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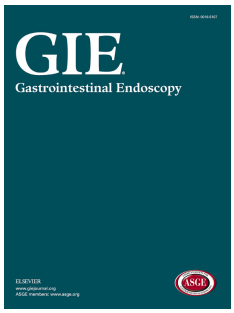

Fully covered self-expanding metal stents for benign biliary stricture after orthotopic liver transplant: 5-year outcomes

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Fully covered self-expanding metal stents for benign biliary stricture after orthotopic liver transplant: 5-year outcomes

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ABSTRACT

Background and Aims

Minimally invasive treatments of anastomotic benign biliary stricture (BBS) after orthotopic liver transplantation (OLT) include endoscopic placement of multiple plastic stents or fully covered self-expandable metal stents (FCSEMSs). No multi-year efficacy data are available on FCSEMS treatment after OLT.

Methods

We prospectively studied long-term efficacy and safety of FCSEMS treatment in adults 18 years and older with past OLT, cholangiographically confirmed BBS, and an indication for ERCP with stent placement. Stent removal was planned after 4 to 6 months, with subsequent follow-up until 5 years or stricture recurrence. Long-term outcomes were freedom from stricture recurrence, freedom from recurrent stent placement, and stent-related serious adverse events (SAEs).

Results

In 41 patients, long-term follow-up began after FCSEMS removal (n=33) or observation of complete distal migration (CDM) (n=8). On an intention-to-treat basis, the 5-year probability of remaining stent-free after FCSEMS removal or observation of CDM was 48.9% (95% CI, 33.2%−64.7%) among all patients and 60.9% (95% CI, 43.6%−78.2%) among 31 patients with over 4 months of FCSEMS indwell time. In 28 patients with stricture resolution at FCSEMS removal or observed CDM (median 5.0 months indwell time), the 5-year probability of no stricture recurrence was 72.6% (95% CI, 55.3%−90%). Sixteen (39%) patients had at least 1 related SAE, most commonly cholangitis (n=10).

Conclusions

By 5 years after temporary FCSEMS treatment of post-OLT BBS, approximately half of all patients remained stent-free on an intention-to-treat basis. Stent-related SAEs (especially cholangitis) were common. FCSEMS placement is a viable long-term treatment option for patients with post-OLT BBS.

ClincialTrials.gov number, NCT01014390; CTRI/2012/12/003166

Key words: cholangiopancreatography, endoscopic retrograde; liver transplantation/adverse effects; orthotopic liver transplantation; prospective studies; metal stent removal

BACKGROUND AND AIMS

Approximately 6% to 12% of patients who undergo liver transplantation subsequently develop an anastomotic biliary stricture.[1] Anastomotic strictures in the early posttransplant period may be attributed to, among other factors, scarring, donor-recipient bile duct mismatch, edema of the healing anastomosis, peritransplant infection, anastomotic leaks, and possibly to surgical technique.[2] Late anastomotic stricture tends to result from fibrotic healing due to ischemia at the end of the donor or recipient bile duct.[2] Even though most clinicians assume early strictures are associated with a better prognosis and generally do not need intensive treatment, the literature on this subject is conflicting.[2-4]

Symptomatic anastomotic strictures warrant clinical intervention because biliary obstruction can lead to jaundice, cholangitis, common bile duct stones and potentially biliary cirrhosis in chronic cases.[5] Endoscopic management is the first-line treatment for anastomotic strictures after orthotopic liver transplantation (OLT).[4] Multiple plastic stents (MPSs) or fully covered self-expandable metal stents (FCSEMSs) as endoscopic treatment options have been studied in randomized controlled trials (RCTs).[6,7] Progressive plastic stent placement of anastomotic strictures after OLT is highly efficacious and saves 80% of patients from undergoing complicated surgical repair or even retransplantation; however, the protocol is demanding and burdensome, necessitating 4 or more ERCP procedures with adverse events occurring in 1 out of 5 procedures.[8] Although FCSEMSs has the advantage of fewer anticipated stent exchanges, a 2013 systematic review[9] and two 2017 meta-analyses[10,11] of observational data did not suggest a clear overall advantage of SEMS use over MPSs for biliary anastomotic stricture after OLT. A 2019 meta-analysis[12] including 4 RCTs concluded that FCSEMSs and MPSs had equal anastomotic biliary stricture resolution and recurrence and similar overall rates of adverse events or stent migration. A trend towards a higher stricture recurrence rate in FCSEMS disappeared when trials with shorter stent indwell time were excluded.[12] Anastomotic stricture resolution rates are higher for liver transplant patients treated with more than 12 months of stent placement and a higher total number of stents.[4] Accordingly, a 2018 meta-analysis of 4 RCTs of metallic versus plastic stents to treat biliary stricture after OLT mentioned the importance of long-term follow-up to support evidence-based conclusions regarding stricture recurrence in these patients, stating that “a follow-up of 12 months is probably not enough to make firm assumptions on long-term efficacy (especially in the FCSEMS group because more is known about the chance of recurrence in the MPS group).”[13]

To estimate long-term efficacy and safety of FCSEMS in this patient population, we studied 41 patients with a history of OLT who participated in a prospective cohort study of FCSEMS to treat anastomotic biliary stricture.[14] Participants were followed up to 5 years after FCSEMS removal or after observation of complete distal stent migration (CDM) to assess maintenance of stricture resolution, rates of freedom from stent placement, and long-term safety.

METHODS

Study design

This analysis is part of a multicenter, prospective, nonrandomized observational study (ClincialTrials.gov NCT01014390 and CTRI/2012/12/003166) of an FCSEMS to treat benign biliary stricture (BBS) including 187 total participants in 3 patient subgroups: patients with chronic pancreatitis, with a history of cholecystectomy, or with a history of OLT. Methods of the main study were documented previously.[14] Patients from 8 of the 13 original study sites were represented in the current analysis. The Independent Ethics Committee at each study site approved the study protocol, and all study participants provided written informed consent. An Independent Medical Reviewer reviewed all stent- or stent-removal-related serious adverse events (SAEs), all reinterventions and all deaths. The medical reviewer was a gastroenterologist experienced in treating biliary obstructions and performing interventional endoscopic procedures, and not employed by the study sponsor or by a clinical study site. The study was sponsored and funded by Boston Scientific Corporation.

