of abstract and full text. Disagreements were resolved by consensus. Data items were extracted into a spreadsheet developed in advance of the review. Data elements extracted included: study characteristics (objective, study type, inclusion/exclusion criteria, country, type of intervention(s), endpoints, funding, number of sites); patient characteristics (including demographics, comorbid conditions); graft characteristics (including type/brand, size, location); patency endpoints; and complications (including infections, interventions, and steal).

Risk of bias in individual studies was evaluated using the approach described by Higgins and colleagues.⁹ Because most of the included studies were observational, we adapted a tool described by Al-Jaishi that was used in a systematic review of AVF.²

Endpoints and definitions

The patency analysis was categorized using the definitions provided by Sidawy.¹⁰ Primary unassisted patency is defined as “the interval from access placement until any intervention designed to maintain or re-establish patency, access thrombosis, or the time of measurement of patency.” Primary assisted patency is “the interval from access placement until access thrombosis, or the time of measurement of patency, including intervening manipulations (surgical or endovascular interventions) designed to maintain the functionality of a patent access.” Secondary patency is “the interval from access placement until access abandonment, thrombosis, or the time of patency measurement including intervening manipulations (surgical or endovascular interventions) designed to re-establish functionality in a thrombosed access.”
The occurrence of infections and complications reported in AVG patients was also abstracted. In studies that did report infection rates, there was commonly an overall percent of patients with infections over the course of the entire study period. Infection rates per patient-year were estimated from the mean follow-up period for each study.

**Statistical analysis**

Meta-analyses of proportions were conducted using random effects models employing STATA (StataCorp LP, V.16.0). Primary outcomes were graft patency measures: primary, primary assisted and secondary patency, measured at 6, 12, 18 and 24 months. Stratified analyses were also performed on variables selected *a priori* to potentially affect the outcomes of interest, such as gender, race, diabetes, country setting (US vs. ex-US), study design (observational-prospective, observational-retrospective, interventional), risk of bias, and industry funding. Heterogeneity was measured using the $I^2$ statistic, which is a measure of the proportion of total variation in mean estimates that is due to heterogeneity across individual studies.

For patency outcomes, most included studies used time to event analysis and published survival curves using the Kaplan-Meier method. If patency outcomes were reported in text and also published in survival curves, the originally reported in-text data were used, provided that a measure of variance was included. For studies that did not report patency outcomes in text or tables, a published algorithm was used to reproduce individual patient data using DigitizeIt software. Each line in a Kaplan-Meier curve and the resulting output was used, in coordination with the study’s stated patency results, to estimate survival summary statistics for each study.
Patencies at 6, 12, 18 and 24 months, along with their standard errors, were computed, which were then entered into the meta-analyses. No extrapolation of patency outcomes was performed; patency estimates were digitized only at reported time points from K-M curves. As a quality control measure for the digitization software, a sample of papers that reported patency in-text and also had K-M curves was used to compare accuracy of digitization output. Where patency data was not reported in the text or tables, digitized K-M data from the published report were substituted. Some curves could not be digitized because of poor quality of the original publication graphics. Potential publication bias among included studies was assessed using the methods described by Egger, including the use of funnel plots which indicate the direction of potential missing outcomes based on effect sizes of available outcomes.  

Ethics approval

As all data were obtained from published scientific articles, this study was exempt from Institutional Review Board review in accordance with 45 CFR 46.101(b)(4).

RESULTS

Included Publications

A total of 32 studies were included in the analysis (Figure 1). Publication dates ranged from 2007 through 2019, representing a relatively contemporary clinical experience with dialysis access. Characteristics of included studies (Supplemental Tables S2 - S4) indicate that a total of 38 study arms of ePTFE grafts were included, representing 3,381 AVG accesses placed. Fourteen countries were represented, with 13 studies solely from the US. Twenty-one studies (65.6%) were retrospective reports, six (18.8%) were prospective observational studies, and 5
(15.6%) were randomized clinical trials. Risk of bias in reported study design issues was assessed to be low for 20 (62.5%) of the studies.

