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CLINICAL—BILIARY

Fully Covered Self-Expanding Metal Stent vs Multiple Plastic Stents to Treat Benign Biliary Strictures Secondary to Chronic Pancreatitis: A Multicenter Randomized Trial

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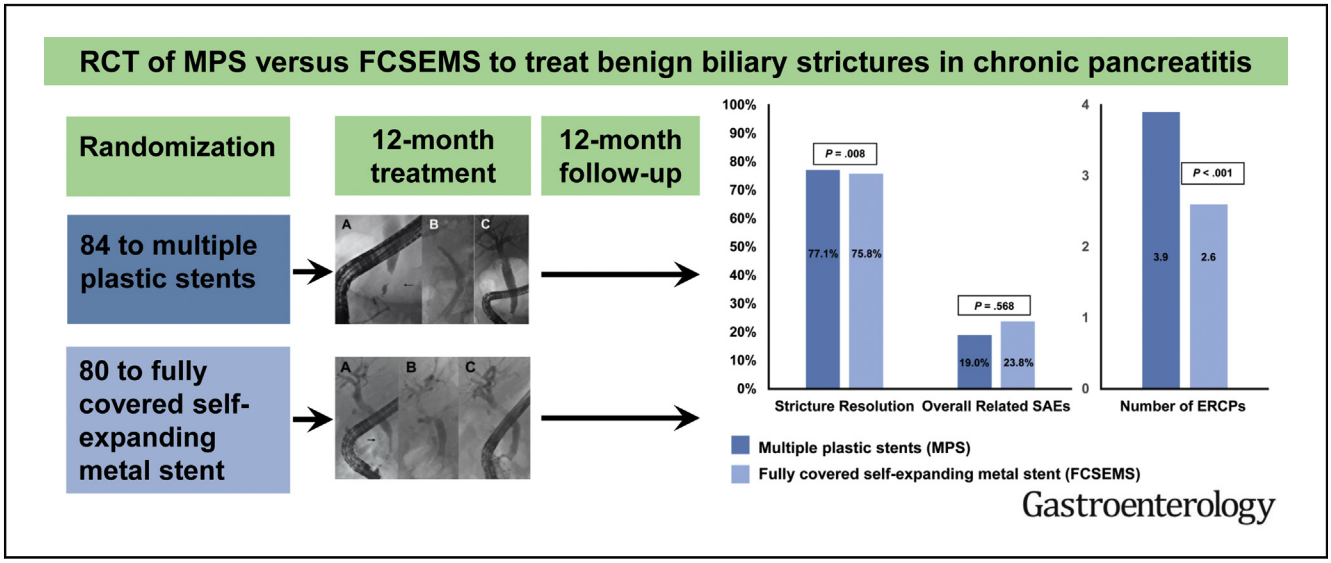

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BACKGROUND & AIMS: Benign biliary strictures (BBS) are complications of chronic pancreatitis (CP). Endotherapy using multiple plastic stents (MPS) or a fully covered self-expanding metal stent (FCSEMS) are acceptable treatment options for biliary obstructive symptoms in these patients. **METHODS:** Patients with symptomatic CP-associated BBS enrolled in a multicenter randomized noninferiority trial comparing 12-month treatment with MPS vs FCSEMS. Primary outcome was stricture resolution status at 24 months, defined as absence of restenting and 24-month serum alkaline phosphatase not exceeding twice the level at stenting completion. Secondary outcomes included crossover rate, numbers of endoscopic retrograde cholangiopancreatography (ERCPs) and stents, and stent- or procedure-related serious adverse events. **RESULTS:** Eighty-four patients were randomized to MPS and 80 to FCSEMS. Baseline technical success was 97.6% for MPS and 98.6% for FCSEMS. Eleven patients crossed over from MPS to FCSEMS, and 10 from FCSEMS to MPS. For MPS vs FCSEMS, respectively, stricture resolution status at 24 months was 77.1% (54/70) vs 75.8% (47/62) ($P = .008$ for noninferiority intention-to-treat analysis), mean number of ERCPs was 3.9 ± 1.3 vs 2.6 ± 1.3 ($P < .001$, intention-to-treat), and mean number of stents placed was 7.0 ± 4.4 vs 1.3 ± .6 ($P < .001$, as-treated). Serious adverse events occurred in 16 (19.0%) MPS and 19 (23.8%) FCSEMS patients ($P = .568$), including cholangitis/fever/jaundice (9 vs 7 patients respectively), abdominal pain (5 vs 5),

cholecystitis (1 vs 3) and post-ERCP pancreatitis (0 vs 2). No stent- or procedure-related deaths occurred. **CONCLUSIONS:** Endotherapy of CP-associated BBS has similar efficacy and safety for 12-month treatment using MPS compared with a single FCSEMS, with FCSEMS requiring fewer ERCPs over 2 years. (ClinicalTrials.gov, Number: NCT01543256.)