The FCSEMS studied was the fully covered WallFlex Biliary RX Stent (Boston Scientific Marlborough, Mass, USA), which is a U.S. Food and Drug Administration-approved for palliative and preoperative use in malignant biliary strictures and for indwell up to 12 months to treat benign biliary strictures secondary to chronic pancreatitis. The FCSEMS was placed at the baseline visit (**Figure 1**), after which patients had telephone or in-person assessments for symptoms of biliary obstruction (right upper quadrant pain, fever/chills, jaundice, itching, dark urine, pale stools, nausea/vomiting), adverse events, and/or device malfunction at 1 week, 3 months, or ad lib in response to concerning symptoms or adverse events. FCSEMS removal was planned at 4–6 months with the expectation that a shorter indwell time (compared with standard 12-month indwell for plastic stents and FCSEMS for other indications) would prevent late adverse events in the immunosuppressed post-OLT patients.[14] After stent removal, assessments were performed at 1, 3, 6, 12, 18, and 24 months, then annually up to 5 years. Patients were followed until 5 years after FCSEMS removal or until stricture recurrence (managed with new stent placement), whichever occurred earlier.

Patient population

Eligible patients were 18 years and older with cholangiographic confirmation of a bile duct stricture and an indication (eg, clinical symptoms, abnormal laboratory values with known bile duct stricture, planned exchange of plastic stents) for ERCP with stent placement to treat BBSs of the common bile duct. Patients with or without documented history of previous treatment with any number of plastic stents were eligible. Exclusion criteria included history of live liver donor transplantation, malignant biliary stricture, stricture location within 2 cm of bile duct bifurcation, prior biliary SEMSs, suspected stricture ischemia based on imaging of hepatic artery

Occlusion, or endoscopic evidence of biliary cast syndrome, bile duct perforation, known fistula, or symptomatic duodenal stenosis with gastric stasis.

Stricture resolution and long-term endpoints

Stricture resolution was established at the time of endoscopic FCSEMS removal or observation of complete distal migration (CDM), and was defined by lack of need for recurrent stent placement at that time.

The long-term efficacy endpoint was freedom from stricture recurrence defined by absence of recurrent stent placement during 5-year follow-up post-stent removal or observation of CDM. This was assessed on an intention-to-treat basis during 5 years of follow-up after FCSEMS removal or observation of CDM for all patients, and in the subset of patients observed to have stricture resolution at the time of FCSEMS removal or observation of CDM.

The safety endpoints were (1) SAEs related to the stent or to stent removal or (2) any SAEs occurring within 30 days before stricture recurrence. An SAE was defined as an event that led to death, serious deterioration in the health (life-threatening illness or injury, permanent impairment of bodily structure or function or medical/surgical intervention required to prevent such an impairment, or new or prolonged hospitalization), or fetal death, distress, or abnormality.

Statistical analysis

Baseline characteristics of the patients and their baseline endoscopic procedure were calculated, including mean, median, standard deviation (SD), interquartile range (IQR), and range for

continuous variables (age, time from transplant, serum total bilirubin, and alkaline phosphatase), and stratified incidence for categorical variables (sex, primary reason for transplant, stricture location, history of plastic stent placement, stricture location, and size of the FCSEMS placed). Freedom from stricture recurrence and freedom from recurrent stent placement were analyzed using Kaplan-Meier techniques, differences between those with and without migration were tested using the log-rank test. Univariate and multivariate analyses were used to determine whether baseline characteristics predicted outcomes. Specifically, logistic regression using a Firth bias adjustment was used for stricture resolution, and Cox proportional hazards models were performed for serious adverse events and freedom from stricture recurrence. Both were performed using the model building technique of stepwise regression, with $P \leq 0.10$ for covariates to stay in the model and $P > 0.10$ to exit the model. The significance level for all analyses was set at 0.05. All analyses were performed using SAS version 9.4.

RESULTS

Baseline characteristics and endoscopic stent placement

Of 42 patients enrolled, 1 could not be evaluated due to death from an infection that was unrelated to the study. This patient had not experienced any FCSEMS or FCSEMS placement related adverse event and had no signs of FCSEMS dysfunction at the time of death. Forty-one patients with a history of OLT were included in the current analysis of 5-year outcomes after FCSEMS removal or after observation of CDM (**Figure 2**). The OLT cohort had a mean age of 56.7 ± 11.5 years and was predominantly male (82.9%, 34/41) (**Table 1**). All patients had received transplants from cadaveric donors, with a mean time since transplant of 32.9 (range 0.1 to 234.5) months. Alcoholic cirrhosis (39.0%, 16/41) and hepatitis B or C (26.8%, 11/41) were

the most common primary reasons for liver transplant; other documented reasons included cryptogenic cirrhosis (9.8%, 4/41), hepatocellular cancer (7.3%, 3/41), primary biliary cirrhosis (4.9%, 2/41), primary sclerosing cholangitis (2.4%, 1/41) and autoimmune hepatitis (2.4%, 1/41), acute liver failure (2.4%, 1/41), and other (4.9%, 2/41). Most (95.1%, 39/41) patients had a history of sphincterotomy, and almost half (48.8%, 20/41) had undergone prior plastic stent placement.

At the baseline endoscopic examination, patients were found to have strictures located in the proximal (39.0%, 16/41) and mid (61.0%, 25/41) common bile duct. Plastic stents were removed from 14 (34.1%) patients, ranging from 1 stent (26.8%, 11/41) to 3-5 stents (2.4%, 1/41) before FCSEMS placement. FCSEMS placement was technically successful with satisfactory positioning in all patients. The most common size of study FCSEMS placed at the baseline visit was 10 mm x 80 mm in 32 (78.0%) patients (**Table 1**).

