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LONG-TERM OUTCOMES AFTER ENDOVASCULAR STENT PLACEMENT FOR LONG-SEGMENT SUPERFICIAL FEMORAL ARTERY LESIONS

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Abstract

Objective: Endovascular intervention is commonly pursued as first-line management of symptomatic, long-segment superficial femoral artery (SFA) disease. The relative effectiveness and comparative long-term outcomes among bare metal stents (BMSs), covered stents (CSs), and drug-eluting stents (DESs) for long-segment SFA lesions remain uncertain.

Methods: A retrospective cohort study identified patients with symptomatic SFA lesions measuring at least 15cm who successfully received an endovascular stent (BMS, CS, or DES). The outcomes were patency, patient presentation upon stent occlusion, amputation-free survival (AFS), and all-cause mortality. Proportional hazards regressions and a multinomial logistic regression model were used to control for significant confounders.

Results: A total of 226 procedures were analyzed (BMS: 95 [42%]; CS: 74 [33%]; DES: 57 [25%]). There were no significant differences among the three stent types with respect to age,

prevalence of either diabetes or end-stage renal disease, or smoking history. The median length of the SFA lesion varied across the cohorts (BMS: 28cm (interquartile range [IQR] 20-30cm); CS: 26cm [IQR 20-30cm]; DES: 20cm [IQR 16-25cm]; P = .002). The unadjusted primary patency of BMSs at 12-, 24-, and 48-months following index stent placement was 57%, 47%, and 44%, respectively. This is compared to 62%, 49%, and 42% for CSs, and 81%, 66%, and 53% for DESs, respectively (log-rank P = .044). In adjusted models, however, there were no significant differences in primary patency among the stent types. Compared to CSs however, DESs were associated with improved primary-assisted patency (hazard ratio [HR] for patency loss: 0.35, P = .008) and secondary patency (HR: 0.32, P = .011). Across the entire follow-up period, stent occlusions occurred in 38 (40%) BMS cases, 42 (57%) CSs, and 11 (19%) DESs (P < .001). Of these, acute limb ischemia (ALI) occurred in 2 (5%) BMS cases, 14 (33%) CSs, and 1 (9%) DES (P = .010). After adjustment, the relative risk of presenting with ALI as opposed to claudication was 27 times greater among occluded covered stents compared to bare metal stents (P = .020). There were no significant differences in AFS or all-cause mortality across the three cohorts.

Conclusions: For long-segment SFA lesions, DESs are associated with improved primary-assisted and secondary patency over long-term follow-up. In the event of stent occlusion, covered stents confer an increased risk of acute ischemia.

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BACKGROUND

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Peripheral arterial disease

Peripheral arterial disease (PAD) is a chronic condition that significantly impedes adequate circulation to the lower extremities. Caused by atherosclerosis, common PAD risk factors include: age, race, smoking, diabetes, hyperlipidemia, hypertension, chronic renal insufficiency, and genetic factors.[1, 2] More recent literature has also implicated dietary composition, inflammatory states, infection, and environmental toxins in the pathogenesis of PAD.[3] This becomes increasingly important as PAD is recognized as a marker for systemic atherosclerosis and is a coronary artery disease risk equivalent among both men and women.[4]

Though the majority of lower extremity atherosclerotic disease is asymptomatic, clinical manifestations of PAD range from intermittent claudication, defined as reproducible lower extremity muscle discomfort on exertion that is relieved by rest[5], to chronic limb-threatening ischemia (CLTI), largely identified by the presence of ischemic rest pain and/or tissue loss (in the form of either ulceration or gangrene). The Society for Vascular Surgery has developed the Lower Extremity Threatened Limb Classification System in order to objectively stratify a given individual's risk of lower extremity amputation based on the presence of wounds, ischemia, and foot infection (WIfI).[6] The WIfI classification system has four clinical stages (stages 1-4), each associated with an increasing risk of limb loss. Considering that WIfI stage 4 is associated with a 23% one-year amputation rate[7], it is

imperative to accurately identify and characterize the severity of PAD in order provide therapy that maximizes an individual's functional outcome.

Treatment for PAD relies on both lifestyle modification (smoking cessation and a structured exercise regimen) as well as medical management of concomitant hypertension, hyperlipidemia, and hyperglycemia.[8] However, when a patient's symptoms significantly limit their daily activities or persist despite medical management, revascularization is often recommended.[1] This type of intervention, in turn, often requires treatment of the superficial femoral artery (SFA), the most commonly diseased artery in lower extremity PAD.[9, 10]

Review of relevant anatomy

The SFA is the primary artery supplying the lower extremity. It originates from the common femoral artery near the groin, traverses the length of the thigh, and crosses the adductor canal in the distal thigh before diving posteriorly and turning into the popliteal artery near the level of the knee (**Figure 1**). Since the popliteal artery subsequently goes on to supply the distal lower extremity by way of three runoff vessels, arterial flow through the SFA is critically important in the treatment of PAD.

The SFA's anatomic location predisposes it to unique physical forces that have direct implications on the durability of any operative intervention performed in the area. It is a long artery, measuring as long as 35-40cm in some individuals. This considerable length, coupled with a relatively high atherosclerotic disease burden undoubtedly poses unique challenges and complexities to potential PAD-related treatments.[10] Further, by traversing the thigh, the SFA is subject to external biomechanical forces (torsion, contraction/elongation,

compression, and flexion) applied by large muscle groups during most types of physical activity.[11] This physical complexity, in turn, demands attention when determining an optimal treatment strategy for a patient with symptomatic PAD of the lower extremity.

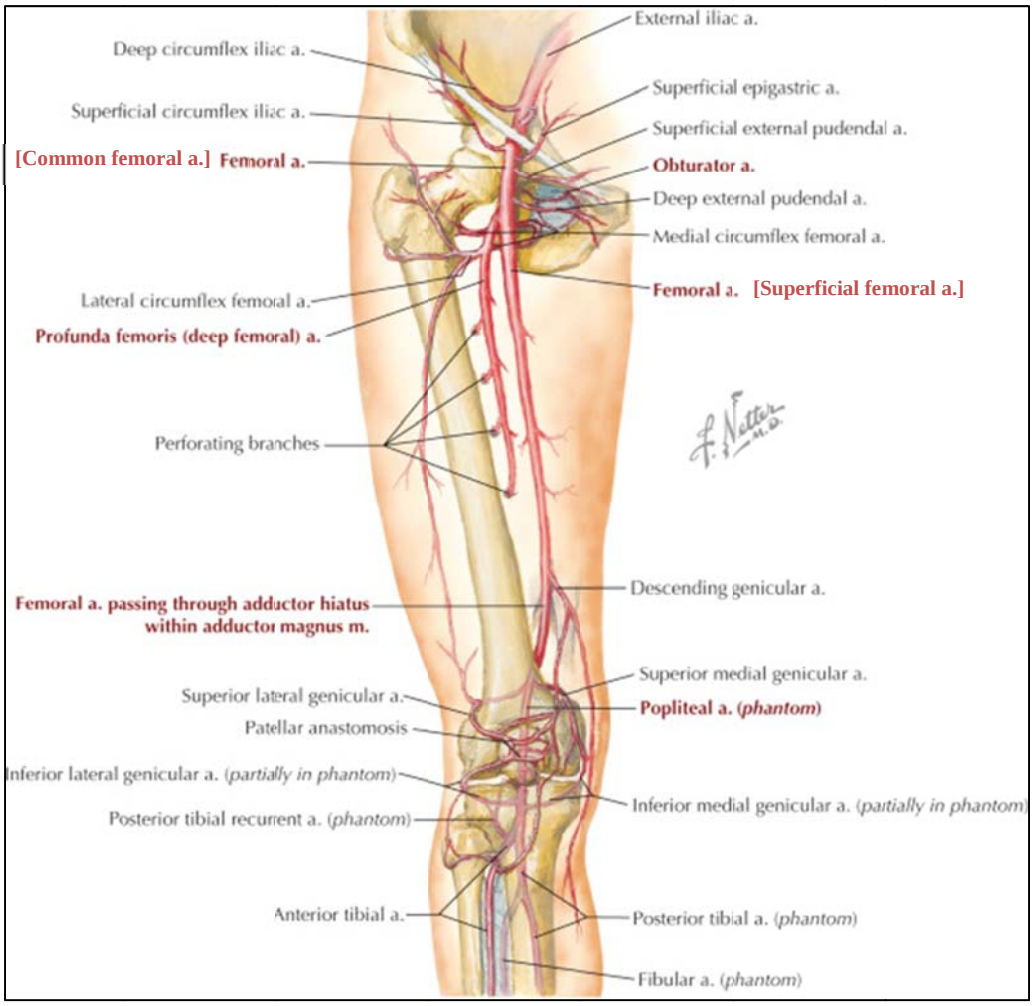


Figure 1. Anatomy of the superficial femoral artery, adapted from *Netter's Clinical Anatomy*.[12] The SFA courses along the medial thigh, originating from the common femoral artery near the groin, and terminating at the popliteal artery near the knee.