Keywords: Benign Biliary Strictures; Biliary Stenting; Chronic Pancreatitis; Plastic Stents; Randomized Trial; Self-Expandable Metallic Stents.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Endotherapy using multiple plastic stents or a fully covered self-expanding metal stent can be used to treat benign biliary strictures secondary to chronic pancreatitis. A multicenter, international randomized trial was conducted to test whether a fully covered self-expanding metal stent was noninferior to multiple plastic stents to treat patients with chronic pancreatitis–associated benign biliary strictures with signs or symptoms of biliary obstruction.

NEW FINDINGS

Eighty-four patients with chronic pancreatitis–associated benign biliary strictures were randomized to 12-month treatment with multiple plastic stents and 80 were randomized to 12-month treatment with a single fully covered self-expanding metal stent. After 12 months of posttreatment follow-up, patients treated with multiple plastic stents had similar rates of stricture resolution and serious adverse events, and a higher mean number of endoscopic retrograde cholangiopancreatography procedures and mean number of stents placed, compared with patients treated with a fully covered self-expanding metal stent.

LIMITATIONS

Eleven patients crossed over from multiple plastic stents to a fully covered self-expanding metal stent, and 10 from a fully covered self-expanding metal stent to multiple plastic stents.

IMPACT

For patients with chronic pancreatitis–associated benign biliary strictures, similar efficacy and safety were seen for 12-month treatment using multiple plastic stents compared with a single fully covered self-expanding metal stent, with a fully covered self-expanding metal stent requiring fewer endoscopic retrograde cholangiopancreatography procedures over 2 years.

In advanced chronic pancreatitis (CP), 10% to 30% of patients may develop symptomatic benign biliary stricture (BBS) in which biliary obstruction may lead to jaundice, persistent cholestasis, acute cholangitis, and secondary biliary cirrhosis.[1,2] Benign strictures causing chronic cholestasis, jaundice, and cholangitis deserve treatment to avoid secondary biliary cirrhosis and surgery.[3] Although no treatment is required in asymptomatic patients with CP-associated BBS, biliary drainage is indicated in symptomatic patients. Clinical decision-making is complex for this condition and varies among specialists,[4] with endotherapy, radiologic, surgical, and medical treatment as options. Endotherapy using multiple plastic stents (MPS) or a single removable fully covered self-expanding metal stent (FCSEMS) are acceptable options for patients with biliary obstructive symptoms associated with BBS. Long-term results for these treatments have been published in single-arm studies[5,6] and a randomized controlled trial (RCT) comparing both options.[7] The published RCT required 6 months of stent treatment, specifically with three 10-Fr plastic stents at randomization and an additional three 10-Fr at 3 months totaling six 10-Fr plastic stents in the MPS arm compared with one 10-mm-diameter FCSEMS in the other arm. The need for additional long-term RCT data on endoscopic CP management was highlighted in European Society of Gastrointestinal Endoscopy[8] and American Society for Gastrointestinal Endoscopy[9,10] guidelines.

To provide additional good-quality evidence regarding optimal endoscopic management in this patient population, we conducted a randomized noninferiority trial comparing 2-year efficacy and safety outcomes of MPS and FCSEMS to treat BBS in patients with CP. The aim of the trial was to determine whether the 24-month rate of stricture resolution in patients with CP-associated BBS randomized to 12-month treatment with FCSEMS is noninferior to the rate for patients receiving 12-month treatment with MPS.

Methods

Study Design

This study was an open-label, multicenter, randomized noninferiority clinical trial conducted at 14 centers in 11 countries. The study was approved by the institutional review boards and medical ethics committees of all participating sites, and was registered in the ClinicalTrials.gov database (NCT01543256) on March 2, 2012. Study participation began in September 2012 and ended in September 2020. All participants provided written informed consent before randomization. All authors had access to the study data and reviewed and approved the final manuscript.

