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Are Metallic Stents Really Safe? A Long Term Analysis in Lung Transplant Recipients.

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Running Title: Metallic stents in Lung transplantation

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Abbreviations:

AR - Acute rejection

BAL - Broncho-alveolar lavage

BOS - Bronchiolitis Obliterans syndrome

FEV1 - Forced expiratory volume in 1 s

FOB – Fiberoptic bronchoscopy

FVC – Forced vital capacity

RTI - Respiratory tract infection

SEMS – Self-expandable metallic stents

ABSTRACT: 200 (MAX 200)

Background:

Airway complications affect 20% of all lung transplant (LTx) recipients. Self expandable metallic stents (SEMS) stents are one treatment option but use in benign airway disorders is controversial. Long-term safety of SEMS was studied in LTx.

Methods:

Between 1/1998 and 2/2008, all LTx-recipients with SEMS were analyzed retrospectively in a single center. Complications were recorded until September 2008.

Results:

In 65/706 (9.2%) recipients, 111 (95% non-covered) bronchial SEMS were implanted at a median 133 (55 - 903) days after transplantation. Median follow-up was 777 days (7-3.655). Clinical improvement was noted in 80%. FEV1 increased by 21±33%.

Most frequent early complications were migration (3%) and mucus plugging (11%). No procedural related deaths were noted. Re-stenosis occurred in 34 patients (52%) at a median of 85 (7 – 629) days after insertion. In multivariate analysis, stent insertion before postoperative day 90 was independently associated with an increased risk of re-stenosis (p=0.003, hazard ration 3.29, 95% CI 1.50 -7.18). In 40% of recipients, new bacterial airway colonization occurred after SEMS-insertion. In SEMS patients, 5 year survival was significantly lower than in the total cohort (60 vs. 76%, p=0.02).

Conclusions:

Late complications in LTx-recipients treated with SEMS are frequent. The major problems are re-stenosis and airway colonization.

INTRODUCTION:

Airway complications are a continuing problem following lung transplantation and can be divided into necrotic or obstructive lesions [1]. Approximately 20% of lung transplant recipients are effected [1-3]. Necrotic lesions frequently heal spontaneously, with surgical repair rarely required. In symptomatic obstructive lesions suggested interventional techniques include balloon dilatation [4], desobliteration **(**e.g. laser application, argon plasma coagulation [5], brachytherapy [6] and stent insertion [7]).

Repeated balloon dilatation is recommended as a first-line therapy. Up to 26% of LT recipients with airway stenosis respond to a single balloon dilatation [4], thermal desobliteration is effective but has a high recurrence rate [5]. Both techniques allow time for the lesion to mature into a fibrous stricture, which is more suitable for stent placement.

Classically, placement of a stent or prosthesis is indicated in case of external compression [8] of the airway but stents in LTx-recipients are frequently used in recurrent endoluminal lesions as well. A variety of different stent models have been commercially available over the last 20 years. Silicone stents are rarely used in post-LTx patients due to their decreased inner diameter, worse adaptability when target lesions are complex or angulated and frequent need for ventilation through interstices in this cohort. Most experience in LTx has been gained with self-expanding metallic stents. Successful insertion of SEMS with flexible bronchoscopy under and increasingly without general anesthesia has been increasingly reported [9]. Concern remains about the safety of metallic stents in treating benign tracheal lesions [10]. Complications such as migration, bleeding, atelectasis, infection, re-stenosis, fracture, have been reported.

SEMS consist of a self-expanding, knitted metallic mesh usually made from nitinol, a nickel-titanium alloy [11]. The knitted design of these stents permits axial and radial movements of the wire filaments, which allows excellent adaptation and prevents longitudinal expansion of the stent when compressed. Despite being commercially available for more than 10 years

now, the literature regarding the long-term outcome of SEMS in lung transplant recipients remains sparse.

We undertook this study to assess the long-term complications and survival in patients with airway complications after lung transplantation after insertion of a single type of SEMS.