Traditional therapeutic approaches

Management of long-segment SFA lesions greater than 15cm in length has traditionally involved an open arterial bypass operation as indicated by consensus recommendations.[1] In such a procedure, a vein or prosthetic conduit is used to connect patent arterial segments above and below the SFA occlusion, thereby reestablishing in-line blood flow to the distal lower extremity. Though this continues to represent the current gold standard[10], the dramatic evolution of intraoperative imaging modalities and endovascular therapy over the last two decades has shifted practice to a minimally invasive, endovascular approach that confers less morbidity and faster recovery than open operations.[13, 14]

Endovascular stents and reported outcomes

Endovascular treatment modalities are vast and include numerous tools to treat atherosclerotic SFA lesions. These therapeutic options can largely be classified as: 1) percutaneous plain balloon angioplasty, or 2) angioplasty with additional scaffolding in the form of intraarterial endoprostheses (i.e., endovascular stents; **Figure 2**). Though effective for short, simple lesions, angioplasty has inferior patency rates when compared to stents for more complex disease patterns.[15] Therefore, primary endovascular stenting has become a preferred treatment for long SFA lesions.

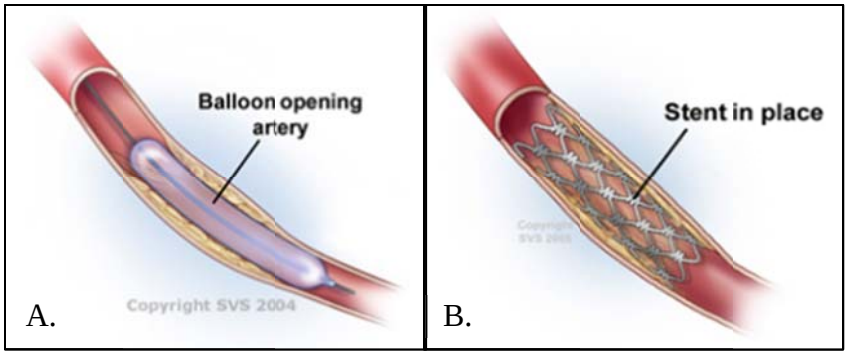


Figure 2. Endovascular treatment modalities for lower extremity peripheral arterial disease includes: (A) plain balloon angioplasty in which an endovascular balloon is used to open an atherosclerotic lesion, and (B) angioplasty accompanied by stent deployment in order to augment vessel patency[16].

Three stent types are currently used: 1) bare metal stents, 2) covered stents, and 3) bare metal drug-eluting stents (**Figure 3**). Bare metal stents first revolutionized the field of endovascular therapy by providing a more durable option than angioplasty alone for post-angioplasty residual stenosis greater than 50% of the vessel's diameter.[15] In current form, these devices are self-expanding nitinol stents that are flexible and attempt to provide sufficient radial strength to combat the dynamic biomechanical forces acting on the SFA. Even with these characteristics, however, reported 12-month primary patency rates vary greatly from 46% to 92% based on lesion length.[10, 17] From a pathophysiologic perspective, occlusion and failure of a bare metal stent is largely driven by intimal hyperplasia, an endothelial proliferative reaction that occurs throughout the stent's length.

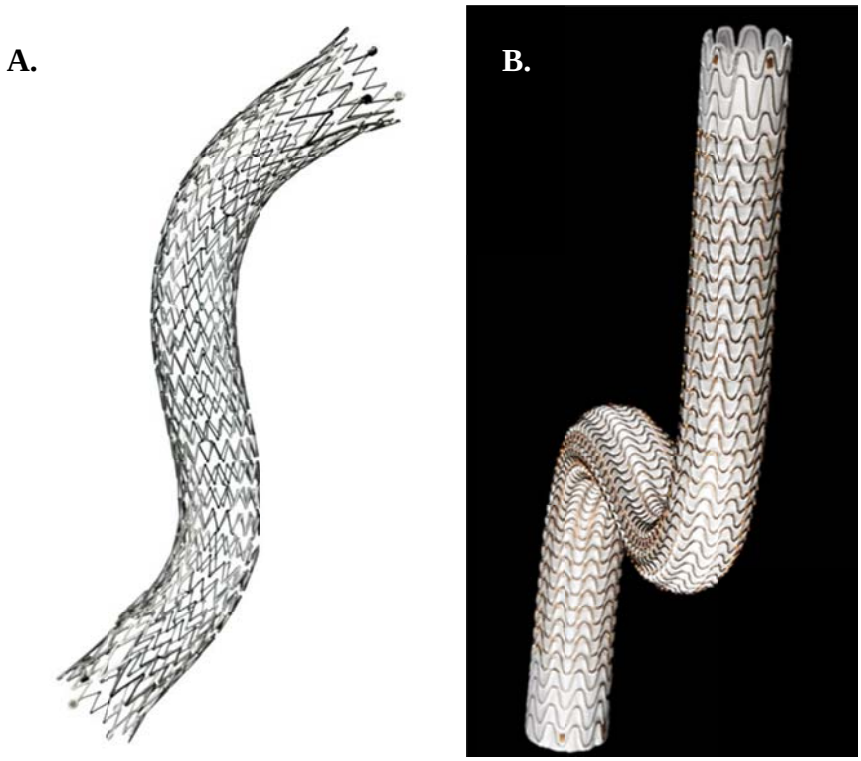


Figure 3. Among the different types of endovascular stents used in the treatment of peripheral arterial disease, (A) self-expanding nitinol bare metal stents were introduced first.[18] (B) Heparin-bonded covered stents use a prosthetic ePTFE lining along the luminal surface of the nitinol scaffolding aimed at preventing in-stent occlusion.[19] Drug-eluting stents closely resemble the bare metal stent pictured in (A) and are coated by an antiproliferative agent in further attempts to improve patency.

In an attempt to improve patency rates, covered stents were introduced. These devices are essentially the same self-expanding nitinol stents as described previously, but are covered on their luminal surface with heparin-bonded, expanded polytetrafluoroethylene (ePTFE), a prosthetic material that prevents hyperplasia-related in-stent occlusion. Several landmark trials have studied patency rates of covered stents with mixed results. To illustrate,

VIASTAR[20] reported a 12-month primary patency rate of 71% for covered stents used in long-segment SFA lesions, as compared to 37% for bare metal stents. Similarly, the multi-center, single-arm VIPER trial[21] reported primary patency rates as high as 88% when the covered stent was optimally sized. At 36-months post-intervention, however, VIBRANT[22] reported similar patency rates between covered and bare metal stents: 24% vs. 26%, respectively. As with bare metal stents, the mechanism of failure of covered stents remains intimal hyperplasia, but localized to the stent's edges. Therefore, even if covered stents do have improved short-term patency rates, any advantage seems to be extinguished within three years of stent placement.

With continued advancement of endovascular technology, yet another type of stent emerged in order to combat the risk of intimal hyperplasia-related in-stent occlusion. Drug-eluting stents attempt to use local concentrations of antiproliferative agents to maintain stent patency.[15] Until September 2018 there was only one FDA-approved drug-eluting stent available for use in the United States: the Zilver PTX stent (Cook Medical; Bloomington, IN), a self-expanding nitinol stent with a polymer-free paclitaxel coating.[23] Prospective comparisons of drug-eluting stents to plain balloon angioplasty revealed an improvement in five-year primary patency rates: 66% versus 43%, respectively.[24]

Reporting standards for stent patency

With the increase in the number of studies investigating stent patency, updated reporting standards for the endovascular treatment of PAD were published in 2016 by the Society for Vascular Surgery.[25] These standards used two factors in defining patency: 1) the

timing of re-intervention, and 2) whether the intervention was performed for in-stent occlusion (as opposed to stenosis). With these, three different types of patency were described:

- Primary patency – "the interval from the time of the original intervention until any intervention designed to maintain or re-establish patency is performed"
- Primary-assisted patency – "patency of the endovascular intervention achieved with the use of additional or secondary surgical or endovascular procedures, as long as occlusion of the primary treated site has not occurred"
- Secondary patency – "patency obtained with the use of an additional or secondary surgical or endovascular procedure after occlusion occurs."