**Primary and Primary Assisted Patency**

Overall patency results for the 32 studies included in this meta-analysis are shown in in Table 1. (For each patency outcome, rates reported in the manuscript were within 1% of the data digitized from the published K-M curves, apart from a single primary assisted patency rate for which the difference was 5%, where the stated value was used.) Patency rates followed expected patterns over time. Primary patency at 6 months (56%; 95% C.I. 51% - 62%) was higher than at 24 months (28%; 95% C.I. 22% - 33%); primary assisted patency rates were a few percentage points higher than primary rates, (59%; 95% C.I. 52% - 67%) at 6 months with some increase in the gap over primary patiency with time (34%; 95% C.I. 29% - 39%) at 24 months. The 95% confidence intervals for primary and primary assisted patency overlapped for all time periods reported.

**Secondary Patency**

For PTFE grafts, the average secondary patency in these 32 studies trended from 80% (95% C.I. 75% – 84%) at 6 months, to 70% (95% C.I. 64% – 75%) at 12 months, to 59% (95% C.I. 53% - 65%) at 18 months, and 54% (95% C.I. 47% - 61%) at 24 months.

**Statistical Heterogeneity**

Statistical heterogeneity was present in all of the patency analyses. The $I^2$ statistic was above 85% for most reported patency rates, indicating substantial heterogeneity. Only for primary
assisted patency (which had the fewest number of studies) was $I^2$ in a range that is often considered to be moderate levels of heterogeneity. The forest plots (Figs 2-3, Supplemental Figure S6) reflect this heterogeneity in study outcomes across the 32 publications. Figures 2, 3, and Supplemental Figure S6 show the mean secondary patency, with 95% confidence intervals, at 12, 18 and 24 months. The wide variability in outcomes is clear, with differences in the 95% confidence intervals of secondary patency between studies approaching 60% in some cases.

In order to summarize patency outcomes from the 32 studies, we generated aggregated Kaplan-Meier curves for primary, primary assisted, and secondary patency. Calculation of aggregated Kaplan-Meier curves was weighted by the number of patient in each study. These curves, based on all included data, illustrate trends in primary, primary assisted and secondary patency (Fig 4). Error bars indicate 95% confidence intervals for patencies at 6, 12, 18 and 24 months. While confidence intervals for primary and primary assisted patency overlap at each time point, secondary patency clearly separates from primary and primary assisted patency and its 95% confidence interval for secondary patency does not overlap with other patency rates. The width of the secondary patency confidence interval at 6 months was 9% (75%-84%), while at 24 months was 14% (49%-63%).

**Infections**

Infection rates could be analyzed in 14 studies, contributing 17 study arms and 1,418 access placements, and representing 44% of all included studies and 42% of PTFE graft placements. Definitions of reported infections varied substantially, and included descriptions of site infections, infections requiring hospitalization, and infections requiring graft excision. These
varying definitions of “graft infection” substantially complicated the aggregate interpretation. In addition, most studies that did report infections, did so as a proportion of patients experiencing infections over the entire study period, rather than as the rate of infections per patient year. Infection rates on a per-patient-per-year basis could be estimated from some reports, but there was some uncertainty in such calculations, since often only mean follow-up periods were reported. Nonetheless, because gaining a full understanding of PTFE infectious complications is important, we calculated infections based upon total numbers of reported infections and, in several cases, the mean follow-up period for the study. This gave an overall annual infection rate of 9% per patient-year (Fig 5).

**Stratified Analyses**

Stratified analyses of secondary patency identified some differences in patency rates across studies of differing types. These are summarized in Figure 6, with full forest plots provided in Supplemental Figures S7 – S22. Studies conducted within the US had lower secondary patency rates at both 12 and 24 months as compared to ex-US studies. Standard ePTFE grafts had lower mean secondary patency than those study arms including concomitant drug therapy (e.g. dipyridamole) or involving hybrid grafts (e.g. cuffed grafts). Notably, the difference between secondary patency rates in retrospective studies versus those in prospective controlled trials exhibited the largest differentials in these strata, with prospective controlled trials reporting higher secondary patency rates than retrospective or non-controlled trials. This may indicate that the patient care patterns and intensity of follow-up utilized during prospective, randomized controlled trials may differ from the “real-world” care patterns that are typical for dialysis
access. Hence, the overall better outcomes observed in randomized controlled trials may not be reflective of typical clinical practice and outcomes in hemodialysis patients.

Regarding gender effects, there was little difference in secondary patency for studies with below-average, versus above-average, proportions of male participants. Secondary patency rates tended to be higher in studies with above-average proportions of participants of black race, which may be in conflict with preconceptions held by some investigators. Consistent with other literature reports, however, patency rates tended to be better when patient cohorts contained below-average proportions of diabetics. Higher secondary patency rates were also found in studies that were scored as having lower risk of bias, and those that had no industry funding.