Migration and stricture resolution assessed at time of stent removal

Twenty-five (61.0%) patients underwent FCSEMS removal during the planned period of 4 to 6 months (median indwell 153 days), 8 (19.5%) underwent removal before 4 months (median indwell 22 days), and 8 (19.5%) were observed to have spontaneous CDM after an estimated median indwell of 167.5 days (**Figure 1**). Six patients had over 6 months of indwell time, including 5 with stent removal within 198 days (6.6 months), and 1 with removal at 355 days (11.8 months). Successful endoscopic removal of all 33 (100%) FCSEMS that had not completely migrated was achieved using forceps/graspers/snares (n=31) or a stent-in-stent

technique (n=2). The FCSEMS covering was observed to not be compromised for any stent at the time of removal.

Twenty-four (58.5%) patients were noted to have stent migration at the time of FCSEMS removal; of these, 8 were spontaneous CDM, 8 were partial distal migrations, and 8 were proximal migrations; within these groups, 4, 3, and 2 patients, respectively, were symptomatic at the time of FCSEMS removal and were restented with a plastic stent(s) immediately. A multivariate model suggested that "over 1 year since transplant" was associated with significantly lower risk (hazard ratio [HR], 0.4; 95% CI, 0.2−0.8; *P*=0.018), and "alcoholism as reason for transplant" was associated with higher risk (HR, 2.8; 95% CI, 1.2−6.4; *P*=0.013) of any stent migration. "Alcoholism as reason for transplant" was also associated with higher risk (HR, 5.7; 95% CI, 1.2−26.8; *P*=0.029) of proximal migration.

Twenty-eight (68.3%; 95% CI, 51.9%−81.9%) patients had either stricture resolution or observation of complete distal migration and did not require recurrent stent placement. Univariate/multivariate analyses did not reveal independent predictors for stricture resolution observed at the time of stent removal.

Freedom from recurrent stent placement after stent removal

Among all 41 patients, the probability of remaining free from recurrent stent placement by 5 years after FCSEMS removal was 48.9% (95% CI, 33.2%−64.7%) (**Figure 3A**). Post hoc analyses showed that among 31 patients with an implanted stent for more than 4 months, the probability of remaining stent-free by 5 years after FCSEMS removal was 60.9%. In addition,

75.5% (95% CI, 54.5%−96.5%) of patients without migrations compared with 27.9% (95% CI, 9.1%−46.8%) of patients with migrations remained stent-free by 5 years after FCSEMS removal (P = 0.004) (**Figure 3B**).

Freedom from stricture recurrence in patients with stricture resolution at time of stent removal

Among the 28 patients who had stricture resolution or observation of CDM at the time of FCSEMS removal (after median 151 days [5.0 months] indwell time), the probability of being without stricture recurrence by 5 years after stent removal was 72.6% (95% CI, 55.3%−90%) (**Figure 4**).

Seven (7) patients had stricture recurrence during follow-up, with median time to recurrence of 3.4 (IQR, 1.8−6.6) months. All recurrent strictures were at the original location and occurred by 15 (range 1.7–14.7) months after stent removal. All recurrent strictures were successfully managed with recurrent stent placement; no patients required reintervention with bypass surgery. Univariate/multivariate analysis did not reveal independent risk factors for stricture recurrence.

Serious adverse events related to stent or stent removal

Among all 41 participants, 16 (39%) had at least one FCSEMS- or FCSEMS-removal-related SAE, with cholangitis (n=10) and abdominal pain (n=4) being the most common (**Table 2**). Univariate and multivariate analyses showed that compared with those with transplantation less than 1 year before enrollment, patients with transplantation at least 1 year before enrollment had

a significantly lower risk of adverse events (HR, 0.3; 95% CI, 0.1 to 0.8) and cholangitis specifically (HR, 0.2; 95% CI, 0.1 to 0.7).

Among the 7 patients who had stricture resolution after FCSEMS treatment and then experienced stricture recurrence during follow-up, 5 had cholangitis/fever and/or elevated liver function tests within 30 days before recurrence.

DISCUSSION

We studied the efficacy and safety of FCSEMSs to treat anastomotic stricture in patients with OLT followed for up to 5 years after FCSEMS removal. On an intention-to-treat basis, the probability of remaining stent-free was 49% for all patients and 61% for those with a stent indwelling for the full intended 4 to 6 months. Among patients with stricture resolution at the time of FCSEMS removal, the 5-year probability of being without stricture recurrence was 73%. All recurrent strictures were at the original location and occurred no later than 15 months after stent removal. Spontaneous complete distal migrations occurred in 20%, and SAEs related to the stent or stent removal occurred in 39% of participants.

Since Costamagna et al[15] described the technique in 2001, progressive dilation by insertion of increasing numbers of multiple plastic stents has been the most widely used endoscopic treatment for BBS. An average of 3 to 4 ERCP procedures are required to dilate, deploy stents, up-size, and ultimately remove all stents once the stricture has resolved,[16] and the repeated endoscopic interventions may extend up to 24 months to achieve sustained clinical success.[10] FCSEMS treatment of BBS has been studied since 2009,[17] and 4 randomized trials comparing

FCSEMS to multiple plastic stents to treat BBS in cohorts including post-OLT patients have been conducted since 2014.[6,7,18,19] Prospective and retrospective cohort studies and randomized trials focused on post-OLT patients have consistently reported FCSEMS to be noninferior to multiple plastic stents with respect to stricture resolution, stricture recurrence and overall adverse events,[10-13] with one RCT reporting a higher stricture recurrence rate in the FCSEMS groups when the stents were removed early.[7] A 2019 meta-analysis of data from 4 RCTs concluded that FCSEMS were associated with a reduced number of procedures and were a cost-sparing intervention overall.[12] However, because only 205 patients were represented in the RCTs and follow-up was as short as 1 year, experts have emphasized the need for further RCTs with larger sample size and longer follow up (eg, at least 2 years[13]) for more definitive findings. In our study, strictures recurred as late as 15 months after FCSEMS removal, which supports that follow-up of at least 2 years is important for a thorough evaluation of FCSEMS efficacy and safety.