Current limitations of the literature

Though there have been several prospective studies attempting to elucidate outcomes among these three stent types, significant gaps in the literature prevent direct comparability and broad generalization of the results. A significant limitation is the wide range of lesion lengths reported in these studies, with mean lesions measuring anywhere from 6.5cm among drug-eluting stents[26] to 19cm among covered stents.[20-22] As lesion length can confound the relationship between the type of stent used and its subsequent patency rate[13], this difference undoubtedly influences the interpretation of these results. Additionally, the variation in follow-up time raging anywhere from 12 months to 5 years serves as yet another barrier to the direct comparison of these stents. Taken together, though these stents are superior to

balloon angioplasty alone, the relative effectiveness and comparative outcomes among bare metal, covered, and drug-eluting stents, particularly in long-segment SFA lesions, continue to remain uncertain.

Public Health Significance

PAD is associated with significant morbidity and mortality burdens worldwide.[10] Nationally, more than 15 million people over the age of 40 are estimated to have PAD. With insurance claims data indicating an annual prevalence of 12% and an incidence of 3% [27], the management of PAD is estimated to cost between $200-400 billion per year.[14] Importantly, the prevalence of PAD increases with age, reaching nearly 23% among Americans greater than 80 years of age.[27] Considering that PAD is a coronary artery disease risk equivalent, it is not surprising that individuals with PAD also have a 2-3 times increased risk of all-cause mortality within three years of diagnosis.[28]

In addition to a significant risk of mortality, PAD similarly negatively impacts quality of life.[29] Surgical intervention is performed at an estimated rate of approximately 600 per 100,000 people[30], with intermittent claudication associated with a 1% per year risk of limb loss[1, 31] as compared to a substantially higher one-year amputation risk of 25% among CLTI patients.[1, 32] Most striking, however, is the nearly 50% one-year mortality rate among Medicaid PAD patients who undergo a major lower extremity amputation.[27] With such profoundly negative impacts on a substantial proportion of the population, identifying effective and durable treatment options for PAD is crucial for avoiding amputation, maintaining quality of life, and decreasing premature PAD-related deaths.

Specific Aims

The objective of this study was to identify pragmatic differences in clinically-relevant outcomes associated with the three primary stents types used in the treatment of long-segment, atherosclerotic, superficial femoral artery (SFA) disease. The central hypothesis was that drug-eluting stents will have superior patency and limb preservation rates when compared to bare metal and covered stents. The enduring goal of this study was to identify the optimal endovascular treatment modality for these complex SFA lesions in an attempt to minimize PAD-associated morbidity. To accomplish these goals and objectives, three specific aims were addressed:

Aim 1: To assess long-term primary patency rates among bare metal, covered, and drug-eluting stents used for SFA lesions measuring at least 15cm in length. We hypothesized that drug-eluting stents will have superior primary patency rates across long-term follow-up of at least 12 months in duration.

Aim 2: To assess long-term primary-assisted patency, secondary patency, amputation-free survival, and all-cause mortality rates among the three stent types. We hypothesized that drug-eluting stents will have greater primary-assisted and secondary patency when compared to bare metal and covered stents. We also hypothesized that there will be no significant difference in either amputation-free survival or all-cause mortality.

Aim 3: To assess differences in patient symptomatology in the event of stent occlusion. We hypothesized that covered stents are associated with a greater incidence of acute limb ischemia at the time of stent occlusion when compared to bare metal and drug-eluting stents.

METHODS

Study Design

A single-center, retrospective cohort study was conducted.

Study Setting

The setting for this study was the Michael E. DeBakey Veterans Affairs (VA) Medical Center in Houston, TX.

Study Subjects

Subjects were included in the study if they: 1) were an adult (at least 18 years of age); 2) had an endovascular stent successfully placed for a symptomatic, long-segment, atherosclerotic SFA lesion measuring at least 15cm in length, with technical success defined as residual stenosis of less than 30% on completion angiography; and 3) had the index stent placed between May 2008 and December 2017. Of note, “symptomatic” was defined as a preoperative indication of intermittent claudication, ischemic rest pain, and/or tissue loss, with or without concomitant infection.

Patients were excluded from the study if they: 1) underwent an index operation for a target lesion in a vessel other than the SFA; 2) required a concomitant open arterial bypass to address the index SFA lesion; 3) did not attain intraoperative restoration of arterial flow across the target lesion as evident on completion angiogram; or 4) were pregnant at the time of operative intervention. Patients were also excluded if the stented arterial segment crossed the patella and terminated in the below-knee popliteal artery.

Data Collection

Data was collected exclusively through electronic medical review and data abstraction. Prospective data was not collected, no biological specimens were obtained, and no patients were contacted for this retrospective cohort study.

The exposure of interest was the type of stent used to treat the long-segment SFA lesion: bare metal, covered, or drug-eluting. The primary outcome of interest was primary patency. Secondary outcomes of interest included: primary-assisted patency, secondary patency, interventions required to maintain patency, patient symptomatology in the event of stent occlusion, amputation-free survival (defined as survival without a major lower extremity amputation proximal to the ankle), and all-cause mortality. Stent occlusion was primarily determined by duplex ultrasonography, computed tomography scan, or angiography showing no flow through the stent. Patency was determined based on definitions provided by the Society for Vascular Surgery reporting standards.[25] Additionally, baseline data on the following pre-operative confounders was collected within six months of stent placement: demographics, comorbidities, medication use, and smoking history (specific variables are included in **Table I** and **Table II**).

Data Handling

All data collected through electronic medical review and data abstraction were protected by robust firewalls and institutional computers. Additionally, the data folders further restricted access to those that were cleared to view the data (i.e., the principal investigator and research staff).

Data Analysis

Continuous variable distributions were visualized and assessed for normality. Descriptive statistics among the three cohorts (bare metal, covered, and drug-eluting stents) were presented and compared using either analysis of variance (ANOVA) or the non-parametric Kruskal-Wallis test. A Bonferroni correction was applied when assessing pairwise comparisons among the three cohorts. Proportions for categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Kaplan-Meier survival estimates were used to assess unadjusted patency rates (including primary, primary-assisted, and secondary patency) and amputation-free survival. Cox proportional hazards regression models were used to control for clinically and statistically significant confounders. An adjusted multinomial logistic regression model was also used to assess patient symptomatology in the event of stent occlusion. Statistical significance was set at a two-sided alpha of 0.05. All statistical analyses were performed using Stata 14.0 (StataCorp; College Station, TX).

Human Subjects and Safety Considerations

This study was approved by the Baylor College of Medicine Institutional Review Board as well as the VA Research and Development Committee. As requested by the UTHealth Committee for Protection of Human Subjects, a SMART IRB reliance agreement was also established between Baylor College of Medicine (the lead site) and UTHealth.

JOURNAL ARTICLE

Long-Term Outcomes after Endovascular Stent Placement for Long-Segment Superficial Femoral Artery Lesions

Journal of Vascular Surgery

INTRODUCTION

Complex, long-segment atherosclerotic disease of the superficial femoral artery (SFA) is a persistently challenging clinical dilemma.[1] Based on consensus recommendations, this pattern of disease has traditionally been managed by surgical revascularization.[2] Currently, however, with the continued evolution of therapeutic capabilities, an endovascular approach is frequently pursued even for complex femoropopliteal disease.[3]

In the setting of this increased technical feasibility, there is relatively limited data on outcomes following primary stent placement for long-segment SFA disease, and there is even less data available that directly compares the different types of stents routinely used for this indication.[4, 5] Since the sustained durability of plain balloon angioplasty is limited in complex lesions[5, 6], addressing this gap in the literature will assist in defining the specific role endovascular stents have in managing long-segment SFA disease.