METHODS:

Study design

A retrospective cohort study was performed in single university center between 1st January 1998 and 28th February 2008. Inclusion criteria were patients undergoing lung transplantation and technically successful insertion of SEMS with follow-up of at least 7 days. Patient demographics are shown in table 1.

Follow-up was performed until 30th September 2008. The primary outcome was the occurrence of in-stent re-stenosis. Secondary outcomes included graft survival and BOS-free survival.

Prior to enrollment, the project had been approved by the Institutional Review Board. There was no financial support from the pharmaceutical industry or any manufacturer of medical supplies.

Procedures

Prior to stent insertion, all patients underwent evaluation by fiberoptic bronchoscopy (FOB). Criteria for stent insertion were symptomatic (e.g. dyspnea, infection, cough, hemoptysis, deteriorating graft function) obstructive lesions with diameter of <5mm and recurrence after repeated balloon dilatation or desobliteration (e.g. argon plasma coagulation) or extensive anastomotic dehiscence.

The commercially available Ultraflex® stent (Boston Scientific, Natick, MA) was used in all patients. Stent insertion was performed by flexible bronchoscopy under general anesthesia or with moderate sedation, as previously described [12].

Before stent placement, airway recanalization was performed by argon coagulation or balloon dilatation as needed. Suitable stent length was estimated by withdrawing the bronchoscope from the distal to the proximal end of the lesion and diameter was estimated by direct vision.

Stents were deployed from its delivery catheter under direct vision without fluoroscopy and subsequent balloon dilatation was performed to allow full stent expansion.

Follow-up

Chest X-rays were performed on the same or following day to evaluate stent position. Spirometry data were collected directly before and 4 days after stent placement. Spirometry with measurements of forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were performed according to ATS/ERS guidelines [13].

All patients received nebulized saline after stent insertion to prevent stent obstruction by secretions. To prevent migration for 3 days after the procedure, patients received antitussive agents and were advised not to perform home spirometry.

All lung transplant recipients received frequent, individual, centre-based life-long follow-up care. Patients were usually seen in our outpatient clinic every 6 weeks. Patients were instructed to use home spirometry daily and to contact the transplant center in case of decline. In the case of acute unexplained respiratory symptoms, prompt attendance at our follow-up clinic was arranged. In case of symptoms, functional impairment or radiological abnormalities, repeat FOB was performed.

Definitions:

Successful treatment was defined by improved clinical symptoms and/or a FEV1 increase of at least 10% from pre-treatment level. Re-Stenosis was defined as inability to pass a standard 4.9 mm bronchoscope (Olympus BF P40 or P180, Tokyo, Japan). Complications were defined as early in stent-related clinical events occurring before day 30 after insertion, with late complications relating to any event thereafter.

Bronchiolitis obliterans syndrome (BOS) was defined as a FEV1 <80% compared to baseline FEV1; defined as the average of the 2 highest measurements obtained at least 3 weeks apart during the postoperative course [14]. Graft loss was defined as death or re-do-transplantation.

Antibiograms of all isolates from lower respiratory tract samples (broncho-alveolar lavage (BAL) in the majority) were identified by standard laboratory methods before and after stent

insertion. Airway colonization of the graft was defined by repeated detection on at least two occasions regardless of the signs of infection.

Statistics:

Data are reported as means (±standard deviation) and time dependent variables are expressed as median, (minimum and maximum). All reported P values are two-sided, unless otherwise indicated. For all analyses, p-values <0.05 were considered statistically significant.

Categorical variables were analyzed by chi-squared test or Fisher´s exact test, the log-rank test was applied to compare re-stenosis-free survival. Medians were compared with the Mann-Whitney test. Means were analyzed with Student´s t-test. Multivariate analysis included Cox stepwise forward regression analysis for re-stenosis-free survival. All variables with a p-value ≤ 0.10 were included and variables with a P-value of >0.10 were excluded in a multivariate analysis. Kaplan-Meier curves were plotted to compare overall and BOS-free survival in patients with or without re-stenosis.