The overall 5-year stricture recurrence rate was 31.7% in our OLT cohort, which was similar to[7,18] or higher than[6,19] stricture recurrence rates in the FCSEMS arm of RCTs in OLT cohorts followed for 1 to 3 years on average. This rate was higher than the estimated 5-year rates of stricture recurrence reported for patients postcholecystectomy (15.4%)[20] or with chronic pancreatitis (22.6%)[21] in the original cohort.[14] The higher rate was understandable considering multiple etiologies for biliary stricture in OLT patients including ischemia of the biliary tree from chronic rejection, or technical biliary adverse events such as kinking or anastomotic leaks.[22] Multivariate analyses in our study did not identify independent predictors of 5-year stricture recurrence, but findings were limited by the small number of participants who could be followed for this endpoint. For example, prior studies have reported that liver transplantation patients with

more than 12 months of plastic stent placement for BBS are less likely to have stricture recurrence compared with those without prior stent placement.[23] Of the 28 participants who were followed for 5-year stricture recurrence, 7 had stricture recurrence, of whom 4 (51.7%) had prior plastic stent placement. A larger study population and details regarding the time period of prior stent placement would have allowed further investigation of this predictor.

Stent- and stent-removal related SAEs occurred in 39% of these patients, primarily due to cholangitis (24.4%). This compares with overall SAE rates ranging from 10% (1/10) to 40.4% (23/57) in 3 RCTs of covered metallic stents versus plastic stents for BBS that included OLT patients.[6,7,18] Biliary adverse events as a whole are common in the OLT patient population, occurring in 10% to 30% after whole-organ OLT and resulting in mortality rates of up to 10% of cases.[22] Age over 60 (seen in 18 [44%] of our participants at baseline) and primary sclerosing cholangitis as the transplant indication (1 participant) are known risk factors for biliary adverse events after liver transplantation.[24] Immunosuppression was a predisposing factor to infections in this cohort, ie, OLT patients undergo intensive perioperative prophylactic immunosuppressive induction therapy to prevent acute cellular rejection in the first months after transplantation, followed by maintenance immunosuppressive therapy for life.[25] Infection risk is lower with tapered immunosuppression by 12 months after transplant; however, a Finnish registry study with 3923 person-years of follow-up estimated that after the first year posttransplant, 1 in 15 liver transplant patients will have an episode of cholangitis or other severe infection each year.[26] Multivariate analyses in our study suggested that longer time since liver transplantation was associated with a lower risk of adverse events and of cholangitis specifically. Patients who develop BBS later in the posttransplant period might be expected to have a more benign course

after surviving the immediate postoperative period when the risks of postoperative adverse events or graft failure are the highest.[2]

Our study had several limitations and considerations affecting interpretation. It was a small prospective study with limited power to estimate patient characteristics associated with the efficacy and safety endpoints, and with no plastic stent comparator. Patients with prior plastic stent placement were eligible for the study and comprised approximately half of the OLT cohort. This could have caused selection bias favoring either strictures that had failed earlier treatment and were more difficult to treat, or inclusion of more patients with a prior sphincterotomy (95% of our cohort) for whom stent migration might have been more likely compared with patients with a native papilla.[7] Because of the small study size, some findings regarding risk factors (eg, association between alcoholism as reason for transplant and stent migration) might have been spurious. The study was not designed to compare FCSEMS with multiple plastic stent placement or variants[27] that have also shown good efficacy. Some authors are employees of the sponsor of the study, some investigators were paid consultants for or have received research funding from the study sponsor, and some have received funding from another manufacturer of FCSEMS. This might have influenced their willingness to participate in the study but would not change their ability to objectively collect data.

In OLT patients with anastomotic biliary stricture treated with FCSEMS, the probability of remaining stent-free by 5 years was approximately 50% for all patients, and over 70% for those with stricture resolution after a median 5.0 months of FCSEMS indwell time. All stricture recurrences occurred by 15 months after stent removal. FCSEMS continues to show good

efficacy and an acceptable level of safety for OLT patients who have post-OLT biliary stricture of their duct-to-duct anastomosis.

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The data, analytic methods, and study materials for this study may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (http://www.bostonscientific.com/en-US/data-sharing-requests.html).

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Figure 1. A, Cholangiogram showing an anastomotic stricture after orthotopic liver transplant treated by (B) placement of fully covered self-expanding metal stent. C, The stricture is resolved after stent removal. Visible coils were placed during radioembolization before transplantation.

Figure 2. Flowchart of patients with a history of orthotopic liver transplant and benign biliary strictures treated with fully covered self-expanding metal stents.

Figure 3. A, Kaplan-Meier analysis of patients who remained free from recurrent stent placement (N=41). The cumulative probability of remaining free from recurrent stent placement after removal of a fully covered self-expanding metal stent (FCSEMS) placement until 5 years after FCSEMS removal was estimated among all patients. Patients who died were treatment failures, or who were lost to follow-up between FCSEMS removal to 5 years' follow-up were censored. Median follow-up time was 62.2 months after FCSEMS . Median time to recurrent stent placement was 5.6 months after FCSEMS placement (range 0.2-19.4; interquartile range, 0.7-7.7). **3, Kaplan-Meier analysis of patients who remained free from recurrent stent placement, by stent migration (N=41).** The cumulative probability of remaining free from recurrent stent placement from removal of a fully covered self-expanding metal stent (FCSEMS) until 5 years later was significantly longer in patients with no stent migration compared with those with migration (75.5% vs 27.9% respectively, p=0.004).

Figure 4. Kaplan-Meier analysis of freedom from stricture recurrence in patients with stricture resolution at the time of endoscopic FCSEMS removal or observation of complete distal migration (n=28). The cumulative probability of being free from recurrent stent placement from the time of fully covered self-expanding metal stents (FCSEMSs) removal until 5 years later in patients who had stricture resolution at removal (n=28) is presented. Patients who died or were lost to follow-up from the time of FCSEMS removal to 5-year follow-up were censored. The median follow-up time after FCSEMS removal was 57.3 months (interquartile range, 21.9-60.2) for 28 patients. The median time to stricture recurrence after FCSEMS removal was 3.4 months (interquartile range, 1.8-6.6) in 7 patients.