Participants

The site investigators screened patients for study eligibility, enrolled participants, and assigned participants to interventions. Eligible patients were aged 18 years or older with documented CP, symptomatic bile duct stricture (defined by cholangitis or persistent jaundice for at least 1 month or

Abbreviations used in this paper: **BBS, benign biliary stricture; CDM, complete distal migration; CP, chronic pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; FCSEMS, fully covered self-expanding metal stent; ITT, intention-to-treat; IQR, interquartile range; MPS, multiple plastic stents; RCT, randomized controlled trial; SAE, serious adverse event.**

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cholestasis associated with at least 3 times normal alkaline phosphatase levels) documented at time of enrollment for naïve stricture or at the time of prior plastic stent placement in strictures that had 1 prior plastic stent inserted,[11] and common bile duct stricture based on imaging assessment of dilatation of the common and/or intrahepatic bile ducts. Excluded were patients with non-CP etiology of BBS or malignant bile duct stricture, a prior biliary metal stent or more than 1 plastic stent of 10 Fr size or smaller for $\geq$ 6 months, developing obstructive biliary symptoms associated with onset of acute pancreatitis, stricture within 2 cm of common bile duct bifurcation, known bile duct fistula or leak, symptomatic duodenal stenosis with gastric stasis, contraindication to endoscopic techniques or devices, participation in another investigational study within 90 days before consent, or exclusion by investigator discretion. A cholangiogram or other common bile duct imaging was performed before stent placement in all patients.

Randomization

Within each study site, eligible patients were randomized (1:1 allocation ratio using blocks of 4) into 12-month treatment with sequential placement of MPS (any brand) vs 1 placement of a biliary FCSEMS (Fully Covered WallFlex Biliary Stent; Boston Scientific, Marlboro, MA) (Figure 1). Randomization schedules were computer-generated in advance, using a pseudo-random number generator and loaded into the Electronic Data Capture (EDC) system. No member of the study team or anyone else at the study site had access to the random number sequence. Site investigators obtained randomization assignments stratified by clinical site from the EDC system at the time of the procedure. For back-up randomization in cases of unsuccessful EDC access, sites were instructed to randomize subjects via back-up envelopes only. The back-up randomized treatment assignments were kept in sequentially numbered, sealed opaque envelopes.

Multiple Plastic Stents

Participants in the MPS arm had 3 or 4 side-by-side MPS stenting procedures during the 12-month treatment period. The size and number of MPSs placed at each procedure was left to the investigator's discretion. The study protocol stated that "for subjects randomized to PS, at least two 8.5 or 10 Fr. PS should be placed whenever possible." After the index procedure, follow-up visits for assessment of biliary obstructive symptoms and adverse events were conducted at 1 month after stent placement in a clinic or telephone visit, and in clinic or hospital visits at 4 months and 8 months for MPS exchange and serum liver enzyme tests. In these follow-up procedures, clinicians had the option to exchange or increase the number of plastic stents. At 12 months, stent removal, a cholangiogram or other common bile duct imaging, and serum liver enzyme tests were performed. At 24 months, assessment of biliary obstructive symptoms and adverse events, and serum liver enzyme tests were performed. Additional visits were conducted at the investigator's discretion, most typically in cases of an adverse event.

Fully Covered Self-Expanding Metal Stent

The protocol for patients who received a single 8-mm or 10-mm-diameter FCSEMS was similar to the MPS arm but excluded the office visits at 4 months and 8 months. The size of the FCSEMS placed at the index procedure was left to the investigator's discretion. The planned FCSEMS indwell period was 12 months.

Study Completion

As described previously, each subject was followed for 2 years after initial stent placement, planning for 12 months of active treatment and 12 months of follow-up thereafter. It was possible that recurrent strictures occurring during follow-up were treated with FCSEMS in the MPS group and with MPS in the FCSEMS group. In such cases, the original treatment assignment was maintained in the final analysis of the primary outcome. A subject was considered lost to follow-up if he or she remained unresponsive to communication after 3 documented attempts by study staff.

Outcomes

The primary clinical outcome was biliary stricture resolution status 24 months after initial stent(s) placement (ie, 12 months after stent removal), defined as absence of restenting after the stenting period and 24-month serum alkaline phosphatase level not exceeding twice the level at the end of the stenting period. Secondary clinical outcomes included technical success of stent placement, number of endoscopic retrograde cholangiopancreatography (ERCP) procedures during 24 months after initial stent placement, total number of stents placed during the study, duration of stent placement procedure, and total treatment time (cumulative duration of stenting of any type) during the 24-month study period. The safety outcome was device- or procedure-related serious adverse events (SAEs) during the full 24-month follow-up period. Stent migration rates were also evaluated.

Statistical Analysis

The hypothesis of the study was that the rate of stricture resolution for FCSEMS is noninferior to MPS in patients with CP-associated BBS. An estimated 66% probability of stricture resolution was within the 95% confidence intervals determined in meta-analyses of studies of BBS outcomes after initial MPS[5,12,13] or FCSEMS stent placement.[14–17] The sample size was calculated for a 1-sided .050 exact test using a noninferiority margin of 20%, where a P value $<$ .05 would suggest that FCSEMS was noninferior to MPS.[18] For 80% power with a 1-sided 5% significance level, allowing for 10% attrition during follow-up, a total of 164 patients were needed to draw noninferiority conclusions with the defined level of certainty.