RESULTS:

During the ten-year observation period, 706 lung transplant procedures involving 1.276 airway anastomoses were performed. In 65/706 (9.2%) lung transplant recipients, 111 self-expandable metallic stents (SEMS) were implanted.

Bronchoscopic technique

All stents were placed using flexible bronchoscopy. General anesthesia was used in 48 (72%) patients, and insertion was performed via laryngeal mask in 13 (20%) patients. Non-covered stents were used in 59 (91%) patients, covered stents in 6 patients. Most frequent used stent length was 20 mm (n=77), while 30 mm (n=26) and 40 mm (n=8) lengths were chosen less frequently. Used stent diameters were 10 mm (n=84), 8 mm (n=20) and 12 mm (n=7). In 25 study subjects (38%) multiple stents were inserted (maximum 7 per patient). In 16 (25%) patients, multiple target lesions were approached. In 12 patients, bilateral SEMS were implanted.

Insertion was performed at a median 133 (50-903) days post surgery. In 72%, the first stent was placed within the first 6 months after LTx. Indications for stent insertion were obstructive lesions in all but one patient who had a pure necrotic lesion.

Target lesions for stent insertion are shown in figure 1. In 76 percent the post-anastomotic region was involved rather than the anastomosis itself and there was predominance on the right side, in which 72 out of 111 stents (65%) were inserted.

Short-term outcome

Successful re-opening of the airways was noted in all patients. Fifty-two out of 65 study subjects (80%) experienced relieve of the clinical symptoms leading to stent insertion. Detailed pulmonary function tests were available in 61 patients. Mean increase in FEV1 and FVC was 299±531 ml (+21±33% compared to pre-insertion) and 187±480 ml (+ 8±18%), respectively. Among the early complications (prior to day 30), symptomatic stent obstruction due to tenacious secretions (mucus plugging) was noted in 7 patients, along with stent migration requiring removal (day 1 and 3) in 2 patients. There was no procedure-related mortality.

Late complications

Study subjects had median 15 (0 – 47) visits to our outpatient clinic after stent insertion (first visit median 20 days after insertion). Median follow-up was 777 days (7 – 3655) days. Two patients were lost of follow-up after 7 and 77 days.

Overall stent-related complications were seen in 52/65 (80%) of patients. Among the late complications, re-stenosis occurred most frequently (n=34), with new bacterial colonization being second (n=26). Isolated pathogens are listed in table 2. Thirteen were colonized with aspergillus species. Further observed late complications were stent fracture (n=6), hemoptysis (n=7) and atelectasis (n=3). Hemoptysis was successfully treated by topical administration of hemostyptic agents or argon coagulation in 6 out of 7 cases. One patient died 128 days after stent insertion and 301 days after left sided LTx from fatal bleeding. Autopsy revealed focal invasive pulmonary aspergillosis of the graft without bleeding source at the stent site.

Re-Stenosis occurred median 85 (17 – 629) days after insertion. Re-stenosis occurred in 33/34 patients (97%) during the first 2 years after insertion (figure 2). Most frequent used treatment modalities (including combinations chosen) were balloon dilatation (n=21), argon coagulation (n=18), cryotherapy (n=2), brachytherapy (n=12) and stent-in-stent insertion (n=8). Besides removal of 2 stents due to migration (both reinserted in a second intervention) no other late stent removal occurred. Risk factors for in-stent stenosis are displayed in table 3. Only stent insertion before day 90 proved an independent covariate associated with re-stenosis.

Outcome

Graft loss (16 deaths and 2 re-do transplantations) was observed in 18 patients (27.6%) after median 727 (35 – 2.371) days. Most frequent causes of graft loss were BOS (n=5), infection (n=5), cardiovascular death (n=3), respiratory failure (n=2), hemoptysis (n=1), malignancy (n=1) and unknown in one patient. Twenty-seven patients (41.5%) developed BOS median 853 (104 – 1848) days after stent insertion. Overall survival was significantly lower in LTx-recipients with SEMS compared to the total cohort during the study period (Figure 3, log rank p=0.02), while BOS-free survival was not affected (p=0.27).