The objective of this study was to assess the comparative effects of bare metal, covered, and drug-eluting stents on clinical outcomes for the treatment of long-segment SFA disease.

METHODS

Patient population and eligibility. A single-center, retrospective cohort study was performed. Adult patients at the Michael E. DeBakey VA Medical Center were included in the study if they successfully received an endovascular SFA stent for an atherosclerotic segment measuring at least 15cm in length between May 2008 and December 2017. Technical success was defined as reestablishment of SFA patency with flow across the target lesion with less than 30% residual stenosis on completion angiography.[7] Cases were excluded if the stented segment traversed the level of the patella and terminated in the below-knee popliteal artery. This study was approved by the Veterans Affairs Research and Development Committee as well as the Baylor College of Medicine Institutional Review Board.

Exposure of interest. The cases were categorized based on the type of index stent used to treat the lesion: 1) self-expanding nitinol bare metal stents (BMSs), 2) covered stents (CSs), or 3) drug-eluting stents (DESs). When deploying a CS across a lesion, care was taken to preserve collateral vessels measuring more than 3mm in diameter[8], and oversizing the stent was avoided.[9, 10] The CSs were self-expanding nitinol stents covered on their luminal surface with heparin-bonded, expanded polytetrafluoroethylene (GORE VIABAHN Endoprosthesis; W. L. Gore and Associates, Inc.; Flagstaff, AZ). The DESs were self-expanding nitinol stents with a polymer-free paclitaxel coating (Zilver PTX; Cook Medical; Bloomington, IN).

Outcomes. The primary outcome was primary patency. Restenosis and occlusion were largely documented by duplex ultrasonography, computed tomography scan, or digital subtraction angiography. Secondary outcomes included: primary-assisted patency, secondary patency, target lesion revascularization (TLR; defined by the first endovascular or open reintervention on the target lesion), acuity of patient presentation in the event of stent occlusion, amputation-free survival (AFS; defined as postoperative survival without a major lower extremity amputation proximal to the ankle), and all-cause mortality. AFS was restricted to patients who initially presented with chronic limb-threatening ischemia (CLTI, defined as ischemic rest pain or tissue loss). Patency and TLR were defined in accordance with the Society for Vascular Surgery reporting standards[7], with estimates over time reported among the entire cohort starting at the time of stent placement.[9, 11]

Confounding variables. Demographic data, preoperative comorbidities, and relevant perioperative factors were collected. Specifically, models controlled for SFA lesion length, runoff, CLTI on initial presentation, diabetes, end-stage renal disease, smoking history, serum albumin, relevant medication use (aspirin, statin, clopidogrel), sex, and age[8, 12-14]. Analyses of outcomes related to mortality were additionally adjusted for clinically relevant comorbidities presented in **Table 1**.

Statistical analysis. Continuous variable distributions were visualized and assessed for normality. Descriptive statistics among the three cohorts were compared using either analysis of variance (ANOVA) or the non-parametric Kruskal-Wallis test for continuous variables. A

Bonferroni correction was applied when assessing pairwise comparisons among the three cohorts. Proportions for categorical variables were compared using Pearson's chi-squared test or Fisher's exact test. Kaplan-Meier survival estimates were used for time-to-event analyses, and unadjusted differences between groups were tested using the log-rank test. Multivariable Cox proportional hazards regressions were used to control for clinically and statistically significant confounders. For outcomes related to patency, hazard ratios were obtained that reflected the adjusted association between stent type and loss of patency. An adjusted multinomial logistic regression model was used to assess patient presentation in the event of stent occlusion. Statistical significance was set at a two-sided alpha of 0.05. All statistical analyses were performed using Stata 14.0 (StataCorp; College Station, TX).

RESULTS

Descriptive characteristics. A total of 205 patients accounted for 226 SFA lesions that were included in the analysis. 95 (42%) lesions were treated with BMSs, 74 (33%) with CSs, and 57 (25%) with DESs. The cohort treated with DESs had a comparatively lower proportion of men (P = .015), a greater prevalence of stroke (P = .007), and a lower serum albumin level (P = .010). There were no significant differences across cohorts in mean age, prevalence of either diabetes or end-stage renal disease, or smoking history. *De novo* atherosclerotic lesions comprised the vast majority of the lesions treated across all cohorts (BMS: 93 [98%], CS: 66 [89%], DES: 51 [90%], P = .107). Descriptive characteristics of the three cohorts are presented in **Table I**.

A greater proportion of DESs were placed for an indication of CLTI (BMS: 39%, CS: 31%, DES: 67%, P < .001), and the three cohorts varied with respect to the distribution of runoff vessels (P = .014). The median lesion length treated in this analysis was 25cm, but when compared across cohorts, there were differences present in both lesion length (P = .002) and follow-up times (P < .001). During index stent placement, coexisting iliac lesions were treated endovascularly in 10 (11%) BMS cases, 10 CS cases (14%), and 9 (16%) DES cases (P = .629). Common femoral artery endarterectomy was performed concomitantly in three (4%) CS cases, and in three (5%) DES cases. Perioperative details are presented in **Table II**.

Patency. A total of 113 (50%) cases maintained primary patency over the course of the study (BMS: 44 [46%], CS: 28 [38%], DES: 41 [72%], P < .001; **Table III**). The unadjusted

Kaplan-Meier estimates for primary patency at 12-, 24-, and 48-months were 57%, 47%, and 44% for the BMS cohort; 62%, 49%, 42% for CSs; and 81%, 66%, 53% for DESs, respectively (P = .044; **Figure 1**). In the adjusted model, there was no statistical association between stent type and primary patency (**Table IV**).

The unadjusted 12-, 24-, and 48-month Kaplan-Meier estimates for primary-assisted patency were 68%, 63%, and 60% for BMSs; 67%, 51%, and 45% for CSs; and 89%, 79%, and 60% for DESs, respectively (P = .004; **Supplemental Figure 1**). The corresponding estimates for secondary patency were 74%, 69%, and 66% for BMSs; 75%, 59%, and 51% for CSs; and 89%, 81%, and 74% for DESs (P = .011; **Supplemental Figure 2**). After adjustment, DESs had a significantly improved primary-assisted patency (HR for patency loss: 0.35, P = .008) and secondary patency (HR for patency loss: 0.32, P=.011; **Table IV**) compared to CSs.

Target lesion revascularization. Across the study's follow-up, a total of 83 (**Table III**) stented lesions collectively required 84 endovascular (BMS: 31/84 [37%], CS: 42/84 [50%], DES: 11/84 [13%]) and 39 open (BMS: 14/39 [36%], CS: 23/39 [59%], DES: 2/39 [5%]) revascularization attempts. The vast majority of both endovascular (76/84 [90%]) and open (32/39 [82%]) reinterventions occurred within 18 months of initial stent placement.

The unadjusted Kaplan-Meier estimates for freedom from TLR at 12-, 24-, and 48-months were 72%, 64%, and 61% for BMSs; 71%, 59%, and 54% for CSs; 87%, 77%, and 64% for

DESs, respectively (P = .042; **Supplemental Figure 3**). After adjustment, however, there was no significant association between stent type and TLR (**Table IV**).

Presentation upon stent occlusion. Stent occlusions occurred in 38 (40%) lesions treated with BMSs, 42 (57%) CSs, and 11 (19%) DESs (P < .001). Details of patient presentation at the time of stent occlusion are presented in **Table III**. In particular, the unadjusted rate of ALI was significantly different among the stent types (BMS: 5%, CS: 33%, DES: 9%; P = .010). Among the cases with ALI, eight (47%) required an open arterial bypass of the target lestion, all of whom were in patients initially treated with CSs. Additionally, eight (47%) individuals who developed ALI subsequently required a major lower extremity amputation, with six (75%) of these amputations in patients with CSs. After adjustment, the relative risk (RR) of presenting with ALI as opposed to claudication was 27 times greater among occluded covered stents compared to bare metal stents (P = .020; **Table V**). Compared to other stents, DESs were not associated with a significantly increased risk of either ALI or ischemic rest pain/tissue loss in the event of stent occlusion.

Amputation-free survival. Among patients with an operative indication of CLTI, there was a total of 18 (18%) major lower extremity amputations (**Table III**). The unadjusted 12-, 24-, and 48-month Kaplan-Meier estimates for AFS were 58%, 47%, and 44% for BMSs; 83%, 69%, and 34% for CSs; and 70%, 70%, and 59% for DESs, respectively (P = .528; **Figure 2**).