Data were summarized using descriptive statistics for continuous variables, including median with minimum and maximum or interquartile range (IQR), and frequency statistics for discrete variables and were tested for differences between the groups with a Mann-Whitney U test and a Fisher's exact test, respectively. Count variables, such as number of procedures/stents, were summarized using mean and standard deviation, and a negative binomial model was performed to test for differences between the groups. Statistical modeling was performed to identify clinical risk factors that might predict the primary and safety outcomes, namely age, male sex, time since CP diagnosis, alcohol as CP etiology, calcifying CP, being a surgical candidate, prior pancreatic plastic stent, baseline

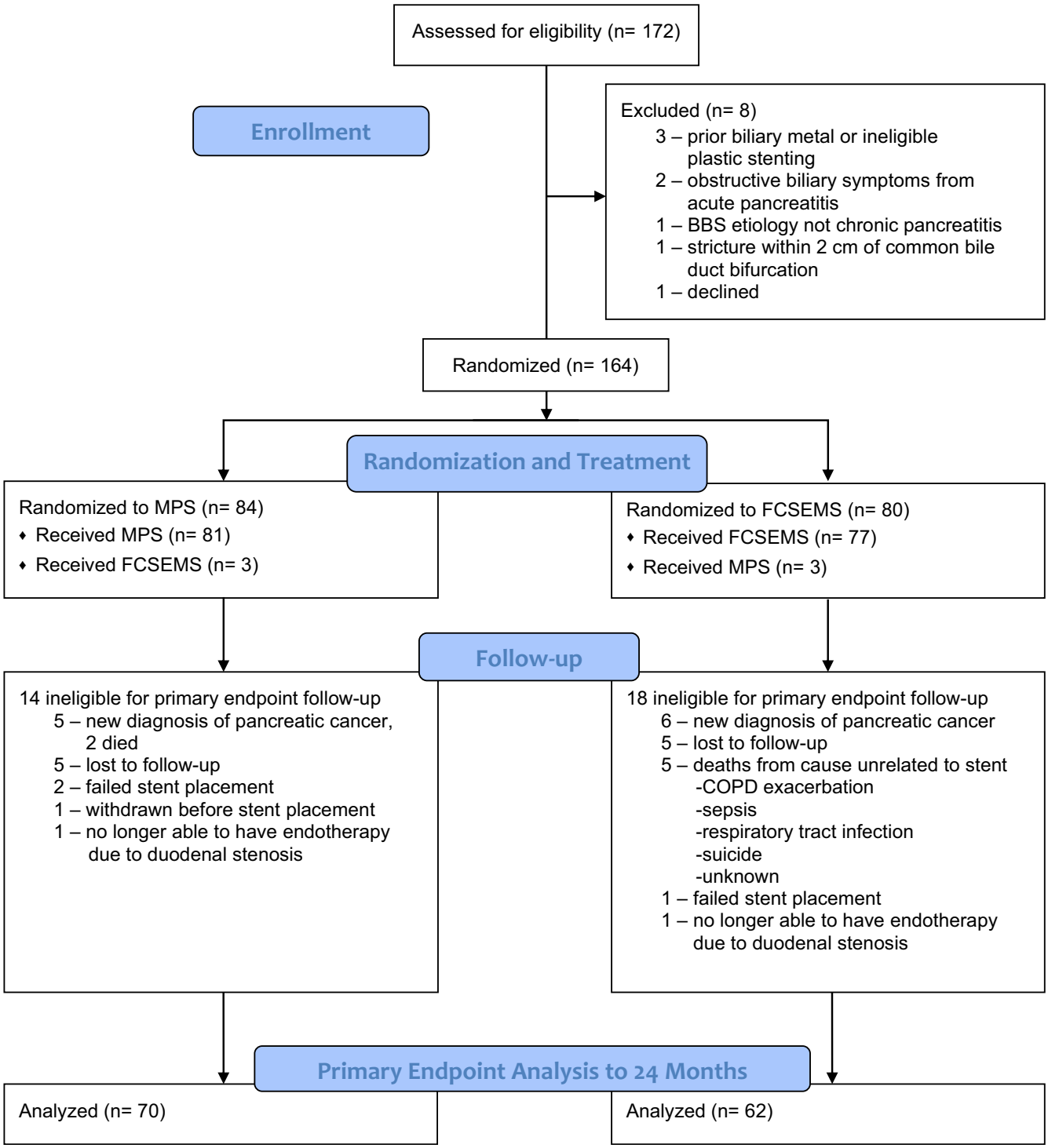

Figure 1. CONSORT diagram of patient enrollment, randomization, and follow-up. COPD, chronic obstructive pulmonary disease.

