Intraductal fully covered self-expandable metal stent versus multiple plastic stents for treating biliary anastomotic strictures after liver transplantation

Sissingh, N.J.; Vries, B.A. de; Inderson, A.; Hoek, B. van; Heide, F. van der; Hooft, J.E. van

Intraductal fully covered self-expandable metal stent versus multiple plastic stents for treating biliary anastomotic strictures after liver transplantation

Noor J. Sissingh, MD,[1] Boudewijn A. de Vries, MD,[2] Akin Inderson, MD,[1] Bart van Hoek, MD, PhD,[1] Frans van der Heide, MD, PhD,[2] Jeanin E. van Hooft, MD, PhD, MBA[1]

Background and aims: Fully covered metal stents (FCSEMSs) are increasingly used for treatment of biliary anastomotic strictures (ASs) after liver transplantation (LT), requiring fewer endoscopic interventions than does treatment with multiple plastic stents (MPSs). Previous studies, however, have reported adverse events such as stent migration and pancreatitis. The intraductal FCSEMS (ID-FCSEMS) potentially avoids these disadvantages. This study aimed to assess the efficacy and safety of ID-FCSEMSs compared with MPSs for AS.

Methods: The cohorts of LT patients treated for AS with endoscopic stenting between 2010 and 2019 from 2 Dutch liver transplantation centers were retrospectively analyzed. Patients treated with ID-FCSEMSs or MPSs were included.

Results: 80 patients (44 with ID-FCSEMSs vs 36 with MPSs) were included, with a median follow-up time of 52 versus 64 months ($P = .183$). Stricture resolution was 93% in the ID-FCSEMS versus 97% in the MPS group ($P = 1.000$) after a median of 19 and 26 weeks, respectively ($P = .031$). The median number of ERCPs was 2 in the ID-FCSEMS group versus 4 in the MPS group ($P < .001$). Stricture recurrence occurred in 33% of ID-FCSEMS versus 29% of MPS patients ($P = .653$) after a median of 24 and 55 weeks ($P = .403$). Stent migration occurred in 16% of ID-FCSEMS versus 39% of MPS patients ($P = .020$). Post-ERCP fever was observed in 34% of ID-FCSEMS patients compared with 14% of MPS patients ($P = .038$). No significant differences were found in pancreatitis rate between the groups, being 6.8% for ID-FCSEMSs and 5.6% for MPSs ($P = .816$).

Conclusion: ID-FCSEMSs for the treatment of AS after LT provides similar stricture resolution and recurrence rates as MPSs, though with a significant reduction of procedures needed. (Gastrointest Endosc 2023;97:704-12.)

Biliary anastomotic strictures (ASs) represent one of the most common adverse events after liver transplantation (LT), and they compromises patients' health and quality of life significantly.[1] For patients with symptoms of biliary obstruction, ERCP including balloon dilation and placement of stent(s) is the therapy of choice.[2-4]

According to the European Society of Gastrointestinal Endoscopy guideline published in 2018, an increasing

Abbreviations: AS, anastomotic stricture; FCSEMS, fully covered self-expandable metal stent; ID-FCSEMS, intraductal fully covered self-expandable metal stent; IR, incidence rate; LT, liver transplantation; MPS, multiple plastic stent.

DISCLOSURE: *Dr Inderson is a consultant for Cook Medical and Olympia and the recipient of research support from Prion Medical. Dr van Hoek received research support from Chiesi and Sandoz, and educational support from Norgine and Abacus Medicine. Dr van Hooft is a consultant for Cook Medical, Boston Scientific, Olympus, Medtronic, and Abbvie, and the recipient of research support from Cook Medical. All other authors disclosed no financial relationships.*

*Dr Sissingh and Dr de Vries contributed equally to this work.

0016-5107
https://doi.org/10.1016/j.gie.2022.11.018

Received September 25, 2022. Accepted November 18, 2022.

Current affiliations: Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands (1) and Department of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, The Netherlands (2).

Reprint requests: J.E. van Hooft, MD, PhD, MBA, Leiden University Medical Center, Department of Gastroenterology and Hepatology, Albinusdreef 2, 2333 ZA Leiden, the Netherlands. E-mail: j.e.van_hooft@lumc.nl.

number of plastic stents should be placed at 3-month intervals for 1 year to expand the diameter of the stricture while maintaining stent patency.[5] This treatment protocol for ASs is associated with excellent success rates in terms of stricture resolution (ranging from 85% to 95%) and stricture recurrence (ranging from 5% to 20%).[6-8] Unfortunately, treatment with MPSs requires multiple ERCP procedures, which repeatedly expose patients to associated burden and adverse events (ie, infection, pancreatitis, bleeding, and perforation), increases health care costs, and limits the capacity of the endoscopy suite.

Therefore, the use of fully covered self-expandable metal stents (FCSEMSs) is gaining popularity because they allow for larger luminal expansion by placement of a single stent, reducing the number of endoscopic procedures. Although the most optimal indwelling time of a FCSEMS has not yet been established, it is often placed for 6 months.[5] A recent meta-analysis by Tringali et al[9] observed similar rates of stricture resolution and stricture recurrence between FCSEMSs and MPSs. Nonetheless, patients treated with transpapillary-placed FCSEMS showed relatively high rates of stent migration (ranging from 10% to 33%)[6,8] and ERCP procedural- or stent-related pancreatitis (13%).[6]

To overcome these problems, a new intraductal fully covered self-expandable metal stent (ID-FCSEMS) with a transpapillary extraction string has been developed (Niti-S Kaffes Biliary Stent; Taewoong Medical, Gyeonggi-do, South Korea). This new stent could potentially prevent stent migration and pancreatitis because its shorter length enables a complete intraductal insertion while being easily removable because of the extraction string.[10] Previous studies have shown promising results in both AS and other types of biliary strictures regarding stricture resolution and stent migration, but those studies were limited by small sample sizes,[10,11] short follow-up periods,[11-13] or lack of a comparative group treated with MPSs as the conventional treatment.[12,13]

Therefore, the aim of this study was to determine the performance of ID-FCSEMSs compared with MPSs based on the number of ERCPs needed to reach efficacy, which is reflected by stricture resolution and stricture recurrence, and safety for the treatment of AS after LT.