In the adjusted model, there were no associations between stent type and AFS in patients with CLTI (**Table IV**).

Of the 128 SFA lesions treated in patients with claudication, there were a total of seven (5.5%) major lower extremity amputations, all of which occurred in the CS cohort. Further, with respect to the timing of limb loss, four of these seven (57%) amputations occurred more than 12 months after the SFA was initially stented.

All-cause mortality. Among all patients, 42 (46%) individuals with BMSs, 30 (43%) with CSs, and 10 (19%) with DESs (P = .003; **Table III**) died during the follow-up period. The unadjusted Kaplan-Meier survival estimates at 12-, 24-, and 48-months were 90%, 80%, and 77% for BMSs; 94%, 87%, and 72% for CSs; and 85%, 85%, and 77% for DESs, respectively (P = .999; **Figure 3**). After adjustment, there was no significant association between the stent type and all-cause mortality (**Table IV**). This association was further maintained when DESs were compared to all other stents collectively (HR 0.57, 95% CI 0.25-1.34, P = .199).

DISCUSSION

In this study, we directly compared the long-term outcomes of bare metal, covered, and drug-eluting stents in the treatment of symptomatic, long-segment SFA lesions measuring at least 15cm in length. After robust adjustment for clinically and statistically significant confounders, our results did not identify a significant difference among these stent types with respect to long-term primary patency, TLR, or all-cause mortality when used to treat complex SFA disease. DESs appear to have improved primary-assisted and secondary patency across long-term follow-up, and though there is not a difference among the stents with respect to amputation-free survival, occlusion of covered stents is associated with a significantly increased risk of acute ischemia relative to bare metal stents.

Despite landmark trials studying these outcomes, considerable gaps in the literature prevent direct comparison and generalization of the results to long SFA lesions. A significant limitation is the wide range of lesion lengths reported in these studies, with mean lesions measuring anywhere from 6.5cm among drug-eluting stents[13] to 19cm among covered stents.[4, 5, 9] Since the cumulative length of the index lesion can influence relevant outcomes[14], this difference undoubtedly impacts the interpretation of these studies relative to one another. Additionally, the variation in preoperative symptoms, study design, eligibility criteria, outcome definitions, and reported follow-up all serve as additional barriers to the direct comparison of these results.[6, 15] Our analysis attempts to provide a head-to-head assessment among these widely used endovascular prostheses, thereby helping to define the pragmatic role of these stents when specifically used in long-segment SFA lesions.

The unadjusted 12-month primary patency estimates for BMSs, CSs, and DESs in this analysis were 57%, 62%, and 81%, respectively. When compared to the available literature that either exclusively investigates long-segment SFA disease or provides sub-group analysis of complex lesions, 12-month primary patency for these stents ranges from 37-83% for BMSs[5, 16], is reported to be 71% for CSs[5], and ranges from 53-78% for DESs.[17, 18] Though our observed primary patency for CSs appears to be lower than that in the literature (62% vs. 71%)[5], it actually compares favorably to a 12-month primary patency of 53% reported in the VIBRANT trial which included lesions with a mean length of 18cm.

After adjustment for relevant confounders, there was no statistically significant difference in primary patency rates among the three stent types included in this analysis. In contrast, DESs appear to provide an improvement in primary-assisted and secondary patency when compared to CSs in our study. Interestingly, this association with secondary patency is not readily evident from the literature if only assessing 12-month Kaplan-Meier estimates which actually suggest the opposite: higher patency rates in CSs (90-92%[5, 9]) compared to DESs (80-88%[17, 19]). Not only does this underscore the advantage of direct comparison for these stents, but it also highlights the role of appropriate risk adjustment when interpreting patency rates over time.

In this study, we present Kaplan-Meier estimates through four years of follow-up for DESs and five years for BMSs and CSs. Based on these rates and corresponding confidence

intervals, patency generally appears relatively stable beyond 18 months after SFA stenting. Among DESs used to treat shorter lesions, similar trends are reported in the literature for primary patency over a five-year follow-up period.[20] Though this has also been implied for long-segment lesions, patency for complex disease patterns beyond 24 months is infrequently reported.[4, 16] Considering that the vast majority of the reinterventions in this study correspondingly occurred within the first 1-2 years, these findings underscore the importance of routine follow-up during the first 18 months after a complex SFA lesion is treated.[2]

In the event of stent occlusion, those treated with covered stents were significantly more likely to present with ALI as opposed to claudication when compared to bare metal stents. This was true even after adjustment for baseline comorbidities, medications, lesion length, runoff, and preoperative CLTI. These findings support similar observations reported by others, [12, 21, 22] and may be due to the mechanism by which stents fail. In the case of BMSs, for example, in-stent restenosis occurs gradually as a result of neointimal hyperplasia throughout the length of the stent.[4, 5, 23] In CSs, however, this proliferative reaction is located at the stent's edges, a physiological consideration that can cause thrombosis of the stent graft over a relatively short period of time, resulting in an acute presentation.[24, 25]

In randomized controlled trials, no differences were noted in amputation rates between BMSs and either CSs or DESs.[4, 5, 13] Similarly, we did not observe a difference in either unadjusted or adjusted amputation-free survival estimates among patients with CLTI. With respect to mortality, however, meta-analytic pooled data (n = 4432 cases; 11% with CLTI) indicates

that five-year all-cause death is significantly increased in patients treated with paclitaxel-coated devices (including both balloons and stents).[26] Another nationwide analysis of claims data (n = 16,560; 51% CLTI), however, shows no association between paclitaxel-coated devices and all-cause mortality.[27] Though our multivariable analysis (which controlled for comorbidities, medications, and initial presentation) did not reveal a difference in all-cause mortality in this particular patient population with long SFA lesions, dedicated investigation is necessary in order to accurately assess long-term survival.

The limitations of this study must also be considered. Compared to the other stent types, the DES cohort had a smaller sample size with shorter follow-up. Though this is expected given that DESs are a relatively newer technology, this inherently decreases the relative accuracy of the cohort's long-term outcome estimates. This is most evident in our analyses of AFS as restricted to patients with CLTI, and clinical presentation in the event of stent occlusion. This may have additionally prevented us from identifying a significant difference in primary patency across the cohorts. Additionally, with three exposure groups and the absence of prospective randomization, there were statistically significant baseline and perioperative differences among the cohorts. Even with robust risk adjustment that accounted for not only these differences, but other clinically relevant confounders as well, the retrospective nature of the study still imparts the possibility of residual confounding. Further, given our patient population, these results are not directly generalizable to women.

CONCLUSION

For long-segment SFA lesions treated with endovascular stents, drug-eluting stents appear to have improved primary-assisted and secondary patency rates as compared to covered stents. The majority of open and endovascular reinterventions occur within 18 months after stent placement, which warrants routine follow-up during this time period. Though there is no difference in amputation-free survival among patients with preoperative CLTI, covered stents have an increased risk of presenting with acute limb ischemia in the event of stent occlusion, an association that can influence decision-making algorithms and patient counseling.