serum bilirubin level, or gallbladder in situ. This modeling was performed using Cox proportional hazards techniques using exact ties. The primary outcome power calculation and *P* value were calculated using StatXact version 12 (Cytel, Cambridge, MA); all other analyses were performed using SAS version 9.4 (SAS institute, Cary, NC). All analyses were considered significant if the *P* value was $< .05$.

In addition to the intention-to-treat analysis (ITT), as-treated analyses were also performed, with recognition of inherent biases for each analysis type.[19] The as-treated study groups comprised patients who were treated with 1 type of stent throughout the study, namely treated with MPS only or with FCSEMS only, regardless of baseline randomization. This group was used to test differences in number of ERCPs,

number of stents placed, procedure duration, and total treatment time.

Results

Enrollment was completed with 84 patients randomized to the MPS arm and 80 to the FCSEMS arm (Figure 1). No significant differences in baseline variables were found between both study arms in the ITT cohort (Table 1). Median baseline age was 52 years (range 26–74) and median years since first diagnosis of CP was 1.9 (range 0.1–35.8). At the time of randomization, 43.9% (72 of 164) of patients had a prior single plastic stent indwelling, median alkaline phosphatase level was 290.0 (range 46.0–1909.0), and median bilirubin level was 1.3 (range 0.1–25.3) mg/dL, with similar values for each measure in both arms ($P = .755$, $P = .273$, and $P = .590$, respectively).

The as-treated study population comprised patients who were treated with 1 type of stent throughout the study. Of 138 patients included in the as-treated patient population, 60 patients treated with MPS and 53 patients treated with FCSEMS were eligible for analysis of the primary outcome 24 months after initial treatment.

Primary Outcome

Stricture resolution status at 24 months after randomization was 77.1% (54 of 70) in the MPS arm and 75.8% (47 of 62) in the FCSEMS arm ($P = .008$ for noninferiority) (Figures 2–4). The upper confidence limit for the difference in stricture resolution status suggested that the greatest amount by which the FCSEMS stricture resolution rate could be lower than that for MPS was 14.2%, which was within the noninferiority margin of 20%.

Of 31 patients who failed the primary endpoint (had no stricture resolution), 29 were restented and 2 had surgery. Univariate analysis showed that none of the predefined candidate clinical risk factors were associated with successful stricture resolution (P value range .09–.91).

Secondary Outcomes

Technical success. Technical success of stent placement at baseline was 97.6% (82 of 84) for the MPS arm and 98.6% (79 of 80) for the FCSEMS arm ($P = .99$). Of 90 patients who had an FCSEMS at any point during the study, 72 underwent uneventful endoscopic removal in one procedure. Seven FCSEMS removals used a SEMS-in-SEMS removal technique[20] due to the presence of tissue overgrowth embedding the proximal, distal, or both FCSEMS ends; this technique consisted of placement of an additional FCSEMS through the original FCSEMS aimed at inducing pressure necrosis of the hyperplastic tissue over the ends of the stent, followed in all cases by uneventful removal of both FCSEMS 9 to 121 days later. There were no reports of deficiencies in the covering of the FCSEMS in any of the 7 cases.

Number of ERCPs, number of stents and procedure duration, and treatment duration. In the ITT analysis, the mean number of ERCPs during 24 months after randomization, including the procedure during which the last stent(s) were removed, was 3.9 ± 1.3 in the MPS arm and 2.6 ± 1.3 in the FCSEMS arm ($P < .001$) (Figure 2,

Table 1. Baseline Characteristics of Patients (N = 164)