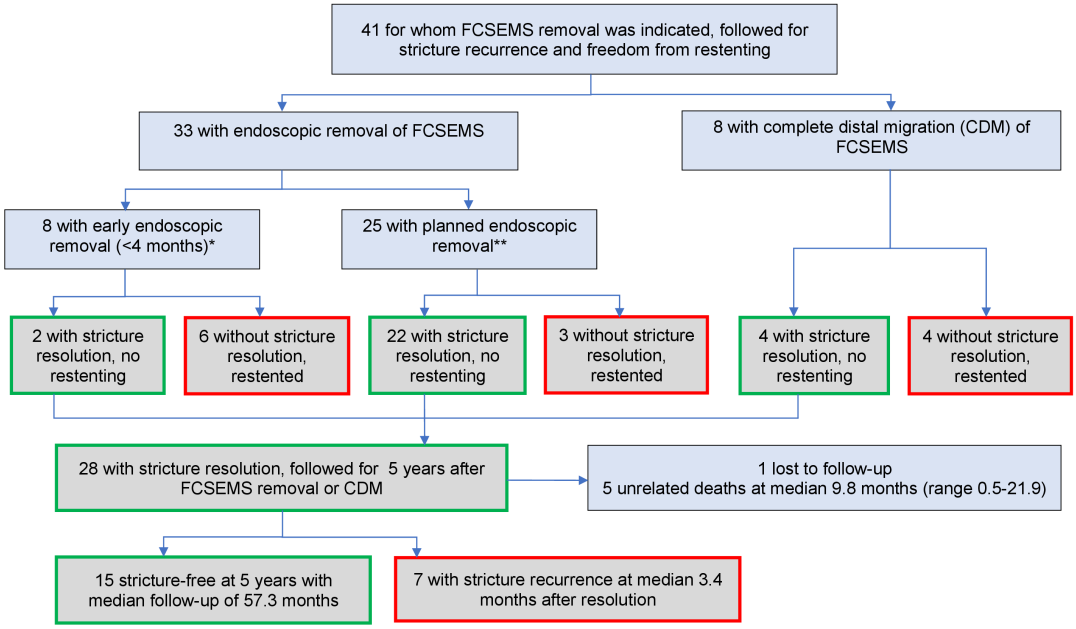
Table 1. Baseline characteristics of patients and their procedures (N=41)

Characteristic	Mean ± SD (range) or % (n/N)
Patients	
Age, mean years	56.7 ± 11.5 (28.0,77.0)
Male	82.9% (34/41)
Primary reason for liver transplant	
Alcoholic cirrhosis	39.0% (16/41)
Hepatitis B or C	26.8% (11/41)
Other	34.1% (14/41)
Time from transplant, months	32.9 ± 53.2 (0.1,234.5)
Total bilirubin level, mg/dL	4.5 ± 8.1 (0.3,35.4)
Alkaline phosphatase level, IU/L	332.6 ± 429.4 (39.0,2282.0)
Baseline procedure	
Stricture Location	
Mid	61.0% (25/41)
Proximal	39.0% (16/41)
Gallbladder in situ	0.0% (0/41)
Sphincterotomized	95.1% (39/41)
Prior plastic stent placement only	22.0% (9/41)
Prior balloon dilation only	9.8% (4/41)
Prior plastic stent placement and balloon dilation	17.1% (7/41)
Plastic stents removed	
0	65.9% (27/41)
1	26.8% (11/41)
2	4.9% (2/41)
3-5	2.4% (1/41)
Study stent size	
8 x 80 mm	2.4% (1/41)
10 x 60 mm	19.5% (8/41)
10 x 80 mm	78.0% (32/41)
Technical success	100% (41/41)

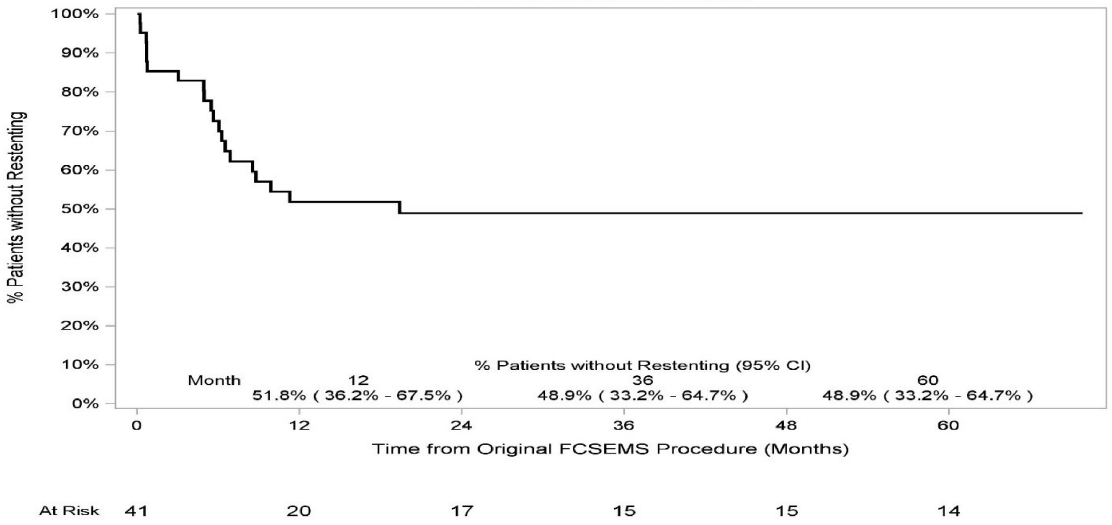
Table 2. Stent or stent-removal-related serious adverse events (SAEs) among all patients (N=41)