Tables

Table I. Descriptive characteristics and comorbidities of cases included in the study

Variable	Overall (N=226)	Bare Metal (n=95)	Covered (n=74)	Drug-Eluting (n=57)	P-value
Age, years (mean, SD)	65.0 (7.1)	65.4 (7.7)	64.0 (6.2)	65.8 (6.9)	.277
Male	221 (97.8)	94 (99.0)	74 (100)	53 (93.0)	**.015**
Race/ethnicity					
Caucasian	143 (63.3)	56 (59.0)	54 (73.0)	33 (57.9)	.125
African American	59 (26.1)	31 (32.6)	13 (17.6)	15 (26.3)	
Other*	24 (10.6)	8 (8.4)	7 (9.5)	9 (15.8)	
BMI, kg/m^2 (mean, SD)	28.2 (5.1)	27.7 (4.7)	29.0 (5.4)	28.1 (5.2)	.279
Hypertension	207 (91.6)	84 (88.4)	70 (94.6)	53 (93.0)	.325
Hyperlipidemia	175 (77.4)	72 (75.8)	59 (79.7)	44 (77.2)	.830
CAD	109 (48.2)	40 (42.1)	38 (51.4)	31 (54.4)	.275
CHF	36 (15.9)	17 (17.9)	10 (13.5)	9 (15.8)	.742
Myocardial infarction	37 (16.4)	19 (20.0)	13 (17.6)	5 (8.8)	.183
CVA	23 (10.2)	7 (7.4)	4 (5.4)	12 (21.1)	**.007**
Diabetes	123 (54.4)	56 (59.0)	33 (44.6)	34 (59.7)	.117
Current smoking	112 (49.6)	45 (47.4)	42 (56.8)	25 (43.9)	.293
Past smoking	83 (36.7)	42 (44.2)	25 (33.8)	16 (28.1)	.111
COPD	33 (14.6)	15 (15.8)	10 (13.5)	8 (14.0)	.908
ESRD	3 (1.3)	2 (2.1)	0	1 (1.8)	.480
Albumin, g/dL (median, IQR)	3.7 (3.3-3.9)	3.7 (3.3-3.9)	3.7 (3.5-4.0)	3.5 (2.9-3.8)	**.010**
Preoperative medications					
Statin	168 (74.3)	79 (83.2)	47 (63.5)	42 (73.7)	**.015**
Aspirin	149 (65.9)	69 (72.6)	44 (59.5)	36 (63.2)	.176
Clopidogrel	70 (31.0)	22 (23.2)	25 (33.8)	23 (40.4)	.070
Warfarin	9 (4.0)	5 (5.3)	3 (4.1)	1 (1.8)	.626

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident;

ESRD, end-stage renal disease; IQR, interquartile range; SD, standard deviation

Note: Unless otherwise specified, variables are presented as n (%)

*Includes those categorized as Hispanic or Native American

Table II. Perioperative characteristics of cases included in the study

Variables	Overall (N=226)	Bare Metal (n=95)	Covered (n=74)	Drug-Eluting (n=57)	P-value
Indication					
Claudication	128 (56.6)	58 (61.1)	51 (68.9)	19 (33.3)	
Rest pain	24 (10.6)	3 (3.2)	9 (12.2)	12 (21.1)	**<.001**
Tissue loss	74 (32.7)	34 (35.8)	14 (18.9)	26 (45.6)	
ABI (mean, SD)	0.64 (0.22)	0.66 (0.19)	0.65 (0.25)	0.58 (0.22)	.146
Toe pressure, mmHg (mean, SD)	45.6 (26.2)	47.3 (23.5)	50.5 (28.8)	36.1 (24.3)	**.015**
WIfI Stage					
Stage 1	77 (37.8)	31 (36.5)	29 (43.3)	17 (32.7)	
Stage 2	82 (40.2)	33 (38.8)	31 (46.3)	18 (34.6)	.135
Stage 3	27 (13.2)	13 (15.3)	5 (7.5)	9 (17.3)	
Stage 4	18 (8.8)	8 (9.4)	2 (3.0)	8 (15.4)	
Runoff vessels					
1	82 (36.3)	40 (42.1)	16 (21.6)	26 (45.6)	
2	83 (36.7)	31 (32.6)	37 (50.0)	15 (26.3)	**.014**
3	59 (26.1)	23 (24.2)	20 (27.0)	16 (28.1)	
Lesion length, cm (Median, IQR)	25 (20-30)	28 (20-30)	26 (20-30)	20 (16-25)	**.002**
Number of stents (Mean, SD)	3.2 (1.1)	3.0 (1.1)	3.1 (0.9)	3.4 (1.1)	.125
Stent diameter, mm (Median, IQR)	6.0 (6.0-6.6)	6.4 (6.0-6.8)	5.8 (5.6-6.0)	6.2 (6.0-6.5)	**<.001**
Operative time, hr (Median, IQR)	1.9 (1.4-2.3)	1.7 (1.3-2.2)	1.9 (1.4-2.4)	2.0 (1.7-2.4)	**.007**
Operative EBL, mL (Median, IQR)	25 (20-30)	25 (20-30)	25 (20-50)	20 (20-35)	.099
LOS, days (Median, IQR)	1 (0-1)	0 (0-1)	1 (0-1)	1 (0-3)	**.005**
Follow-up time, mo (Median, IQR)	55 (20-88)	67 (43-88)	82 (37-107)	20 (13-32)	**<.001**

Abbreviations: ABI, ankle-brachial index; EBL, estimated blood loss; hr, hours;

IQR, interquartile range; LOS, hospital length of stay; mo, months; SD, standard deviation; WIfI, wound, ischemia, foot infection classification

Note: Unless otherwise specified, variables are presented as n (%)

Missing observations: 22 missing observations in the WIfI Stage variable

Table III. Unadjusted event rates for postoperative outcomes across the entire follow-up period

Outcome	Overall (N=226)	Bare Metal (n=95)	Covered (n=74)	Drug-Eluting (n=57)	P-value
Patency					
Primary	113 (50.0)	44 (46.3)	28 (37.8)	41 (71.9)	**<.001**
Primary-assisted	135 (59.7)	57 (60.0)	32 (43.2)	46 (80.7)	**<.001**
Secondary	147 (65.0)	62 (65.3)	37 (50.0)	48 (84.2)	**<.001**
Target lesion revascularization	83 (36.7)	35 (36.8)	37 (50.0)	11(19.3)	**.001**
Symptom at stent occlusion[2]					
Claudication	38/91 (41.8)	16/38 (42.1)	18/42 (42.9)	4/11 (36.4)	
Rest pain or Tissue loss	34/91 (37.4)	18/38 (47.4)	10/42 (23.8)	6/11 (54.5)	**.010**
ALI	17/91 (18.7)	2/38 (5.3)	14/42 (33.3)	1/11 (9.1)	
Major amputation[3]	18/98 (18.4)	11/37 (29.7)	2/23 (8.7)	5/38 (13.2)	.070
All-cause mortality[4]	82/205 (40.0)	42/91 (46.2)	30/70 (42.9)	10/53 (18.9)	**.003**

Abbreviations: ALI, acute limb ischemia

[1]Event rates related to patency reflect the number of cases that maintained patency throughout the entire follow-up period.

[2]Describes acuity of patient presentation in the event of stent occlusion. The denominators represent the total number of stent occlusions over the entire follow-up period. Two individuals with bare metal stents were asymptomatic at the time of stent occlusion, identified during noninvasive ultrasound surveillance.

[3]Major amputations restricted to patients with a preoperative indication of CLTI.

[4]All-cause mortality reported with respect to the number of patients, as opposed to the number of cases.

Table IV. Adjusted associations between stent type and postoperative long-term outcomes

Outcome	CS compared to BMS*			DES compared to BMS*			DES compared to CS*		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Loss of patency[1]									
Primary patency	1.04	0.66-1.64	.849	0.57	0.29-1.12	.102	0.54	0.28-1.05	.071
Primary-assisted patency	1.53	0.92-2.53	.100	0.54	0.24-1.21	.133	0.35	0.16-0.76	**.008**
Secondary patency	1.53	0.88-2.65	.128	0.49	0.20-1.21	.122	0.32	0.13-0.77	**.011**
Target lesion revascularization	1.41	0.84-2.35	.195	0.89	0.40-1.96	.772	0.63	0.30-1.34	.233
Amputation-free survival[2]	0.64	0.24-1.73	.378	0.49	0.19-1.27	.141	0.76	0.23-2.52	.657
All-cause mortality	1.11	0.53-2.33	.782	0.60	0.24-1.50	.274	0.54	0.21-1.39	.201

*Denotes the reference stent type

[1]Hazard ratios for patency reflect the associations between stent type and the loss of patency over time.

[2]Amputation-free survival restricted to patients with a preoperative indication of CLTI. Hazard ratios reflect the association between stent type and having a major amputation or dying over time.