Characteristic	Median (range) or % (x/n) MPS (n = 84)	FCSEMS (n = 80)	*P* value
Median age, *y*	53.0 (26.0,74.0)	51.0 (28.0,74.0)	.176
Male	85.7% (72/84)	87.5% (70/80)	.821
Median time since CP diagnosed, *y*[a]	1.7 (0.1,32.4)	3.1 (0.1,35.8)	.768
Gallbladder in situ	85.7% (72/84)	86.3% (69/80)	.999
CP etiology alcoholic	67.9% (53/78)	76.1% (54/71)	.282
Calcifying CP	77.5% (62/80)	79.7% (59/74)	.845
Candidate for surgery	79.2% (61/77)	83.3% (60/72)	.538
Prior plastic stent	45.2% (38/84)	42.5% (34/80)	.755
Prior biliary sphincterotomy	47.6% (39/82)	49.4% (39/79)	.875
Prior pancreatic sphincterotomy	32.9% (27/82)	32.9% (26/79)	.999
Biliary or pancreatic sphincterotomy (prior or at baseline study procedure)	90.5% (76/84)	96.3% (77/80)	.212
Median baseline bilirubin, *mg/dL*[a]	1.4 (0.2,17.7)	1.0 (0.1,25.3)	.590
Median baseline alkaline phosphatase, *IU/L*[a]	262.5 (78)(55.0,1909.0)	337.0 (74) (46.0,1871.0)	.273

CP, chronic pancreatitis; FCSEMS, fully covered self-expanding metal stent; MPS, multiple plastic stents.
[a]Median (n) (range) are shown if n < group N.

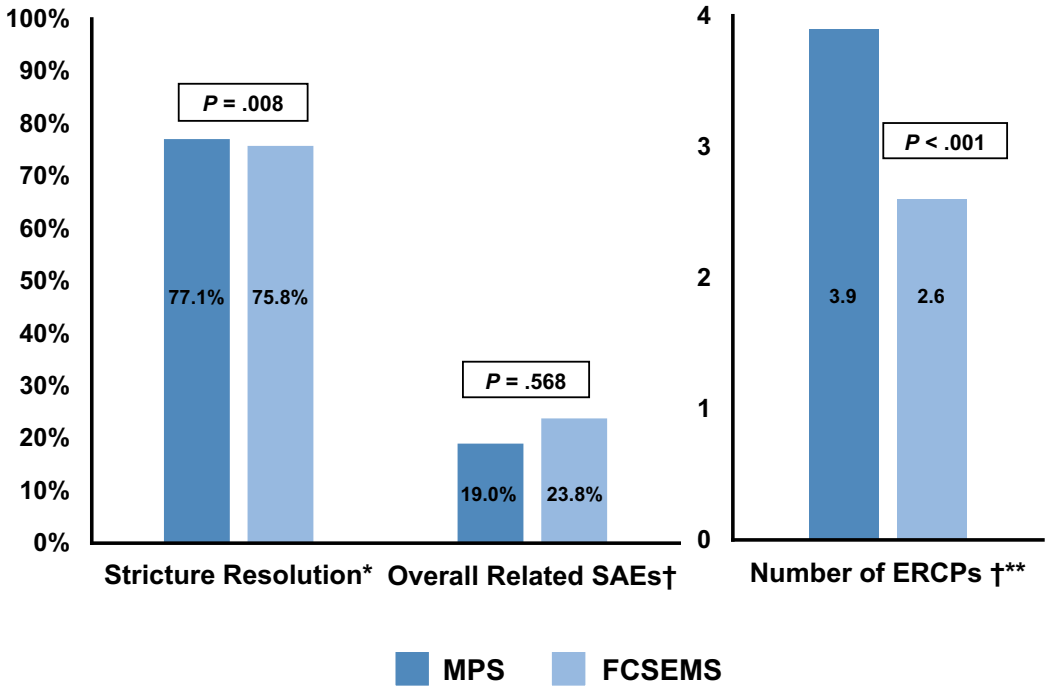

Figure 2. Summary of main outcomes (ITT analysis). *For stricture resolution, $P < .05$ suggests that FCSEMS is noninferior to MPS. †For SAEs and number of ERCPs, $P < .05$ suggests different values for FCSEMS and MPS. **Number of ERCPs on an as-treated basis are 3.9 (MPS) and 2.2 (FCSEMS), $P < .001$.

Table 2). Results were similar in the as-treated analysis (3.9 vs 2.2, respectively, $P < .001$)

The mean total number of stents placed was 6.7 ± 4.4 in the MPS arm and 2.3 ± 3.3 in the FCSEMS arm ($P < .001$; Figure 2, Table 2) in the ITT analysis, reflecting crossover from FCSEMS to MPS and vice versa that led some patients to be treated with more than 1 type of stent during the course of the study, and additional FCSEMS used for SEMS-in-SEMS removal in 7 patients. In the as-treated analysis, the mean total number of stents placed was 7.0 ± 4.4 in the MPS arm and 1.3 ± .6 in the FCSEMS arm ($P < .001$).