DISCUSSION:

In this study, we present the largest cohort of LTx recipients with airway complications after insertion of SEMS, with detailed long-term follow-up of median 2 years. Stent related complications during follow-up were noted in 80% of study subjects with in-stent stenosis and airway colonization as the leading complications. Long-term survival was impaired in patients with SEMS.

There have been previous publications reporting complications during follow-up of patients after SEMS- insertion. Most of these report on patients with malignant airway disease [9, 15-19], LTx-recipients were infrequently included in series [17, 19]. To our knowledge, five

small case series involving up to 33 patients are published on exclusive use of SEMS in LTx-recipients [7, 20-23].

The long-term complication rate in subjects with malignant airway disease treated with SEMS is not comparable with LTx recipients. Follow-up in published series was just 47 to 128 days and covered tracheal stents were used in the majority [9, 16, 18]. Airway disease in LTx in contrast involves mainly the bronchi.

SEMS have undergone technical evolution and the Ultraflex-stent has shown lower rate of complications like mucus plugging, migration, long-term stability compared to the first and second generation SEMS and has excellent adaptability [24]. Published case series with Ultraflex-Stents in LTx-patients [20-22] involved 7 to 30 patients with a follow-up between 263 and 400 days, compared to 777 days in our study. Our first patient with Ultraflex-stent is alive more than 10 years after insertion and bronchoscopy performed 3.547 days after insertion revealed a patent stent lumen.

The vast majority of our SEMs recipients experienced some complication, appearing higher than the 22-67% of other reports [9, 16, 18]. This is explained by the longer follow-up period and the closer microbiological work-up. Microbiological data was not reported in most other publications.

Our re-stenosis rate was 52%, higher than in other studies reporting a re-stenosis rate of 10-47% [9, 17, 18, 20, 21]. This may be due to our longer follow-up, given that re-stenosis have occurred up to 2 years after insertion and that we used mainly non-covered stents. The higher re-stenosis rate when placed during the first three postoperative months can be explained by pronounced tissue inflammation in early lesions, which increases the risk of stent in-growth.

Lower airway tract colonization is a common phenomenon in patients with impaired pulmonary defense and airway remodeling. In LTx recipients with airway homeostasis and under immunosuppression bacterial colonization is frequent. Two recent studies in unselected LTx-recipients have described an incidence of pseudomonas colonization in 41 and 42 %, respectively [25, 26] comparable to the 45% in our study. In contrast, a total 77% of our stent

patients showed any bacterial airway colonization, which is higher than expected.

Noppen reported an 80% incidence of bacterial colonization (most frequently Staphylococcus aureus) after placement of silicone stents in non-transplant patients without prior colonization [27], while bacterial airway colonization decreased from 45 to 25% following therapeutic rigid bronchoscopy without stent placement [28]. Colonization in LTx-patients with SEMS was studied by Burns and demonstrated 56 % of BAL specimens being positive [21]. Recent papers have shown that pseudomonas colonization of the allograft was associated with a higher a risk for BOS. BOS remains the major obstacle to long-term survival after LTx [25, 26].

Clinical improvement rates and other observed complication rates (mucus plugging, migration, hemoptysis) were comparable to other studies using Ultraflex-stents [9, 16-18, 21].

In our Study, long-term survival in patients with SEMS was lower than in controls, comparable to the results of Chhajed [22]. Higher mortality in LTx-recipients with SEMS may be explained by higher risk of infection and lower functional reserve in case of complications. Like in most other studies, no procedure related deaths were noted [9, 15-20]. Even if the population with stents itself would have a higher mortality than without stenting, it is interesting that the difference in survival became apparent after more than three years. This may indicate the clinical significance of late complications. In 6 % of our patients, later death was even potentially related to local complications such as infection and hemoptysis.