Funnel plots were created to investigate potential publication bias across included studies (Supplemental Figure S5). There is some evidence of publication bias, as reflected in asymmetry of the funnel plots at 12 and 24 months. However, the apparent direction of potential bias was in opposite directions for the funnel plots for secondary patency at 12 months and 24 months, implying that there is little systemic publication bias in this sample of reports. The funnel plots likely reflect the high degree of heterogeneity found in the studies, as well as the low likelihood of very high or very low patency rates that might have “balanced” the funnel plots, as opposed to systematic publication bias.

**DISCUSSION**

We conducted a systematic review of recent studies, spanning from 2007 – 2019, reporting the patency of PTFE grafts that are used for dialysis. In order to identify the most current data, we limited our review to patients treated in the last 20 years. To avoid smaller studies with unstable
estimates, we included study arms with at least 30 patients with PTFE grafts. Because we anticipated the existence of relatively few randomized clinical trials, we included observational studies in this meta-analysis in order to provide a broader cross-section of publications and clinical experience. We believe the data presented here represent the highest quality available estimates for AVG patency in the modern era, and reflect current trends in dialysis access placement and management.

Our results are generally consistent with those reported by other systematic reviews, albeit with slightly improved patency rates as compared to much older studies. Using data from 1966 – 2001, Huber and colleagues reported primary patency rates for PTFE grafts of 58% at 6 months and 33% at 18 months (vs. 56% and 39%, respectively, in our study). 4 Huber also reported secondary patency of 76% at 6 months (vs. 80% in this current analysis) and 55% at 18 months (vs. 59% in this current analysis). In a recent meta-analysis of mixed graft types published in 2016, Almasri and colleagues reported primary patency rates of 40% at 2 years (vs. 28% in this report) and secondary patency of 60% at 2 years (vs. 54% in this report). 49 In a systematic review of early cannulation grafts, Al Shakarchi and Inston reported 12 month primary and secondary patency for Flixene® grafts (Maquet) of 43.3% and 73.4% (vs. 41% and 70% in this analysis, respectively). 50 The same study reported 12 month primary and secondary patency for Acuseal® grafts (Gore) of 43.6% and 70.5%. Hence, the results from this systematic analysis of PTFE studies are generally in line with reports of other graft types that have been published in recent years.
In the last several decades, various improvements have been made in ePTFE grafts for hemodialysis access, including covalent heparin bonding on the luminal surface, and the introduction of self-sealing technologies to help enable early cannulation. Furthermore, technologies for covered stent deployment, drug-eluting stents, and drug-eluting balloons have become part of routine clinical practice in the care of vascular access. As the life expectancy of dialysis patients has increased from 3 years to 5 years or more, there is an increased focus on access durability and functional secondary patency, as opposed to just primary patency. Advances in mechanical and pharmacologic thrombolytic techniques, and the proliferation of access centers that can treat malfunctioning access grafts, mean that transient access thrombosis is no longer a substantial barrier to patient well-being. In contrast, abandonment of a dialysis access conduit, or loss of secondary patency, forces the placement of an indwelling catheter and often the creation of a new surgical access. Our meta-analysis indicates that, on average, 20% of PTFE grafts are abandoned at 6 months after implantation and 30% are abandoned by one year. By two years, nearly half of all PTFE grafts have failed and required replacement in order for the patient to remain on hemodialysis. Therefore, despite the proliferation of minimally invasive treatments and thrombolysis, and despite advances in angioplasty balloons, drug-coated balloons, and stenting options, PTFE arteriovenous graft secondary patency rates remain quite low, as compared to the patency of PTFE vascular grafts in other anatomic locations. Nearly 1 in 2 patients receiving a PTFE graft for hemodialysis access will require another graft, or another form of access, within two years.

As part of this review, we collected information on AVG complications, including infections, interventions, and steal. Of these, only infectious complications had information of sufficient
quality to allow a statistical summary. In contrast, reports of steal and interventions were spotty across the various studies, and the modes of reporting were too highly variable to allow objective comparisons. Closer adherence to publication guidelines of by the Society for Vascular Surgery and the American Association for Vascular Surgery\textsuperscript{10} would facilitate comparisons across studies in the future.