Median stent placement procedure duration was similar between arms in the ITT analysis (28.0 vs 26.0 minutes, $P = .519$, Table 2) and trended lower for FCSEMS in the as-

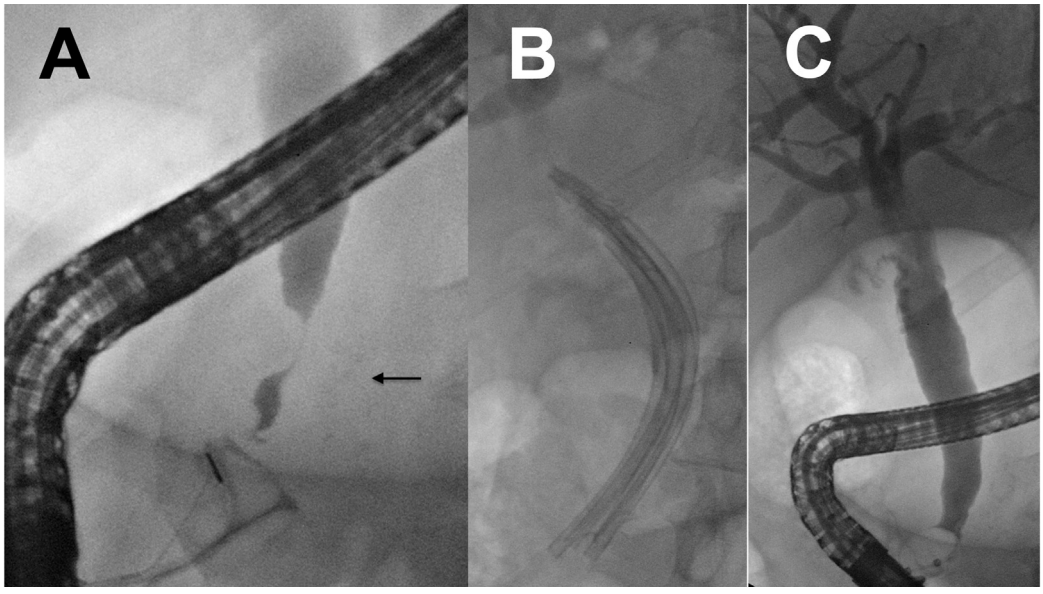

Figure 3. Common bile duct stricture secondary to CP (*A*) (*arrow*, pancreatic calcifications). Five plastic stents (*B*) are inserted with complete stricture dilatation after stent removal (*C*). (Images courtesy of Policlinico A. Gemelli, IRCCS.)

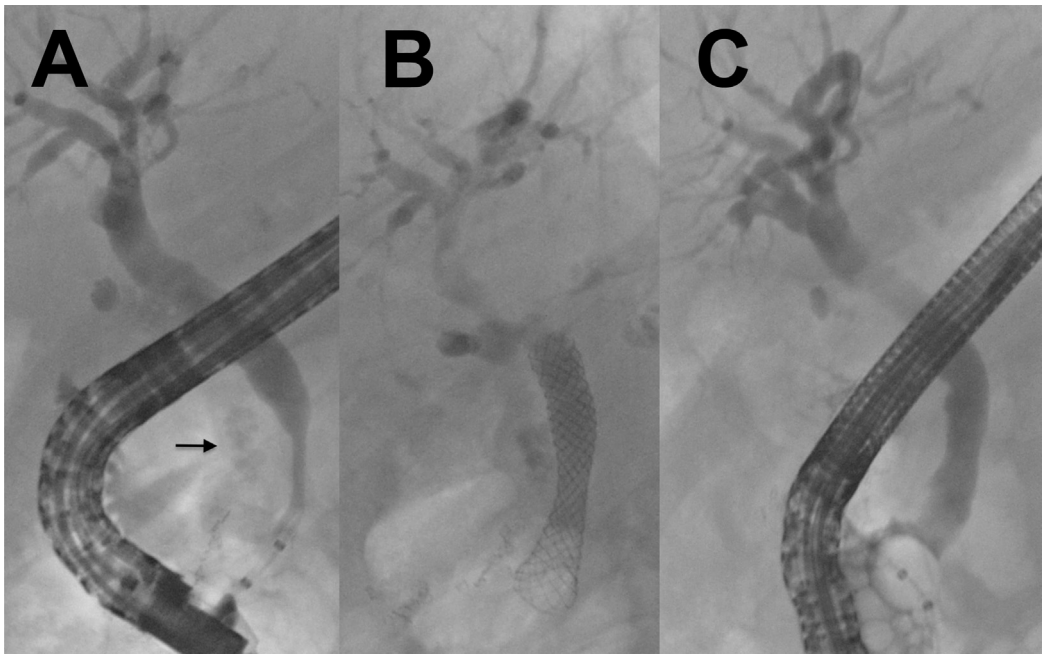

Figure 4. Common bile duct stricture secondary to CP (*A*) (*arrow*, pancreatic calcifications). FCSMES is placed (*B*) obtaining stricture dilatation after metal stent removal (*C*). (Images courtesy of Policlinico A. Gemelli, IRCCS)