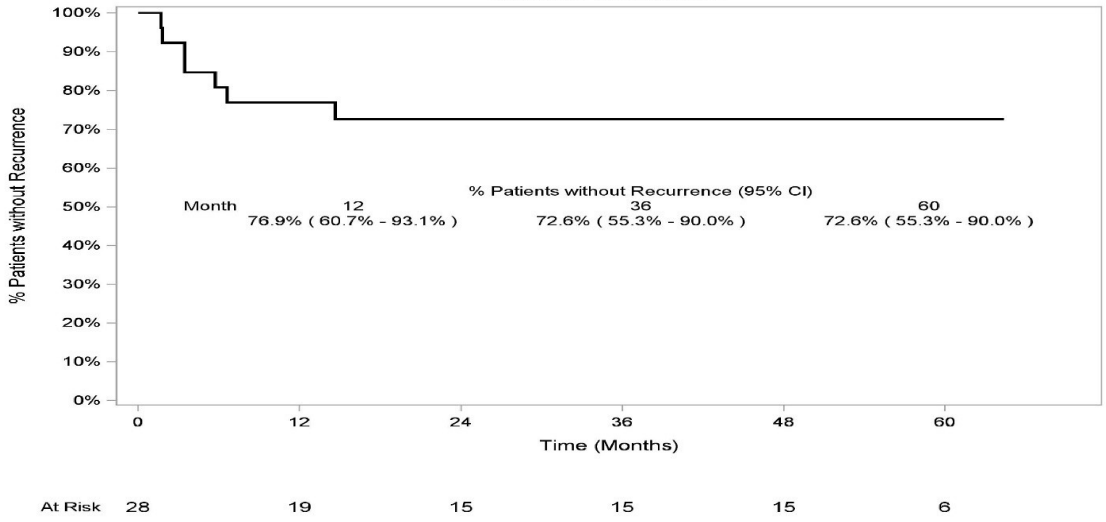
SAE	% (n/N patients)
Cholangitis/fever	24.4% (10/41)
Abdominal pain	9.8% (4/41)
Cholestasis	2.4% (1/41)
Self-limited bleeding in bile duct	2.4% (1/41)
Elevated serum bilirubin	2.4% (1/41)
Total patients with ≥1 SAE*	39.0% (16/41)

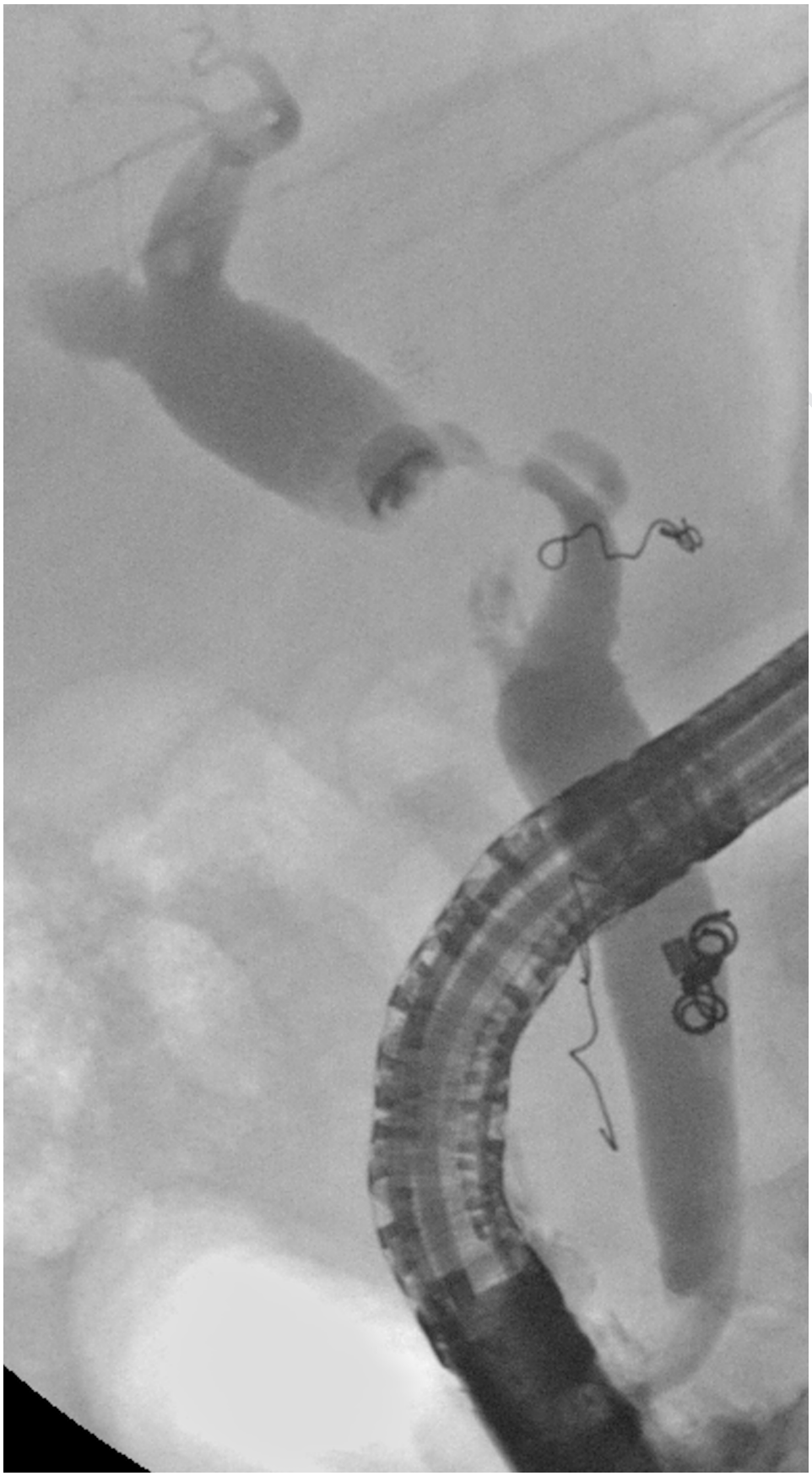
*One patient had both abdominal pain and cholangitis.