MATERIALS AND METHODS

We conducted a multicenter retrospective cohort study from 2 Dutch LT centers: the Leiden University Medical Center, Leiden, The Netherlands, and the University Medical Center Groningen, Groningen, The Netherlands. Between 2010 and 2019, all LT patients from these centers were reviewed for the development of AS. The following inclusions were used: AS confirmed by ERCP, defined as a dominant narrowing at the biliary anastomotic site on cholangiography, and ID-FCSEMS placement in patients from Leiden or MPS placement in patients from Groningen. AS was categorized as a first episode, including strictures without prior treatment or previously managed with balloon dilation or stent placement that was unsuccessful, or a recurring stricture after initial successful treatment. Data were collected from medical charts and endoscopy reports. The need for ethical approval was waived by the medical ethics committee. This study was reported according to the STROBE (Strengthening the Reporting of Observational studies in the Epidemiology) guideline.[14]

Stent procedure

All ERCP procedures were performed by endoscopists with experience of >500 ERCPs. All patients received intravenous antibiotic prophylaxis before the ERCP, and from 2016 rectal diclofenac (100 mg suppository) was routinely given. After guidewire-assisted biliary cannulation, papillotomy was performed at the endoscopist's discretion. In most patients, the stricture was dilated by balloon dilation before stent placement. For patients with an AS to be eligible for treatment with ID-FCSEMSs, the minimal stricture distance to the biliary confluence had to be approximately 2 cm. Based on the diameter of the bile duct on cholangiography, the diameter of the ID-FCSEMS was determined. Over the guidewire, an 8-mm or 10-mm-wide/40-mm-long Niti-S Kaffes Biliary Stent (Taewoong Medical, Seoul, Korea) was placed with the middle radiopaque marker aligning with the AS. The body of the stent resided inside the biliary duct; the extraction string resided transpapillary in the duodenum (Fig. 1). After 6 months, ERCP was scheduled for ID-FCSEMS removal. In the MPS group, 1 or more 10F Advanix Biliary stents (Boston Scientific, Marlborough, Mass, USA) were placed across the stricture. With each successive ERCP every 6 to 12 weeks, stents were removed and, after further balloon dilation (if technically feasible), replaced with an increasing number of plastic stents until the desired diameter had been reached. In both groups, outpatient follow-up visits were regularly scheduled for patients to evaluate cholestatic liver enzymes. ERCP was performed earlier than scheduled if patients experienced acute cholangitis, elevation of cholestatic liver enzymes, or any endoscopy-related adverse events, for example hemobilia. Abdominal imaging was preferably conducted to evaluate the position of the stent before ERCP. If the stricture was still present, the stent or stents were exchanged, and the following ERCP was scheduled according to the protocol. After stent removal, outpatient follow-up visits were planned every 3 months in the first year, and laboratory tests and abdominal imaging were performed to evaluate recurrence of the stricture. After the first year, follow-up visits were scheduled at regular intervals of 6 to 12 months.

Outcome and definitions

The primary outcome was efficacy, reflected by stricture resolution, the number of ERCPs needed to achieve stricture resolution, and stricture recurrence. Stricture resolution was defined as free contrast flow across the previous stricture