The major limitation of this study is the lack of a control group and being a retrospective study. Airway colonization and re-stenosis may occur even without SEMS. Desobliteration techniques have their own side effects. Thermal desobliteration techniques may lead to deep tissue injury with secondary scarring and repeat balloon dilatation may lead to tissue damage. None of these have been to date compared to SEMS in a randomized controlled trial.

In some centers, implantation of prosthesis for a limited time is preferred [20] but removal of an epithelialized SEMS is difficult and potentially hazardous to the patient. Lunn reported on

30 stent extractions and found 32 complications including mucosal tears, retained stent fragments, and airway re-obstruction [29].

Theoretically, silicone stents are suitable as temporary prosthesis because they are easily removable and show no in-growth. In LTx recipients, silicone stents have not gained popularity, because lesions are often complex, have smaller inner diameter and frequently require ventilation through interstices. To date, no ideal airway stent exists that combines the advantages of silicone and metal stents. Biodegradable stents offer an exciting solution in the future: extraction is unnecessary, and the normal airway is preserved after stent resorption. In human studies in benign esophageal strictures, these stents have shown to be clinically effective [30].

Successful prevention of airway complications seems to be a key issue of this often frustrating clinical problem. Surgical techniques to avoid excessive airway ischemia and medical regimens to avoid fungal colonization in the poorly vascularized postanastomotic region were proposed. It has been demonstrated recently that this standardized strategy resulted in a rate of just 4.9 % of obstructive airway complications without need of any airway stent in 235 patients over a 15 year period[31].

In conclusion, SEMS were effective in the short term management of benign airway disorders after LTx but have a high complication rate in the long term. Indication of SEMS in LTx recipients should be critically discussed. The optimal treatment in this setting is unknown. Other therapies such as airway debridement and balloon dilatation should be considered prior to the placement of a SEMS. Permanent insertion of SEMS before 90 days after LTX should be strictly avoided. Removable or biodegradable stents may play a future role for this challenging problem.

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TABLES:

Table 1: patient demographics (n=65)

Age	years	48 (17 -64)
Gender	no. (%)	
female		25 (35)
male		40 (65)
Baseline FEV1	% predicted	77±20
Time since transplantation at first stent	days	133 (50-903)
Number of stents per patient		1 (1-7)
Underlying disease	no. (%)	
Emphysema		30 (46)
Cystic fibrosis		13 (20)
Pulmonary fibrosis		13 (20)
Pulmonary artery hypertension		1 (2)
Other		8 (12)
Procedure	no. (%)	
Single lung transplant		2 (3)
Double lung transplant		61 (94)
Heart-lung transplant		2 (3)
follow-up after stent insertion	days	777 (7 – 3.655)

FEV1- forced expiratory volume in one second, LTx – lung transplantation

Table2: Isolates in recipients with airway colonization

Airway colonization before first stent	no. (%)	
Pseudomonas aeruginosa		17 (26)
Staph. aureus		10 (15)
Escherichia coli		2 (3)
Stenotrophomonas maltophilia		4 (6)
Achromobacter		1 (2)
polymicrobial		6 (9)
any		**29 (45)**
New airway colonization after stent	no. (%)	
Pseudomonas aeruginosa		17 (26)
Staph. aureus		12 (18)
Escherichia coli		2 (3)
Proteus mirabilis		2 (3)
Stenotrophomonas maltophilia		1 (2)
Achromobacter		1 (2)
Acinetobacter baumanii		1 (2)
polymicrobial		14 (22)
any		**26 (40)**

Table 2: Univariate and multivariate analysis (Cox proportional hazard model) of recipients with SEMS on risk factors for stent re-stenosis (n=65).