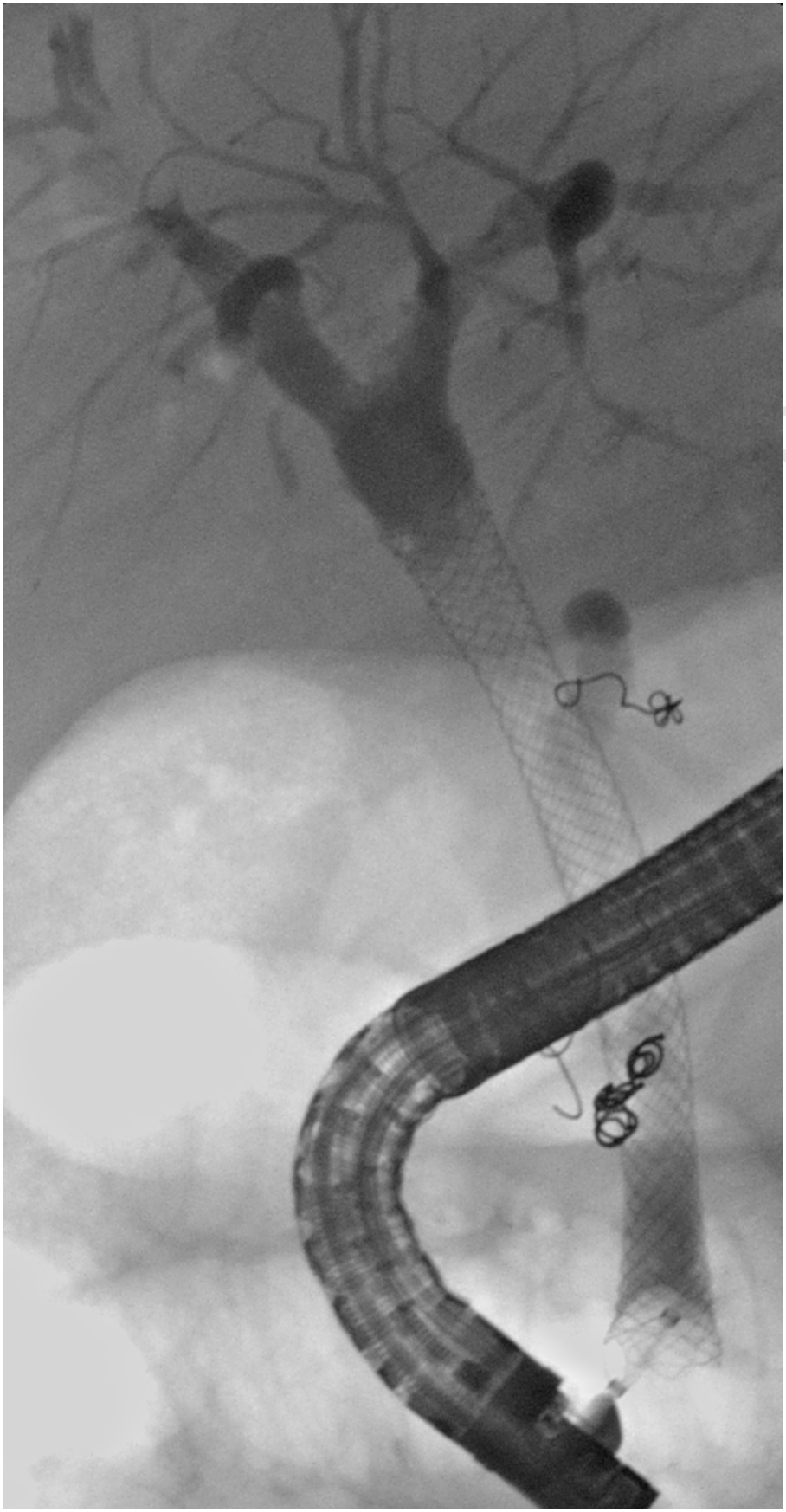


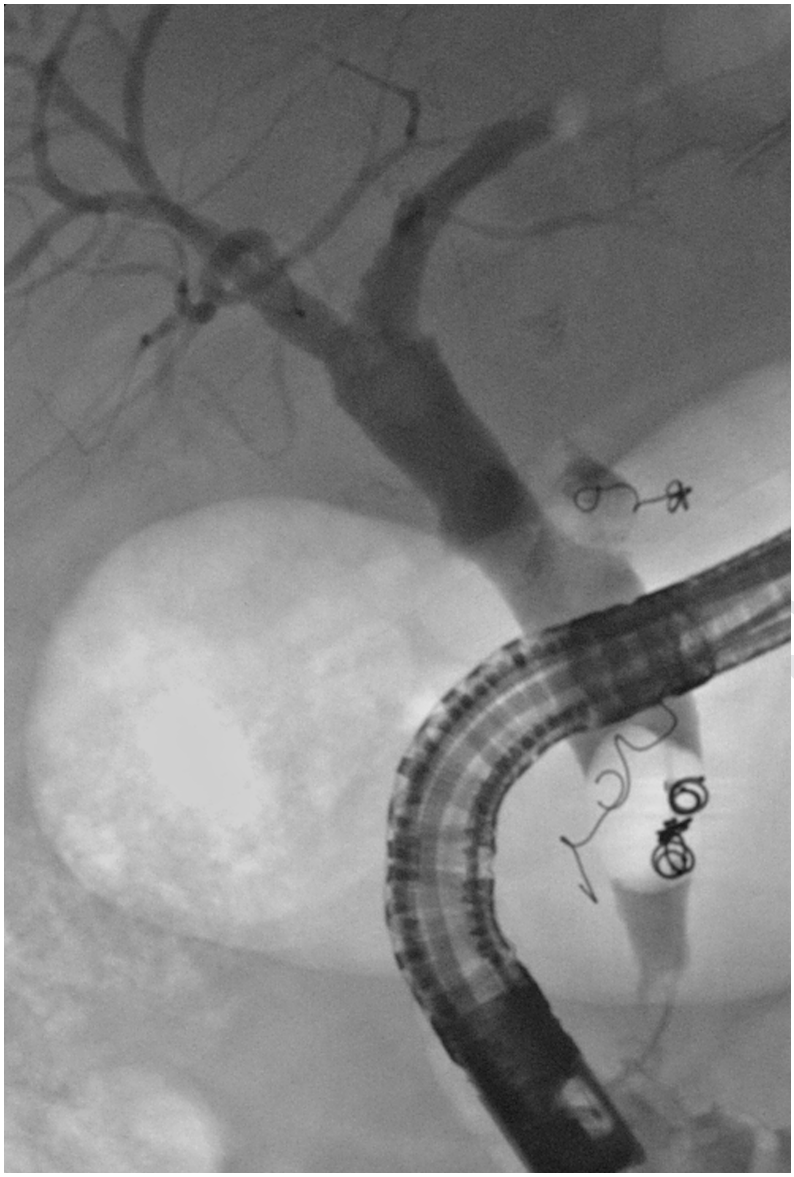
*8 with removal before 4 months due to cholangitis (3), cholestasis (2), asymptomatic migration (2), abdominal pain (1).
**Removal planned at 4-6 months and was later in some cases