The overall rate of PTFE graft infections was 9\% per patient year in this analysis. The rate of PTFE infection is important because sepsis accounts for 9.3\% of hospital admissions, and complications of dialysis access conduits drive 9.2\% of hospital admissions in dialysis patients, with a total spending of $5-6 billion per year. The total number of hospitalizations for infections of hemodialysis access is approximately 58,000 per year in the US alone.\textsuperscript{58} Infection also leads to death in dialysis patients. Septicemia accounts for roughly 8\% of deaths in hemodialysis patients in the US each year.\textsuperscript{58} Of the approximately 78,000 annual deaths of hemodialysis patients, 8\%, or 6,000 patients per year, die from sepsis.

While fistulas are currently the gold standard for dialysis access, in part due to their low infection rates, certain sub-groups of dialysis patients are burdened with higher use of ePTFE grafts and catheters. According to the United States Renal Data System (USRDS) database, female ESRD patients have with lower rates of fistula use – and higher rates of ePTFE graft and catheter use - than do male patients.\textsuperscript{58} Women may be poorer candidates for fistulas than men, in part due to their smaller venous anatomy, making fistula maturation more technically challenging in women.\textsuperscript{59,60} USRDS data show that, at one year after dialysis initiation, the rate of fistula use is only 56\% for women, as compared to 71\% for men. Correspondingly, ePTFE use is
higher: 20% of prevalent female dialysis patients, vs. 12% of men. The rate of hospitalization for vascular access infection for women is 15% per patient-year, while for men it is 11% per patient-year. This may, at least in part, reflect infections related to PTFE AVG use. The observed rate of 9% infection per patient-year is consistent with other data sources pointing to worsened infectious outcomes in patients – especially women – who utilize PTFE grafts for dialysis.

As with all systematic reviews, our results are limited by the quality and characteristics of the included studies. There was significant statistical heterogeneity in our results, which was not well explained by differences in the variables we collected but is not entirely unexpected given the predominance of observational data in our reviews. This heterogeneity likely has many sources, including variability in patient selection, and surgical and interventional approaches, given the range of study designs, patient cohorts, and geographic locations of the publications included in this analysis. Of note, randomized trials had the lowest heterogeneity in our analyses, and also the highest patency rates overall. These trials are likely more selective in their patient selection and provide more consistent follow-up. Unfortunately, missing data for potentially explanatory variables (as shown in Table S3) makes it difficult to definitively explain heterogeneity in this collection of studies.

This meta-analysis provides an up-to-date estimate of the performance of PTFE AVGs, within the context of improved graft designs and improved interventional techniques. In the era of “fistula first”, which has been widely operative during the past 10-15 years, this analysis
provides a summary of the functionality and infection rates for PTFE when used as an access for hemodialysis.
DISCLOSURES

RJH, GN, and RJN were employees of Beta6 Consulting Group at the time of this study, which received a grant from Humacyte. AP is a former employee and a stockholder of Humacyte, Incorporated. LEN is a founder and shareholder in Humacyte, Inc, which is a regenerative medicine company. Humacyte produces engineered blood vessels from allogeneic smooth muscle cells for vascular surgery. LEN’s spouse has equity in Humacyte, and LEN serves on Humacyte’s Board of Directors. LEN is an inventor on patents that are licensed to Humacyte and that produce royalties for LEN. LEN has received an unrestricted research gift to support research in her laboratory at Yale.

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AUTHOR CONTRIBUTIONS

R Halbert: Conceptualization; Formal analysis; Methodology; Writing - original draft; Writing - review and editing

G Nicholson: Conceptualization; Formal analysis; Methodology; Writing - original draft; Writing - review and editing

R Nordyke: Conceptualization; Formal analysis; Methodology; Writing - original draft; Writing - review and editing