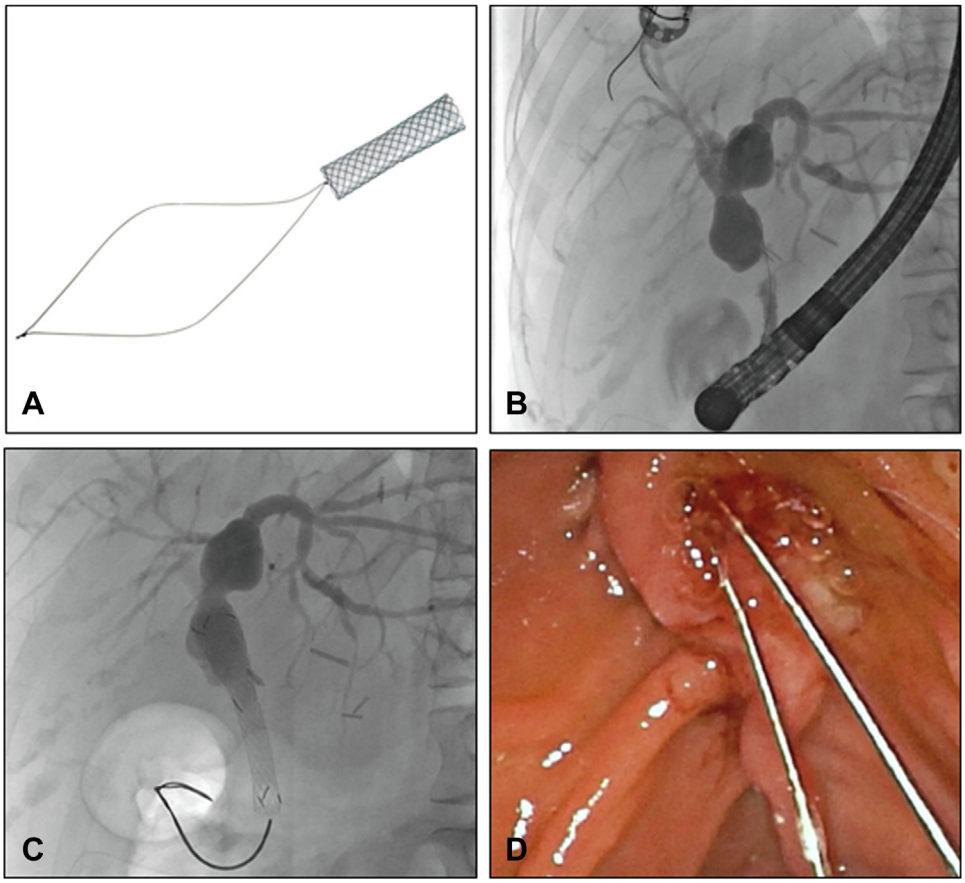


Figure 1. A, Intraductal fully covered self-expandable metal stent. **B,** Anastomotic stricture after liver transplantation. **C,** Stent placed intraductally across stricture. **D,** Retrieval string transpapillary in duodenum.

after stent removal, without the need for replacement of a stent. The number of ERCPs described all ERCPs performed during the treatment period, ie, the period between placement of an ID-FCSEMS or MPS and the date of stricture resolution or, in case of no resolution, the date of removal of the ID-FCSEMS or MPS. Stricture recurrence was defined as clinical or biochemical signs of cholestasis in combination with ERCP showing an AS. Secondary outcomes included other outcomes related to efficacy (ie, time to resolution, time to recurrence, and total length of hospital stay) and outcomes related to safety (ie, cholangitis, bacteremia, fever, pancreatitis, sphincterotomy bleeding, perforation, and stent migration). All adverse events were recorded during the predefined treatment period, including the events related to the last performed ERCP. Hospital stay included all admission days related to ERCP procedures and/or related adverse events. The 2018 Tokyo classification was used to define bacterial cholangitis, counting only events that were classified as definite.[15] Fever in combination with a positive blood culture was defined as bacteremia. Post-ERCP fever was defined as a temperature >38.5°C in the absence of a positive blood culture during the first 2 days after ERCP and without signs of stent dysfunction and a mild clinical course, resulting in full recovery within 48 hours. Pancreatitis was defined according to the 2012 revised Atlanta classification.[16] Sphincterotomy bleeding referred to significant bleeding within 14 days after ERCP requiring an intervention. Perforation had to be identified on endoscopic and/or radiologic imaging. Stent migration was defined as displacement of a stent so extensive that it no longer crossed the AS on the basis of an endoscopy report. The posttreatment follow-up period was defined as the period after stricture resolution until the end of follow-up care. All potential outcomes were evaluated by an adjudication committee. Disagreements were resolved during a consensus meeting.

Statistical analysis

Categoric data are reported as frequency and percentages and, in case of numeric data, as mean with standard deviation (SD) when normally distributed or as median with interquartile range (IQR) when not normally distributed. Both treatment arms were compared by the χ^2 test or Fisher exact test (categoric data) and unpaired *t* test or Mann-Whitney *U* test (numeric data). Inasmuch as duration of treatment between both groups differed, person-time incidence rates (IR) were calculated for stent- and procedure-related adverse events to allow comparison. Multiple instances of a specific adverse event in a single

patient were intentionally included in the calculation of IR to prevent underestimation. IRs are reported in 100 person-weeks; an IR of 1.0 therefore represents 1 event in 100 persons treated for 1 week. A 2-tailed P value of $< .05$ was considered statistically significant. All analyses were conducted with SPSS Statistics version 24.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 80 LT patients who met the inclusion criteria (44 ID-FCSEMS patients and 36 MPS patients) were analyzed. Table 1 demonstrates all baseline characteristics including the indication for LT. The median time between LT and first AS diagnosis was 15.0 weeks (IQR 6.0-28.0) in patients treated with ID-FCSEMS and 18.0 weeks (IQR 7.8-50.0) with MPS. The ID-FCSEMS group consisted of 38 patients (86.4%) with a first episode of AS and 6 patients (13.6%) with recurrent AS after previous successful treatment. In the 38 patients with a first episode of AS, 19 patients (50%) had received prior treatment (12 with a single plastic stent, 3 with MPSs, 2 with FCSEMSs, and 2 with percutaneous biliary drainage) that had failed to resolve the stricture before the start of ID-FCSEMS treatment. The MPS group consisted of 34 patients (94.4%) with a first episode of AS and 2 patients (5.6%) with recurrent AS after previous successful therapy. In the 34 patients with a first episode of AS, 3 (8.3%) had been treated with balloon dilation without stricture resolution before starting treatment with MPSs. The rates of prior sphincterotomy before the treatment of AS in the ID-FCSEMS group and in the MPS group were significantly different (66% vs 14% $P < .001$). The posttreatment follow-up time was 52.0 months (IQR 28.3-71.0) in the ID-FCSEMS group and 64.0 months (IQR 41.0-80.0) in the MPS group ($P = .183$).