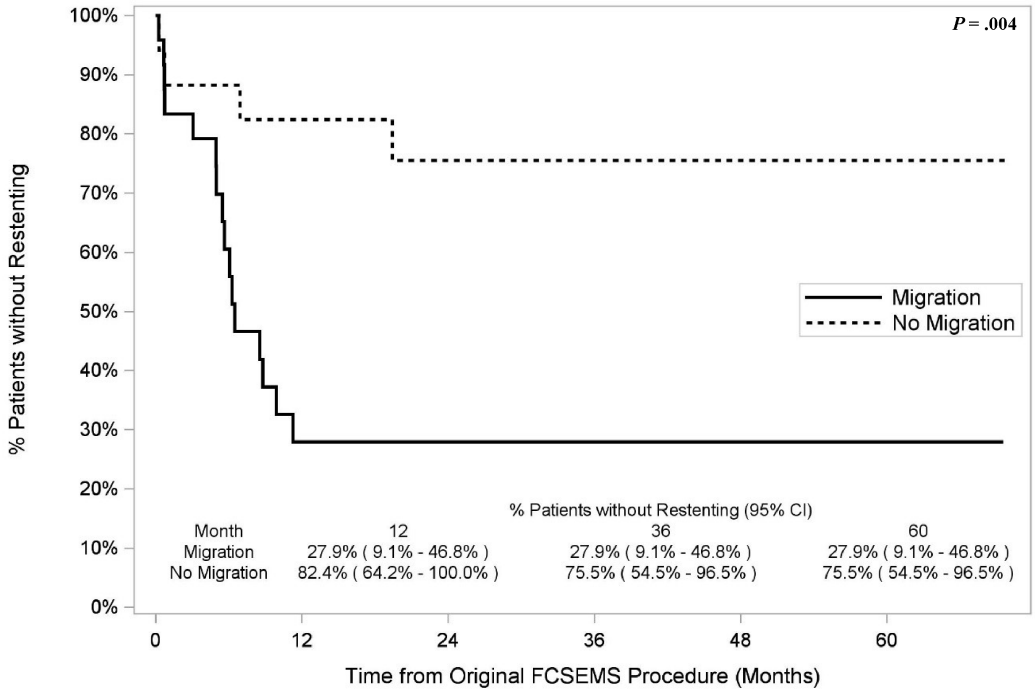

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
% Patients without Restenting
% Patients without Restenting (95% CI)
Month
12
51.8% (36.2% - 67.5%)
36
48.9% (33.2% - 64.7%)
60
48.9% (33.2% - 64.7%)
0
12
24
36
48
60
Time from Original FCSEMS Procedure (Months)
At Risk
41
20
17
15
15
14


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
% Patients without Recurrence
% Patients without Recurrence (95% CI)
Month
12
76.9% (60.7% - 93.1%)
36
72.6% (55.3% - 90.0%)
60
72.6% (55.3% - 90.0%)
0
12
24
36
48
60
Time (Months)
At Risk
28
19
15
15
15
6









At Risk							
	Migration	24	6	6	6	6	6
	No Migration	17	14	11	9	9	8

GIE IRB Checklist

Note that GIE follows the International Committee of Medical Journal Editors (ICMJE)'s Uniform Requirement for Manuscripts Submitted to Biomedical Journals. All clinical trials submitted to GIE should have been registered BEFORE the trial begins through one of the registries approved by the ICMJE, and proof of that registration, including the date registered and the registration number, must be submitted to GIE along with the article. IRBH approval information must be included in the manuscript text, including the date of registration. All clinical trials as defined by the ICMJE must also have been registered before the trial began (not just randomized clinical trials).

Yes	Have you included IRB information in your article? If not, please explain why. Do not merely put NA or your article will be returned for a fuller explanation. Comments:
November 19, 2009.	Please list here the DATE of IRB approval for your study.
ClincialTrials.gov number NCT01014390 (observational study, not RCT)	Proof of registration for randomized clinical trials, including registration number and dates of when patients were enrolled, when trial was registered, and when the trial was started, is required before subject enrollment; have you included this information?

Poley et al. Fully covered self-expanding metal stents for benign biliary stricture after orthotopic liver transplant – 5-year outcomes

Acronyms and abbreviations

BBS: benign biliary stricture

CDM: complete distal migration

CI: confidence interval

ERCP: endoscopic retrograde cholangiopancreatography

FCSEMS: fully covered self-expanding metal stent

HR: hazard ratio

IQR: inter-quartile range

MPS: multiple plastic stents

OLT: orthotopic liver transplantation

RCT: randomized controlled trial

SAE: serious adverse event

SAS: Statistical Analysis System

SD: standard deviation