Table V. Adjusted association between stent type and patient presentation in the event of stent occlusion

Clinical Presentation	CS compared to BMS*			DES compared to BMS*			DES compared to CS*		
	RRR	**95% CI**	**P-value**	**RRR**	**95% CI**	**P-value**	**RRR**	**95% CI**	**P-value**
Claudication	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Rest pain or tissue loss	0.64	0.14-2.89	.558	0.56	0.07-4.42	.578	0.87	0.09-8.33	.906
ALI	26.6	1.67-423.0	**.020**	13.3	0.17-1020	.243	0.50	0.02-15.5	.692

*Denotes the reference stent type

Figures

Figure 1. Unadjusted Kaplan-Meier estimates for primary patency by stent type

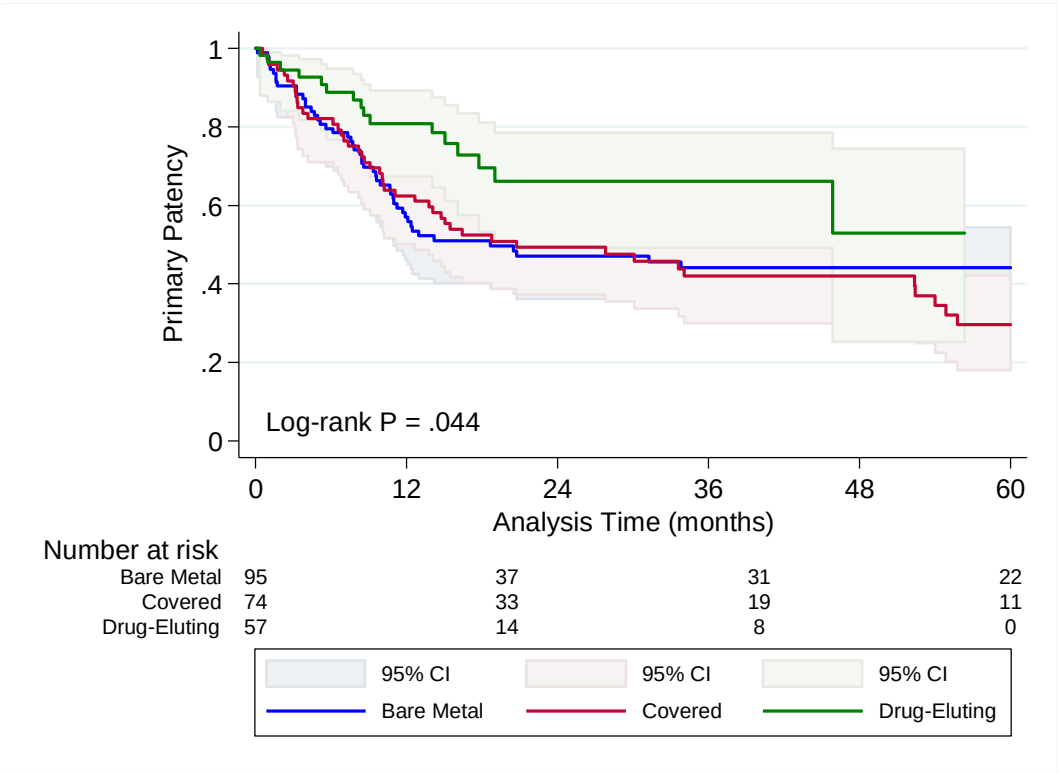


Figure 2. Unadjusted Kaplan-Meier estimates for amputation-free survival by stent type, restricted to patients initially presenting with CLTI

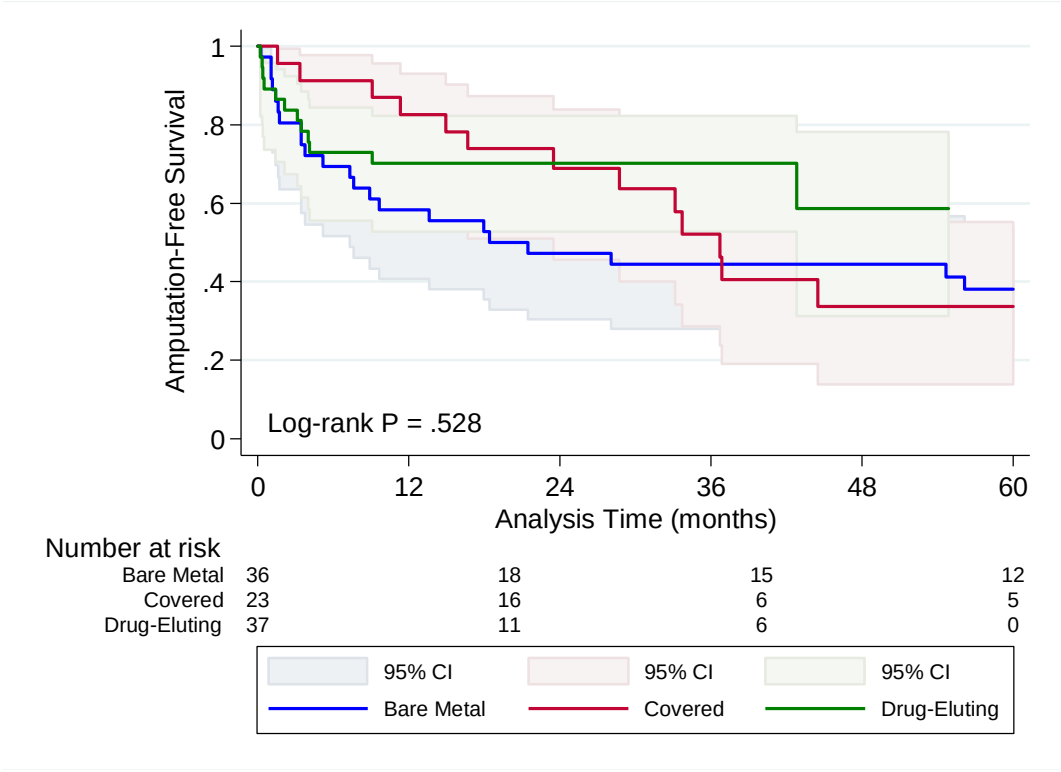
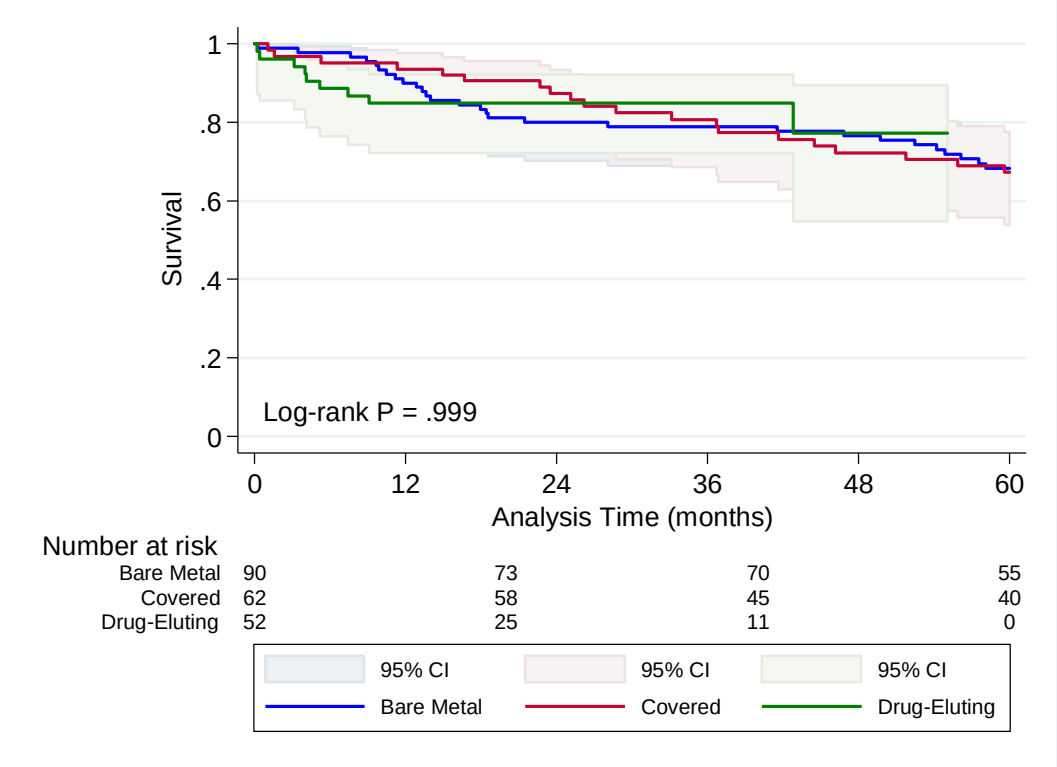
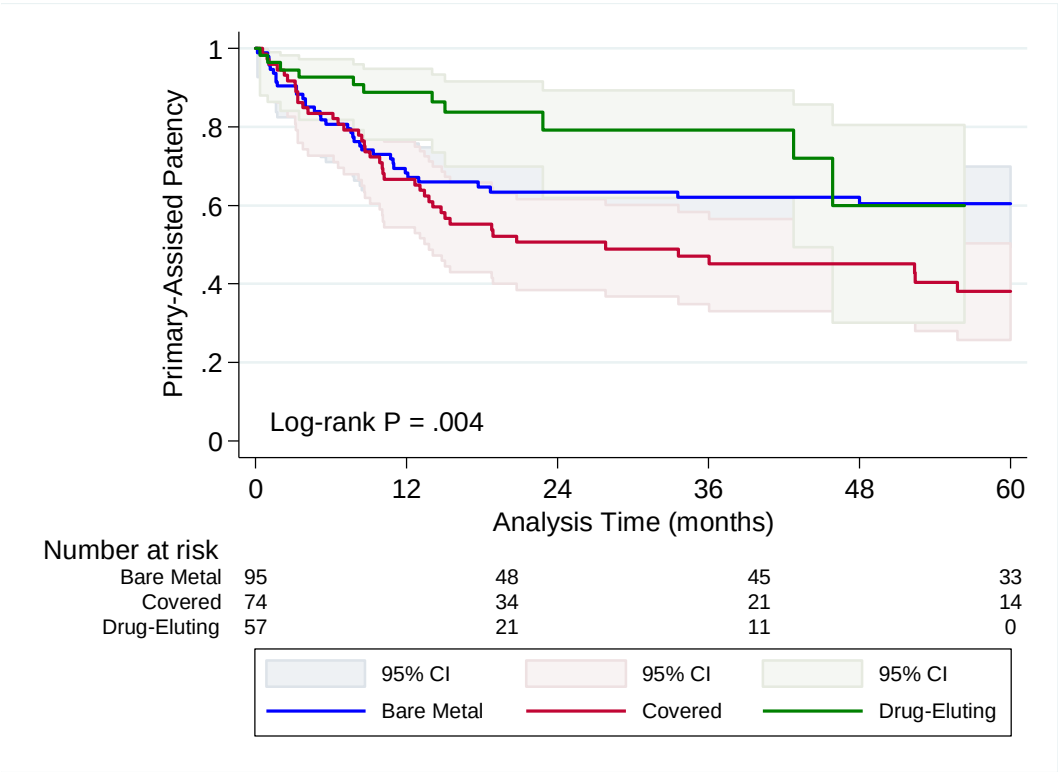