	Univariate analysis			Logistic regression		
	No re-stenosis	Patients with stent stenosis	p-value	p-value	Adjusted hazard ratio	95% confidence interval
Subjects	31	34				
First stent days after LTx	222±203	152±92	0.08	0.23		
age – yrs.	46 (17-64)	50 (17-61)	0.47			
Height – cm	173±10	175±8	0.50			
Gender female - yes	10 (32)	15 (44)	0.15	0.15		
First stent <90 days – yes	2 (6)	9 (26)	**0.001**	**0.003**	**3.29**	**1.50 -7.18**
Interventions before first stent	2 (0-5)	2 (0-6)	0.39			
Bacterial colonization before stent - yes	14 (45)	15 (44)	0.86			
New bacterial colonization after stent - yes	9 (29)	17 (50)	0.22			
Multiple stent targets – yes	5 (16)	11 (32)	0.15	0.62		
Stent in intermediate bronchus - yes	20 (65)	26 (76)	0.32			
Stent length >20mm - yes	5 (16)	9 (26)	0.51			
FEV1-increase post stent % baseline	24±27	18±37	0.29			

SEMS – selef-expandable metallic stent, FEV1- forced expiratory volume in one second, LTx – lung transplantation

FIGURES:

Figure 1: Target lesions for stent insertion (total n=111): intermediate bronchus (n=59), left main bronchus (n=16), right lower lobe bronchus (n=11), right upper lobe bronchus (n=12), middle lobe bronchus (n=1), right lower lobe bronchus (n=1), right main bronchus (n=11)

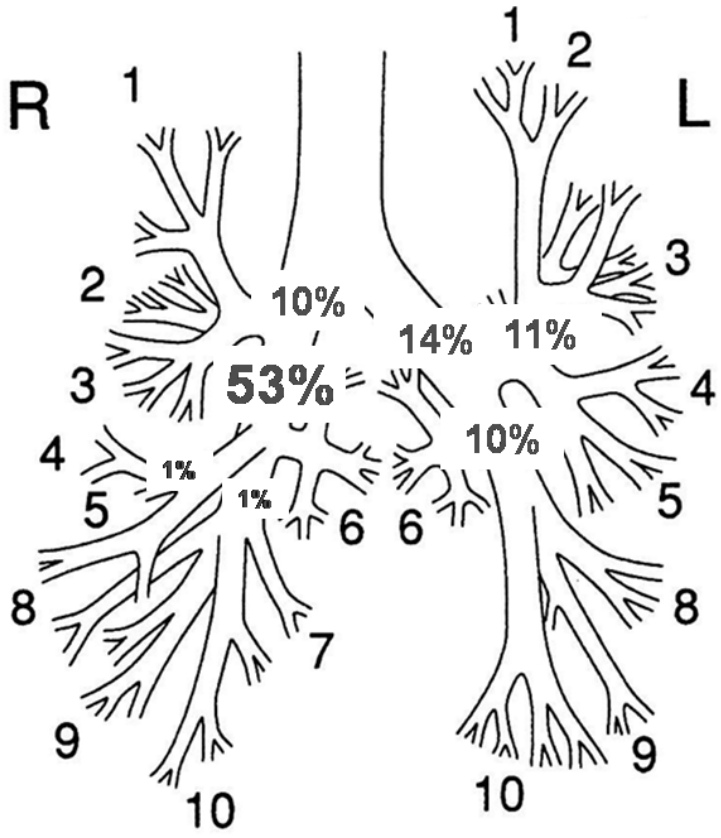


Figure 2: Kaplan-Meier plot of the re-stenosis free survival after SEMS-insertion.