Efficacy

The stricture resolution rates were high in both arms: 93.3% in ID-FCSEMSs and 97.2% in MPSs and did not differ significantly ($P = 1.000$) (Table 2). Stricture resolution was not achieved in 2 patients treated with ID-FCSEMSs. One patient was subsequently treated with an MPS because of concomitant development of perihilar strictures during treatment with ID-FCSEMS, and stricture resolution was achieved. The other patient was treated with balloon dilation; no stent was replaced because the stenosis responded well to dilation, and follow-up procedures would have been complex because of previous gastric bypass surgery. Treatment with MPS failed in 1 patient, after which the treatment was switched successfully to a FCSEMS. After treatment initiation, the median time to stricture resolution was 19.0 weeks (IQR 16.0-26.0) for patients treated with ID-FCSEMSs compared with 26.0 weeks (IQR 16.0-37.0) for patients treated with MPSs, resulting in significant differences in treatment time ($P = .031$). A median total number of 2.0 ERCPs per patient (IQR 2.0-3.0) was required to achieve stricture resolution in the ID-FCSEMS arm versus 4.0 ERCPs (IQR 3.0-5.0) in the MPS arm ($P < .05$). The median total days of hospitalization was shorter in patients treated with ID-FCSEMSs than in patients treated with MPSs (6.0 days [IQR 4.0-8.8] vs 11.0 days [IQR 7.3-19.3]; $P < .05$). In the ID-FCSEMS group, 14 out of 44 initially successfully treated patients (33.3%) experienced stricture recurrence after initial stricture resolution versus 10 out of 36 patients (28.6%) in the MPS group ($P = .805$). Among 24 patients who experienced stricture recurrence, the median times between stricture resolution and stricture recurrence did not differ significantly between patients treated with ID-FCSEMSs and MPSs (23.5 weeks [IQR 13.8-126.5] vs 55.0 weeks [IQR 21.0-149.8]; $P = .403$). Additional data concerning stent-related procedural details are given in Supplementary Table 1 (available online at www.giejournal.org), and Kaplan-Meier curves for both stricture resolution and recurrence can be found in Supplementary Figure 1 (available online at www.giejournal.org). The efficacy of previous studies concerning the use of ID-FCSEMSs in ASs is summarized in Table 4.

Safety

Eight cases of stent migration were observed in 7 patients (15.9%) treated with ID-FCSEMSs. These cases were observed during elective ERCP (n = 8) or ERCP in the setting of progressive cholestatic liver enzymes (n = 2) and cholangitis (n = 1). In 1 case, an SEMS-in-SEMS approach was required for successful removal of the migrated stent. A total of 21 cases of stent migration (n = 14 elective setting, n = 4 progressive cholestatic liver enzymes, n = 2 cholangitis, n = 1 pain) were observed in 14 patients (38.9%) in the MPS group, resulting in a significant difference between the groups with regard to stent migration ($P = .020$). The migration IR for ID-FCSEMSs was 0.87 per 100 person-weeks, compared with migration IR of 2.06 per 100 person-weeks in MPSs ($P = .032$). There were no cases of failed stent removal in either group except for the previously reported case, and no cases of a broken ID-FCSEMS or its retrieval string. In both groups a distal stent migration was seen in the majority of cases (Table 3). During the treatment period, 7 events of cholangitis occurred in 6 patients in the ID-FCSEMS group (13.6%) compared with 12 in 9 patients in the MPS patients (25%) ($P = .195$). The IR of cholangitis in the ID-FCSEMS group was 0.76 per 100 person-weeks compared with 1.18 per 100 person-weeks in the MPS group ($P = .354$). With the exception of fever, other adverse events were comparable between groups. Fever was the main cause of adverse events, with 18 cases in 15 patients (34.1%) in the ID-FCSEMS group and 5 cases in 5 patients (13.9%) in the MPS group ($P = .038$). The IR of fever was 1.96 per 100 person-weeks in ID-FCSEMSs and 0.49 per 100 persons-weeks in MPSs, resulting in a significant difference

TABLE 1. Baseline characteristics

Characteristic	ID-FCSEMS (n = 44)	MPS (n = 36)	*P* value
Age (years)	58.0 (50.8-64.0)	52.0 (31.0-59.8)	.008
Male sex	32 (72.7)	18 (50.0)	.062
Indication for LT			.503
Alcoholic liver disease	11(25.0)	9 (25.0)	
Non-alcoholic steatosis hepatitis	5 (11.4)	4 (11.0)	
Hepatitis C	7 (15.9)	2 (5.6)	
Hepatitis B	2 (4.5)	1 (2.8)	
Primary sclerosing cholangitis	6 (13.6)	2 (5.6)	
Primary biliary cholangitis	3 (6.8)	2 (5.6)	
Acute liver failure	4 (9.1)	5 (13.9)	
Other	6 (13.6)	11 (30.5)	
Presence of HCC	19 (43.2)	8 (22.2)	.049
Type of donor			.816
Heart beating	27 (61.4)	23 (63.9)	
Non-heart beating	17 (38.6)	13 (36.1)	
Time to AS (weeks)	15 (6.0-28.0)	18 (7.8-50.0)	.350
Type of AS			.284
First episode	38 (86.4)	34 (94.4)	
Recurrent stricture	6 (13.6)	2 (5.6)	
Concomitant NAS	6 (13.6)	8 (22.2)	.315
Prior papillotomy	29 (66.0)	5 (13.9)	.001
Posttreatment follow-up (months)	52 (28.3-71.0)	64 (41.0-80.0)	.183

Data are presented as n (%) or median (IQR).
AS, Anastomotic stricture; *HCC,* hepatocellular carcinoma; *LT,* liver transplantation; *NAS,* nonanastomotic stricture; *ID-FCSEMS,* intraductal fully covered self-expandable metal stent; *MPS,* multiple plastic stent.