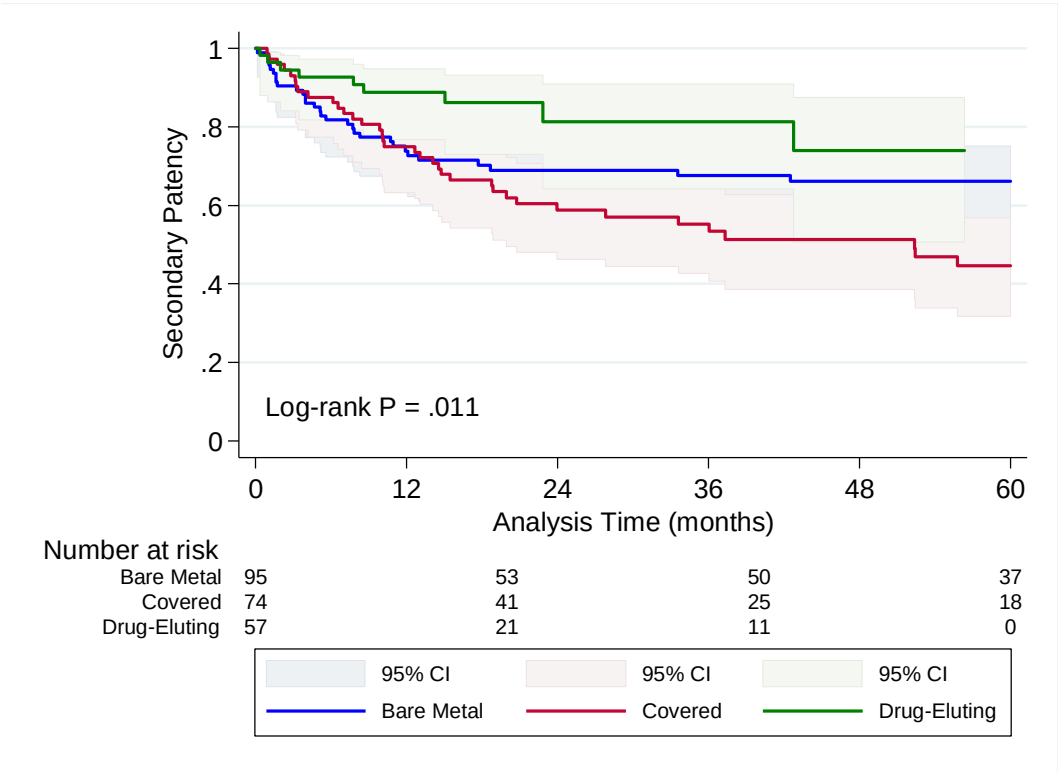
Figure 3. Unadjusted Kaplan-Meier survival estimates by stent type among the entire cohort



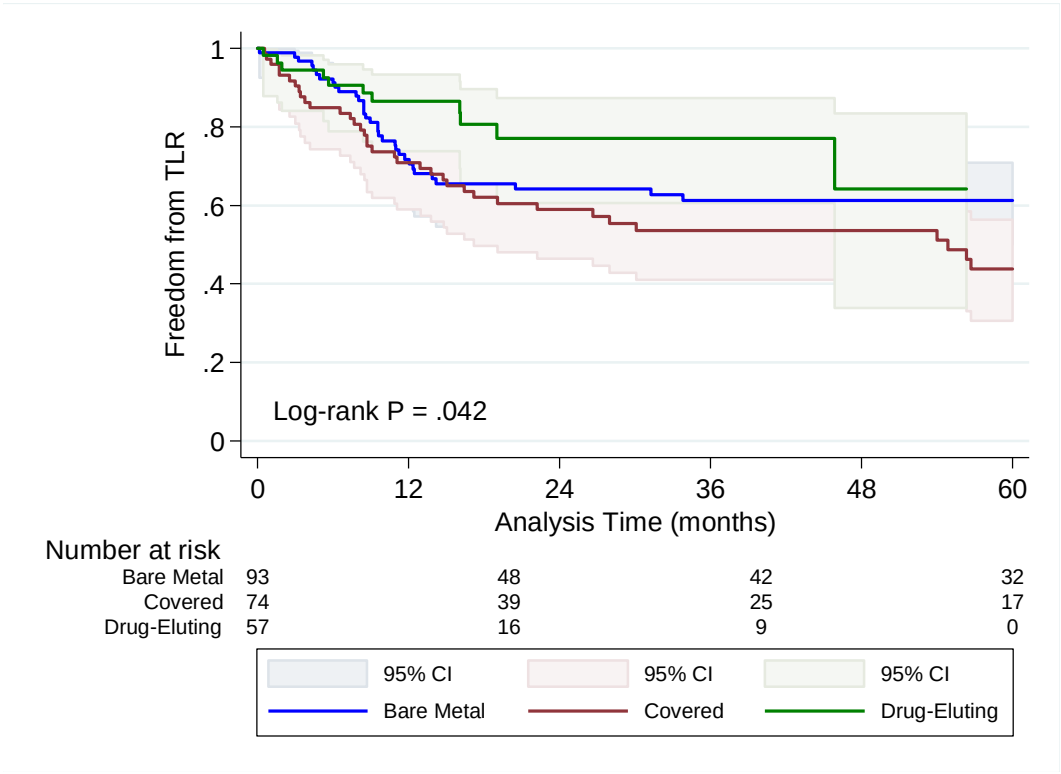
Supplemental Figure 1. Unadjusted Kaplan-Meier estimates for primary-assisted patency by stent type



Supplemental Figure 2. Unadjusted Kaplan-Meier estimates for secondary patency by stent type



Supplemental Figure 3. Unadjusted Kaplan-Meier estimates for freedom from target lesion revascularization (TLR) by stent type



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