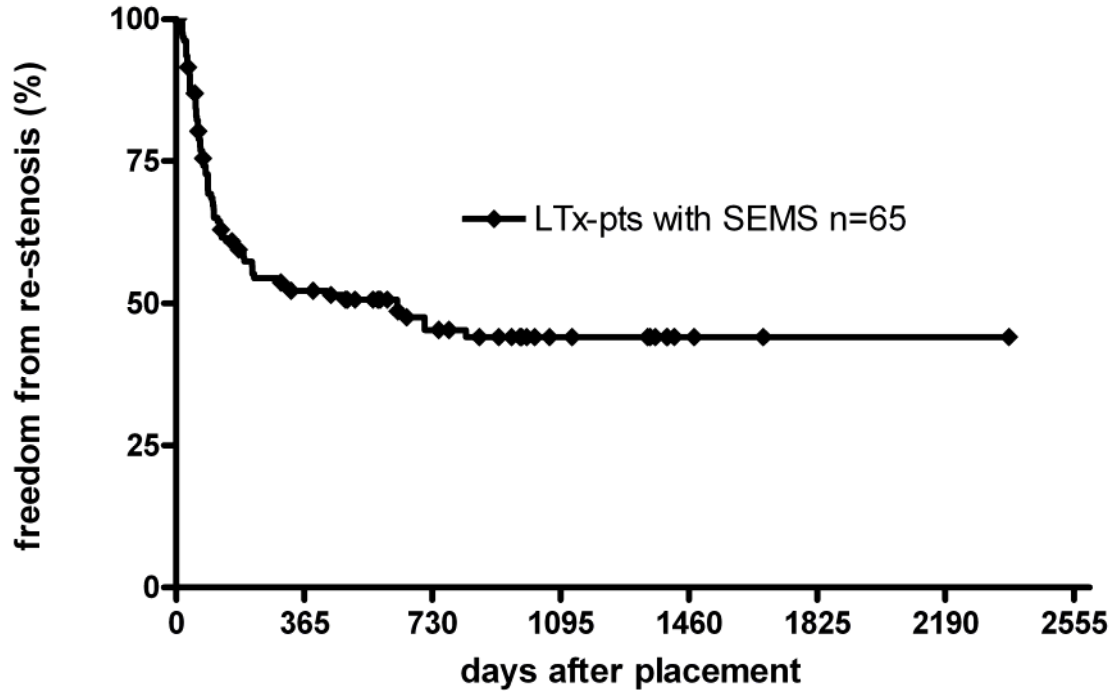
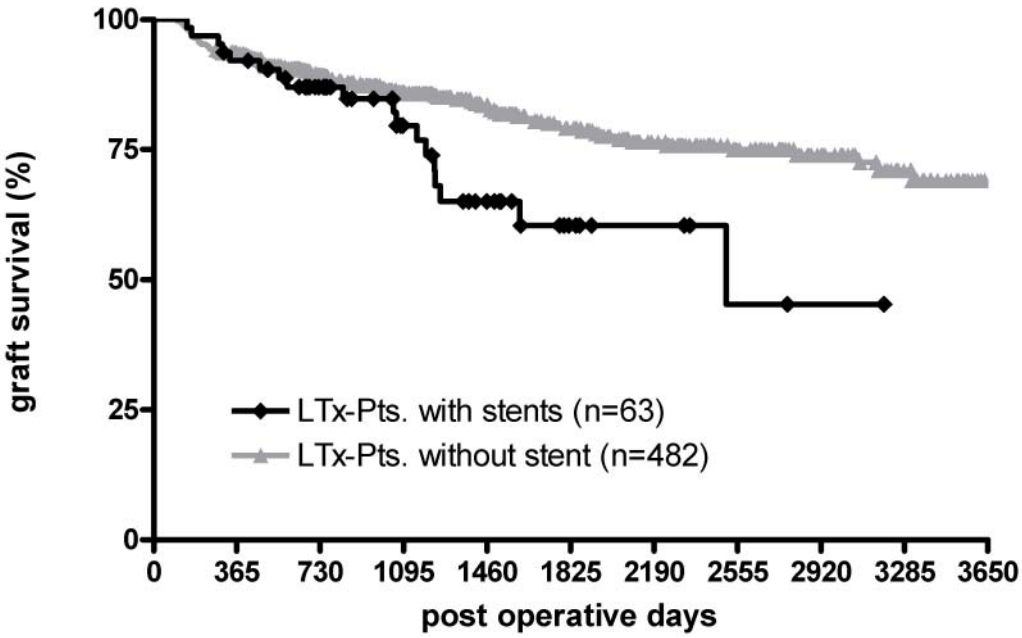


Figure 3: Kaplan-Meier Survival conditional on survival to 90 days comparing patients with or without SEMS (Hannover Medical School 1998-2008), log rank p=0.02



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