TABLE 2. Primary and secondary outcomes related to efficacy

Outcomes	ID-FCSEMS (n = 44)	MPS (n = 36)	*P* value
Primary			
Stricture resolution	42 (93.3)	35 (97.2)	1.000
Stricture recurrence	14 (33.3)	10 (28.6)	.653
Number of ERCP	2 (2.0-3.0)	4 (3.0-5.0)	< .001
Secondary			
Time to resolution (weeks)	19 (16.0-26.0)	26 (16.0-37.0)	.031
Time to recurrence (weeks)	23.5 (13.8-126.5)	55 (21.0-149.8)	.403
Admission days	6 (4.0-8.8)	10 (7.3-19.3)	< .001

Data are presented as n (%) or median (IQR).
ID-FCSEMS, intraductal fully covered self-expandable metal stent; *MPS,* multiple plastic stent.

between groups ($P = .003$). Bacteremia was present in 3 patients treated with ID-FCSEMS and in 1 patient treated with MPS (6.8% vs 2.8%%, $P = .409$). Three patients in the ID-FCSEMS arm (6.8%) experienced post-ERCP pancreatitis compared with 2 patients in the MPS arm (5.6%) ($P = .816$). Sphincterotomy bleeding occurred in 2 patients treated with ID-FCSEMSs (4.5%) and in 0 patients treated with MPSs ($P = .195$). The incidence rates for bacteremia, post-ERCP pancreatitis, and sphincterotomy bleeding are reported in Table 3.

DISCUSSION

This multicenter retrospective cohort study comprising 80 patients with ASs after LT demonstrates that endoscopic

TABLE 3. Secondary outcomes related to safety

Outcomes	ID-FCSEMS (n = 44)	MPS (n = 36)	*P* value
Stent migration	7 (15.9)	14 (38.9)	.020
Distal migration	4 (57.1)	13 (92.9)	.003
Proximal migration	3 (42.9)	2 (14.3)*	.818
Stent migration – IR	.87	2.06	.032
Cholangitis	6 (13.6)	9 (25.0)	.195
Cholangitis – IR	.76	1.18	.354
Fever	15 (34.1)	5 (13.9)	.038
Fever – IR	1.96	.49	.003
Bacteremia	3 (6.8)	1 (2.8)	.409
Bacteremia – IR	.33	.10	.269
Pancreatitis	3 (6.8)	2 (5.6)	.816
Pancreatitis – IR	.33	.20	.573
Sphincterotomy bleeding	2 (4.5)	0	.195
Sphincterotomy bleeding – IR	.22	0	.136
Perforation	0	0	-

Data are presented as n (%) or as *IR,* incidence rate per 100 persons-weeks.
ID-FCSEMS, Intraductal fully covered self-expandable metal stent; *MPS,* multiple plastic stents.
*In 1 person in the MPS group, proximal and distal stent migrations were noted in the same procedure, resulting in 15 migrations in 14 patients.

TABLE 4. Overview of literature on management of anastomotic strictures after liver transplantation

Study	Year	Design	N	Inclusion	Resolution	Recurrence	Migration	Cholangitis	Pancreatitis	Follow-up
Intraductal FCSEMS vs MPS										
Kaffes et al[10]	2014	RCT	20	Post-LT AS	100% vs 80%	30% vs 38%	0% vs 10%	10% vs 40%	0	~2 years
Zeair et al[11]	2017	Retrospective	28	Post-LT AS	92% vs 69%	9% vs 36%	0% vs NA	17% vs 6%	0	NA
This study	2022	Retrospective	80	Post-LT AS	93% vs 97%	33% vs 29%	16% vs 39%	14% vs 25%	7% vs 6%	~5 years
Transpapillary FCSEMS vs MPS										
Côte et al[7]	2016	RCT	102	Naïve BBS (65% post-LT)	93% vs 86%	14% vs 5%	25% vs 16%	4% vs 2%	5% vs 5%	~1 year
Tal et al[8]	2017	RCT	48	Naïve post-LT AS	100% vs 96%	21% vs 21%	33% vs NA	NA	NA	~1 year
Martins et al[6]	2018	RCT	59	Naïve post-LT AS	83% vs 97%	32% vs 0%	10% vs 3%*	NA	13% vs 2%*	~2 years
Cantu et al[19]	2021	RCT	30	Naïve post-LT AS	73% vs 93%	36% vs 7%	29% vs 3%†	7% vs 2%*	4% vs 3%*	~5 years
Intraductal FCSEMS only										
Moon et al[13]	2012	Prospective	29	Refractory BBS (14% post-LDLT)	97% (92% post-LT)	11%	3%	0	0	~1 year
Aepli et al[12]	2017	Retrospective	29	Post-LT AS	100%	24%	3%	7%	0	NA
Sato et al[18]	2020	Prospective	29	Refractory BBS (43% post-LDLT)	97% (% post-LT)	11%	3%	17%	3%	~1 year
Transpapillary FCSEMS only										
Poley et al[20]	2020	Prospective	41	Post-LT AS	68%	51%	20%	24%	0	~5 years

AS, anastomic stricture; *BBS,* benign biliary stricture; *FCSEMS,* fully covered self-expandable metal stent; *LT,* liver transplantation; *LDLT,* living donor liver transplantation; *MPS,* multiple plastic stents; *NA,* not available; *RCT,* randomized controlled trial.
*Percentages based on the number of ERCP procedures.
†Percentages based on the number of stents placed.

treatment with an ID-FCSEMS may be a favorable alternative to treatment with MPS.

ERCP with stent placement is the established first-line treatment for AS after LT and has a high success rate.[5] The optimal stent strategy, however, remains a matter of debate.[17] The main shortcoming of the conventional treatment with MPSs is the need for repeated ERCP procedures and its inherent risk of adverse events, increased

healthcare costs, more waste, and more inconvenience for patients. Although placement of FCSEMSs reduces the number of ERCPs required, the rate of stent migration and pancreatitis remain substantial.[6] The ID-FCSEMS has the potential to overcome the problems of both stent strategies. It provides a continuous strong radial force on the stricture without the need for repeated ERCP and stent placement. Additionally, it has a reduced stent length not covering the distal common bile duct combined with a waist shape, aimed to minimize the risk of pancreatitis and stent migration.