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L Niklason: Conceptualization; Writing - review and editing
RJH, GN, RJN, AP and LN made substantial contributions to the conception or design of the study; were responsible for interpretation of data for the study, drafted and revised it critically for important intellectual content; gave final approval of the version to be published; and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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### Table 1. Summary Results of Meta-analyses of Patency Rates in ePTFE Arteriovenous Grafts

| Follow-up Period | Patency Measure | Study Arms | Number of ePTFE Accesses | Patency Rate, % | 95% CI | $\Gamma^2$ (p-value) |
|------------------|----------------|------------|--------------------------|-----------------|-------|-------------------|
| 6 months         | Primary        | 30         | 2788                     | 56              | (51,62) | 89 (<0.001)       |
|                  | Primary Assisted | 14        | 1281                     | 59              | (52,67) | 88 (<0.001)       |
|                  | Secondary      | 25         | 2126                     | 80              | (75,84) | 88 (<0.001)       |
| 12 months        | Primary        | 31         | 2839                     | 41              | (35,47) | 92 (<0.001)       |
|                  | Primary Assisted | 16        | 1404                     | 46              | (41,51) | 74 (<0.001)       |
|                  | Secondary      | 32         | 2555                     | 70              | (64,75) | 91 (<0.001)       |
| 18 months        | Primary        | 21         | 1700                     | 34              | (27,41) | 92 (<0.001)       |
|                  | Primary Assisted | 10        | 1050                     | 39              | (34,45) | 70 (<0.001)       |
|                  | Secondary      | 22         | 1871                     | 59              | (53,65) | 88 (<0.001)       |
| 24 months        | Primary        | 22         | 1733                     | 28              | (22,33) | 89 (<0.001)       |
|                  | Primary Assisted | 12        | 1232                     | 34              | (29,39) | 68 (<0.001)       |
|                  | Secondary      | 24         | 2053                     | 54              | (47,61) | 92 (<0.001)       |
Figure 1. PRISMA Diagram

PubMed citations (n = 131)
Embase citations (n = 219)
Cochrane Library citations (n = 5)
Clinicaltrials.gov citations (n = 13)
Citations from hand search of AV access systematic reviews (n = 8)

Unduplicated citations (n = 373)

Citations excluded (n = 279)

Full-text articles reviewed (n = 94)

Full-text articles excluded:
- Not English-language: 3
- Not peer-reviewed article: 1
- Conference abstract or letter to editor: 2
- Population treated prior to 2000: 31
- Analyzes prevalent grafts: 3
- Does not report patency outcome: 9
- No PTFE arm: 2
- PTFE N < 30: 8
- Hybrid grafts: 1
- Other: 2

Studies abstracted (n = 32)
Figure 2. Forest Plot of Secondary Patency at 12 Months

Secondary Patency 12 Months-KM

| Study                  | ES (95% CI)   | Weight |
|------------------------|---------------|--------|
| Alleman 2014           | 72 (68, 77)   | 3.45   |
| Anaya-Ayala 2015       | 68 (49, 79)   | 2.76   |
| Arnucese 2017          | 49 (37, 60)   | 3.06   |
| Berard 2015            | 88 (73, 94)   | 3.18   |
| Chiang 2014            | 62 (48, 75)   | 2.88   |
| Davies 2016a           | 71 (64, 78)   | 3.43   |
| Davies 2010b           | 66 (60, 72)   | 3.43   |
| Doria 2015             | 45 (29, 02)   | 2.62   |
| Drouven 2019           | 77 (67, 85)   | 3.23   |
| Elwakil 2013           | 76 (61, 86)   | 2.96   |
| Feldman 2013           | 59 (46, 70)   | 3.00   |
| Glickman 2015          | 79 (71, 85)   | 3.38   |
| Głowacki 2014          | 88 (73, 95)   | 3.13   |
| Jadoul 2015            | 50 (39, 61)   | 3.07   |
| Kakalis 2017           | 90 (80, 95)   | 3.35   |
| Kakos 2011             | 69 (50, 76)   | 3.31   |
| Keuter 2008            | 85 (73, 92)   | 3.22   |
| Khoshevis 2013         | 57 (44, 69)   | 2.98   |
| Ko 2009a               | 99 (89, 100)  | 3.50   |
| Ko 2009b               | 88 (72, 93)   | 3.15   |
| Lee 2007               | 61 (47, 73)   | 2.94   |
| Liopis 2011            | 73 (59, 83)   | 3.01   |
| Marcus 2019            | 57 (48, 65)   | 3.28   |
| Milburn 2008           | 41 (27, 57)   | 2.78   |
| Pharm 2017             | 47 (31, 64)   | 2.63   |
| Sela-Almonacid 2011    | 68 (52, 80)   | 2.66   |
| Scarritt 2014a         | 77 (66, 85)   | 3.23   |
| Scarritt 2014b         | 37 (26, 49)   | 3.07   |
| Shomos 2015a           | 83 (73, 90)   | 3.30   |
| Shemesh 2015b          | 81 (71, 88)   | 3.28   |
| Tozzi 2014             | 93 (79, 98)   | 3.26   |
| Weiss 2007             | 61 (52, 70)   | 3.26   |
| Overall (I^2 = 91.3%, p = 0.000) | 70 (64, 75) | 100.00 |
Figure 3. Forest Plot of Secondary Patency at 24 Months