In the present study, the ID-FCSEMS was found to have an efficacy similar to that of the MPS in terms of stricture resolution (93% vs 97%) and recurrence (33% vs 29%), which was reached with significantly fewer ERCP procedures (2.0 vs 4.0). As a measure of patient burden, treatment with ID-FCSEMSs was also associated with a significant reduction in treatment time and admission days compared with MPSs. Previous studies that evaluated the use of an ID-FCSEMS in AS after LT showed similar rates of stricture resolution (ranging from 92% to 100%) and stricture recurrence (ranging from 9% to 33%).[10-13,18] Moreover, the stricture and recurrence rates observed in our study are comparable with those in previous published data of treatment with MPSs[6-8,10,11,19] and a transpapillary placed FCSEMS (Table 4).[6-8,19,20] Although recurrence rates were similar between groups, a nonstatistical difference in the median time to stricture recurrence was seen in treatment with ID-FCSEMSs when compared with MPSs (24.0 weeks vs 55.0 weeks). A possible cause of this difference could be the reduced treatment time in the ID-FCSEMS group, limiting the long-lasting effect of the stent on the stricture and resulting in faster recurrence. Another explanation could be the inclusion of a large number of patients in the ID-FCSEMS cohort who did not respond to prior therapy, which may correspond to a group with more treatment-resistant strictures in comparison with the MPS group. Nevertheless, the possible risk factors for stricture recurrence after initial success remain unknown and require further study.[21]

As stated earlier, an additional benefit of an ID-FCSEMS over an FCSEMS and MPS is the potential reduced risk of stent migration and adverse events. Stent migration may result from loss of grip on the biliary wall after stricture resolution or from peristalsis before stricture resolution has been achieved, rendering stent migration a complex event to interpret. Our study found a 16% overall migration rate for ID-FCSEMSs. Nonintraductal design FCSEMSs have a stent migration rate of 10% to 33%.[6-8,19,20] Data on treatment with ID-FCSEMSs in AS are limited, reporting migration rates of 0%[10,11] and 3%,[12,13,18] respectively. Therefore, owing to their antimigration properties, intraductal stents seem to have the advantage of better stent retention compared with transpapillary-placed FCSEMSs. Stent migration in the MPS group was substantially increased (39%) in the present study, which is inconsistent with previous published reports.[6-8,10,11,19] A possible explanation is that scores of stent migration were based on either the endoscopy report or clinical suspicion in the medical chart, which could have resulted in an overestimation. A risk of stent migration is the development of bacterial cholangitis resulting from the combination of reduced bile flow and the loss of barrier function between the intestine and bile ducts allowing bacterial translocation. However, only 1 case of stent migration in the ID-FCSEMS group (13%) and 2 cases in the MPS group (10%) were associated with cholangitis, whereas approximately two-thirds of cases were detected during elective ERCP for the treatment of AS and did not have clinical consequences. Another cause of cholangitis after LT is the presence of (concomitant) nonanastomotic strictures. In our study, nonanastomotic strictures were present in 22% of patients in the MPS group compared with 14% in the ID-FCSEMS group. Although not significant, the rate of cholangitis in our study was found to be higher in the MPS group (25%) than in the ID-FCSEMS group (13.6%) and corresponds to previous studies reporting a rate of 0% to 17% in the ID-FCSEMS[10-13,18] group and 2% to 40% in the MPS[7,10,11,19] group. The higher amount of concomitant nonanastomotic strictures therefore could also explain the trend toward a higher prevalence of cholangitis in the MPS group. It should be noted that, unlike in other studies, definitive cholangitis was diagnosed on the basis of the Tokyo guidelines,[15] which rely on signs of both systemic inflammation and cholestasis, and imaging findings. The use of these guidelines also allowed us to differentiate between cholangitis, post-ERCP fever, and bacteremia. This study showed that postprocedural fever occurs more often in patients with ID-FCSEMSs (34%) than in those with MPSs (14%). It is possible that strictures treated with ID-FCSEMSs are, in theory, more prone to bacterial translocation because they are exposed to a stronger radial force than those treated with MPSs. Bacterial translocation may produce fever, progress into bacteremia, and subsequently cause sepsis, especially in immunocompromised patients. In our study, however, a diagnosis of post-ERCP fever was made in the absence of a positive blood culture and was associated with a quick response to antibiotic therapy, with symptoms subsiding within 24 hours. Fever after ERCP was therefore deemed a relatively harmless event. The rates of other, more serious adverse events (ie, bacteremia, pancreatitis, and sphincterotomy bleeding) were low and did not differ between groups.

Considering strengths and limitations, the retrospective and nonrandomized design of our current study has several drawbacks. We compared, in the same era, 2 patient groups from 2 different transplantation centers. As a result, the durations of follow-up differed between groups, and no detailed analysis of cost effectiveness could be provided. In addition, the retrospective nature of the study introduced bias and confounders, which limit the impact of our results and statistical analysis in comparison with a

randomized trial design. For example, the significantly higher rates of prior sphincterotomy in the group with ID-FCSEMSs could have contributed to the overall low rate of pancreatitis and postsphincterotomy bleeding observed in this study. In addition, the large number of patients in the ID-FCSEMS group with strictures that did not respond to prior treatment was significantly higher when compared with the MPS group. The larger portion of "resistant" strictures in the ID-FCSEMS group is a notable confounder, and its effect on the outcome parameters is unknown.

In addition, stent treatment duration was not standardized between groups, which may have contributed to a difference in stricture recurrence. However, the current study constitutes the largest cohort of patients with AS after LT to date. Although most stent series have analyzed an average number of 46 patients and have had limited follow-up times of several months to 3 years (Table 4), our multicenter study comprised a sample size of 80 patients with a relatively long follow-up of 3 and 5 years in the ID-FCSEMS and MPS groups, respectively. Another strength of this study is the similarity in the basic characteristics between treatment groups, despite its retrospective and multicenter character. Furthermore, our outcomes were defined by a strict and concise set of criteria, allowing clear comparison with data from other centers.

Recent meta-analyses[9,22] have shown non-inferiority for FCSEMSs in the treatment of AS after LT with the need for fewer ERCPs. Nonetheless, a high stent migration rate is a reported disadvantage of treatment with FCSEMSs.[7,8,19] In our study, the treatment of AS with ID-FCSEMSs was associated with similar efficacy but a significantly shorter treatment time in comparison with MPSs and the benefit of a low migration rate in the ID-FCSEMS group. The trend seen in our study toward shorter stricture recurrence times, however, could be a potential drawback of ID-FCSEMS treatment. A recent prospective series by Poley et al[20] found that a longer stent indwell time was associated with lower stricture recurrence and emphasized the need for studies with an adequate stenting treatment time and longer follow-up duration. The low migration rates of ID-FCSEMSs improves stent indwell time, allowing longer stent treatment time without the need for additional ERCPs. It could therefore be hypothesized that extending the treatment duration with ID-FCSEMSs could have a positive effect on stricture recurrence and time to stricture recurrence. Our data combined with previous studies suggest the need for a multicenter prospective comparative study of intraductal FCSEMSs versus MPSs with a minimal treatment duration of 6 months, and long follow-up times in predefined groups of treatment-naïve and experienced LT patients.

In conclusion, this retrospective study consisting of 80 patients with a median follow-up time of >50 months shows that intraductal fully covered self-expandable metal stents for the treatment of anastomotic biliary strictures after liver transplantation is promising. The use of an intraductal fully covered metal stent reduces patient burden in comparison with treatment with multiple plastic stents, inasmuch as stricture resolution was achieved earlier with fewer ERCPs and fewer admission days while offering similar effectiveness for stricture resolution and recurrence. A follow-up randomized controlled trial is required to assess whether the treatment of anastomotic strictures with intraductal fully covered metal stent is cost effective over multiple plastic stents.

REFERENCES

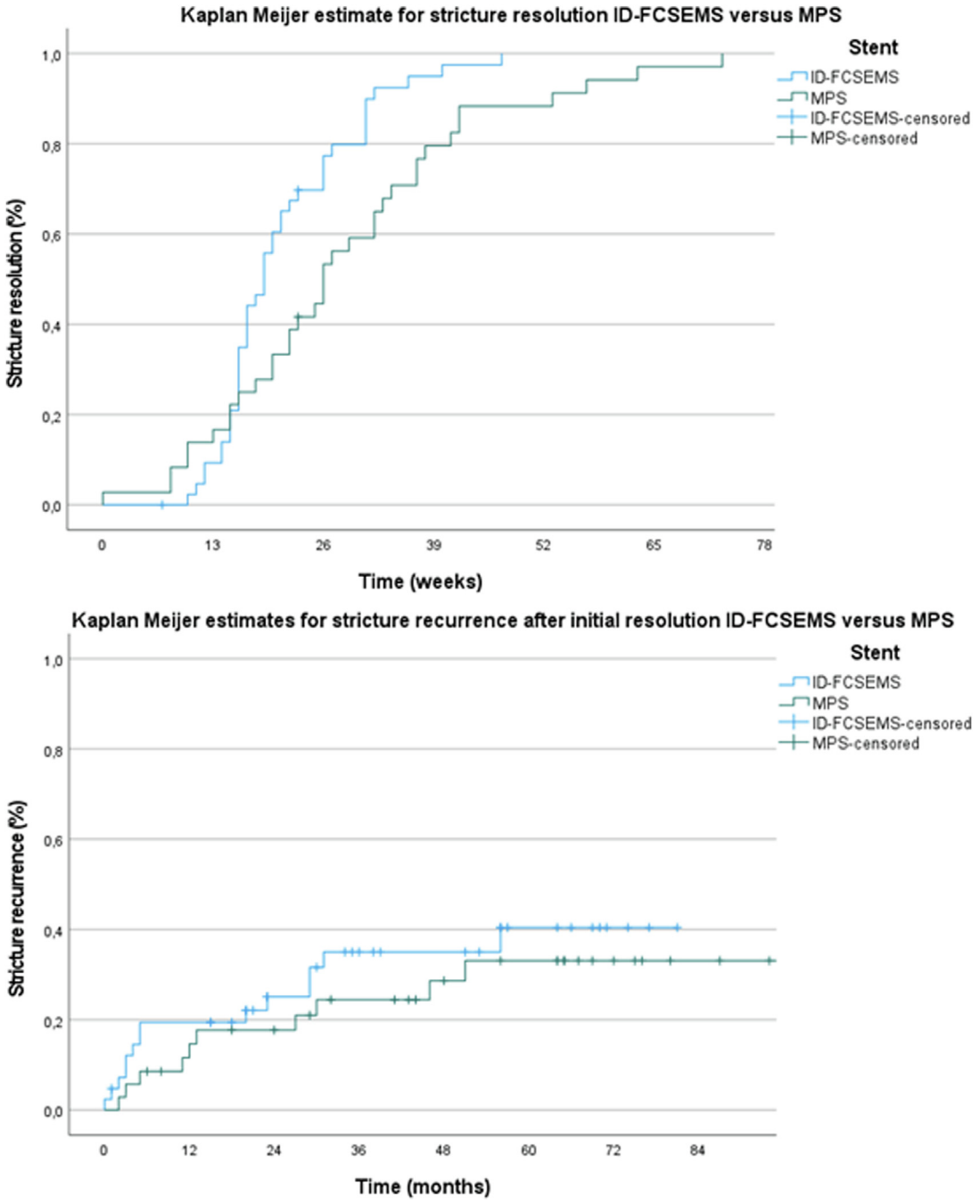
1. Tingle SJ, Thompson ER, Ali SS, et al. Risk factors and impact of early anastomotic biliary complications after liver transplantation: UK registry analysis. BJS Open 2021;5:zrab019.
2. Sharma S, Gurakar A, Jabbour N. Biliary strictures following liver transplantation: past, present and preventive strategies. Liver Transpl 2008;14:759-69.
3. Park JS, Kim MH, Lee SK, et al. Efficacy of endoscopic and percutaneous treatments for biliary complications after cadaveric and living donor liver transplantation. Gastrointest Endosc 2003;57:78-85.
4. Graziadei IW, Schwaighofer H, Koch R, et al. Long-term outcome of endoscopic treatment of biliary strictures after liver transplantation. Liver Transpl 2006;12:718-25.
5. Dumonceau JM, Tringali A, Papanikolaou IS, et al. Endoscopic biliary stenting: indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline - updated October 2017. Endoscopy 2018;50:910-30.
6. Martins FP, De Paulo GA, Contini MLC, et al. Metal versus plastic stents for anastomotic biliary strictures after liver transplantation: a randomized controlled trial. Gastrointest Endosc 2018;87:131.e1-13.
7. Coté GA, Slivka A, Tarnasky P, et al. Effect of covered metallic stents compared with plastic stents on benign biliary stricture resolution: a randomized clinical trial. JAMA 2016;315:1250-7.
8. Tal AO, Finkelmeier F, Filmann N, et al. Multiple plastic stents versus covered metal stent for treatment of anastomotic biliary strictures after liver transplantation: a prospective, randomized, multicenter trial. Gastrointest Endosc 2017;86:1038-45.
9. Tringali A, Tarantino I, Barresi L, et al. Multiple plastic versus fully covered metal stents for managing post-liver transplantation anastomotic biliary strictures: a meta-analysis of randomized controlled trials. Ann Gastroenterol 2019;32:407-15.
10. Kaffes A, Griffin S, Vaughan R, et al. A randomized trial of a fully covered self-expandable metallic stent versus plastic stents in anastomotic biliary strictures after liver transplantation. Therap Adv Gastroenterol 2014;7:64-71.
11. Zeair S, Butkiewicz F, Butkiewicz J, et al. Application of fully covered self-expandable metallic stents with and without antimigration waist versus repeated plastic biliary stent placement in management of anastomotic biliary strictures after orthotopic liver transplantation. Ann Transplant 2017;22:719-24.
12. Aepli P, St John A, Gupta S, et al. Success and complications of an intraductal fully covered self-expanding metal stent (ID-FCSEMS) to treat anastomotic biliary strictures (AS) after orthotopic liver transplantation (OLT). Surg Endosc 2017;31:1558-63.
13. Moon JH, Choi HJ, Koo HC, et al. Feasibility of placing a modified fully covered self-expandable metal stent above the papilla to minimize stent-induced bile duct injury in patients with refractory benign biliary strictures (with videos). Gastrointest Endosc 2012;75:1080-5.
14. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344-9.
15. Kiriyama S, Kozaka K, Takada T, et al. Tokyo guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos). J Hepatobiliary Pancreat Sci 2018;25:17-30.

16. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13(4 Suppl 2):e1-15.
17. Kaffes A. Benign biliary strictures: how we are evolving to the perfect endoscopic strategy. Endoscopy 2019;51:1115-6.
18. Sato T, Kogure H, Nakai Y, et al. A prospective study of fully covered metal stents for different types of refractory benign biliary strictures. Endoscopy 2020;52:368-76.
19. Cantù P, Santi G, Rosa R, et al. Cost analysis of a long-term randomized controlled study in biliary duct-to-duct anastomotic stricture after liver transplantation. Transpl Int 2021;34:825-34.
20. Poley JW, Ponchon T, Puespoek A, et al. Fully covered self-expanding metal stents for benign biliary stricture after orthotopic liver transplant: 5-year outcomes. Gastrointest Endosc 2020;92:1216-24.
21. Alazmi WM, Fogel EL, Watkins JL, et al. Recurrence rate of anastomotic biliary strictures in patients who have had previous successful endoscopic therapy for anastomotic narrowing after orthotopic liver transplantation. Endoscopy 2006;38:571-4.
22. Landi F, de'Angelis N, Sepulveda A, et al. Endoscopic treatment of anastomotic biliary stricture after adult deceased donor liver transplantation with multiple plastic stents versus self-expandable metal stents: a systematic review and meta-analysis. Transpl Int 2018;31:131-51.

SUPPLEMENTARY TABLE 1. Endoscopic stent placement

	ID-FCSEMS (n = 44)	MPS (n = 36)
Stents inserted		
1	40 (91.0)	0
2-3	4 (9.0)	8 (22.0)
4-8	0	23 (64.0)
≥9	0	5 (14.0)
Median no. of stents inserted	1.0 (1.0-1.0)	5.5 (4.0-8.0)
Size of ID-FCSEMS*		-
8-mm / 40-mm	18 (41.0)	†
10-mm / 40-mm	26 (59.0)	
Number of stent exchanges		
0	40 (91.0)	0
1	4 (9.0)	0
2-3	0	24 (66.0)
≥4	0	12 (33.0)

Data are presented as n (%) or median (IQR).
ID-FCSEMS, intraductal fully covered self-expandable metal stent; *MPS,* multiple plastic stent.
*Size of ID-FCSEMS placed at index ERCP.
†Standard stent diameter in MPS group was 10F (3.3 mm, 0.131 in).



Supplementary Figure 1. Kaplan-Meier curves on stricture resolution and recurrence.