Secondary Patency 24 Months-KM

| Study            | ES (95% CI) | % Weight |
|------------------|------------|----------|
| Alleman 2014    | 54 (48, 60)| 4.53     |
| Anaya-Ayala 2015| 37 (23, 54)| 3.81     |
| Arhuidese 2017  | 38 (28, 50)| 4.18     |
| Berard 2015     | 86 (73, 94)| 4.29     |
| Chiang 2014     | 51 (37, 65)| 3.93     |
| Davies 2016a    | 38 (32, 44)| 4.52     |
| Davies 2016b    | 36 (30, 42)| 4.54     |
| Donati 2015     | 29 (16, 47)| 3.81     |
| Drouven 2019    | 73 (62, 82)| 4.29     |
| Elwakeel 2013   | 44 (30, 59)| 3.88     |
| Glowinski 2014  | 76 (60, 88)| 3.96     |
| Jadlowiec 2015  | 33 (23, 44)| 4.22     |
| Kakisis 2017    | 66 (53, 76)| 4.15     |
| Kakkos 2011     | 60 (51, 68)| 4.39     |
| Khoshnevis 2013 | 38 (26, 51)| 4.09     |
| Ko 2009a        | 83 (70, 91)| 4.24     |
| Ko 2009b        | 62 (47, 75)| 3.92     |
| Lee 2007        | 43 (31, 57)| 4.02     |
| Marcus 2019     | 53 (45, 62)| 4.39     |
| Milburn 2008    | 33 (21, 49)| 3.91     |
| Sala-Almonaci 2011| 55 (40, 69)| 3.86     |
| Shemesh 2015a   | 83 (73, 89)| 4.41     |
| Shemesh 2015b   | 73 (62, 81)| 4.31     |
| Weale 2007      | 41 (33, 50)| 4.36     |
| Overall (I² = 91.7%, p = 0.000) | 54 (47, 61)| 100.00  |
Figure 4. Aggregate Kaplan-Meier Curves for Primary, Primary Assisted, and Secondary Patency –

Aggregated patency results

- Primary Patency
- Primary Assisted Patency
- Secondary Patency

Months: 0, 6, 12, 18, 24
Figure 5. Forest plot of infection rate per patient per year

Any Infection, % Per Year

| Study              | ES (95% CI) | %   | Weight |
|--------------------|-------------|------|--------|
| Arhuldes 2017      | 35 (25, 47) | 4.00 |        |
| Berard 2015        | 7 (2, 18)   | 5.64 |        |
| Chiang 2014        | 13 (5, 26)  | 4.55 |        |
| Davies 2016a       | 15 (11, 20) | 7.02 |        |
| Davies 2016b       | 14 (10, 19) | 7.10 |        |
| Elwakeel 2013      | 12 (5, 26)  | 4.51 |        |
| Kakisis 2017       | 3 (1, 11)   | 7.04 |        |
| Kakkos 2011        | 2 (1, 7)    | 7.73 |        |
| Pham 2017          | 6 (2, 20)   | 5.21 |        |
| Sala-Amonacil 2011 | 10 (4, 23)  | 4.81 |        |
| Scarritt 2014a      | 9 (4, 17)   | 6.17 |        |
| Scarritt 2014b      | 23 (15, 35) | 4.42 |        |
| Schlid 2011        | 12 (5, 27)  | 4.08 |        |
| Shemesh 2015a      | 3 (1, 9)    | 7.47 |        |
| Shemesh 2015b      | 3 (1, 9)    | 7.47 |        |
| Tozzi 2014         | 0 (0, 11)   | 5.43 |        |
| Weale 2007         | 4 (2, 10)   | 7.34 |        |
| Overall (I^2 = 82.0%, p = 0.000) | 9 (6, 12) | 100.00 |
Figure 6. Sub-Group Meta-Analyses of Secondary Patency at 12 and 24 Months –