treated analysis (28.0 vs 24.0, $P = .062$). Median total treatment duration during the study (11.8 vs 11.8 months for ITT, 11.8 vs 11.7 for as-treated) were similar between arms (Table 2). The median treatment duration and mean study follow-up (23.7 months, IQR 22.8–24.4 months) closely matched the study plan. The median stent-free time (time from stent removal or observation of complete distal migration [CDM] to restenting) was 360 days for MPS and 362 days for SEMS ($P = .957$). Among the 92 patients who had at least 1 plastic stent in place at some point during the study, a mean of 3 stents were placed during the final MPS procedure.

Safety Outcomes and Stent Migration

Stent- or procedure-related SAEs occurred in 16 (19.0%) MPS patients and 19 (23.8%) FCSEMS patients ($P = .568$) (Figure 2). There was no significant difference in rates of individual SAEs between arms (*P* value range .236–.999 for comparisons) (Table 3). Among 16 patients who developed cholangitis/fever/jaundice (9 for MPS vs 7 for FCSEMS), possible causes based on documented surrounding events were occlusion (4), migration (2), and procedure-related (3) in the MPS arm, and migration (5), occlusion (1), or removal (1) in the FCSEMS arm. Among 4 patients who developed cholecystitis (1 for MPS vs 3 for FCSEMS), treatments included laparoscopic cholecystectomy in 1 MPS patient, and hospitalization (2) or outpatient medical treatment (1) in 3 FCSEMS patients. Other SAEs included abdominal pain (5 vs 5), post-ERCP pancreatitis (0 vs 2), acute-on-chronic pancreatitis (0 vs 2), and perforation of the duodenum (1 vs 0). There were no stent- or procedure-related deaths. Over the duration of follow-up, 11 patients (6.7%) were diagnosed with pancreatic cancer. Univariate analysis

Table 2. Procedure Characteristics for ITT and As-Treated Patient Groups

	ITT			As-treated[a]		
Procedure characteristic	MPS	FCSEMS	*P* value	MPS	FCSEMS	*P* value
Mean number of ERCPs[b]	3.9 ± 1.3 (82)	2.6 ± 1.3 (79)	<.001	3.9 ± 1.2 (69)	2.2 ± 0.9 (69)	<.001
Mean number of stents placed	6.7 ± 4.4 (81)	2.3 ± 3.3 (79)	<.001	7.0 ± 4.4 (69)	1.3 ± 0.6 (68)	<.001
Median procedure duration, *min*	28.0 (302) (5.0,144.0)	26.0 (192) (3.0,182.0)	.519	28.0 (254) (5.0,182.0)	24.0 (143) (3.0,120.0)	.062
Median total stenting time, *mo*	11.8 (80) (0.1,25.4)	11.8 (79) (0.1,25.3)	.975	11.8 (68) (0.1,23.6)	11.7 (68) (0.1,25.0)	.845

NOTE. Mean ± SD or median (no. of procedures) (range) are shown.
ERCP, endoscopic retrograde cholangiopancreatography; FCSEMS, fully covered self-expanding metal stent; ITT, intention to treat; MPS, multiple plastic stents.
[a]"As-treated" refers to patients who were treated with 1 type of stent throughout the study.
[b]Includes stent removal procedures.

Table 3. Patients With at Least 1 Device- or Removal-related SAE, or Stent Migration (ITT analysis, N = 164)

SAE	MPS (n = 84)	FCSEMS (n = 80)	*P* value
Any SAE	19.0% (16/84)	23.8% (19/80)	.568
Abdominal pain	6.0% (5/84)	6.3% (5/80)	.999
Cholangitis/fever/jaundice	10.7% (9/84)	8.8% (7/80)	.794
Cholecystitis (among patients with a gallbladder)	1.4% (1/72)	4.3% (3/69)	.359
Post-ERCP pancreatitis[a]	0.0% (0/84)	2.5% (2/80)	.236
Acute-on-chronic pancreatitis	0.0% (0/84)	2.5% (2/80)	.236
Perforation of duodenum	1.2% (1/84)	0.0% (0/80)	.999
Post-sphincterotomy bleed (among patients who had a sphincterotomy)	0.0% (0/76)	1.3% (1/77)	.999
Other SAE[b]	2.4% (2/84)	2.5% (2/80)	.999
Stent migration	21.4% (18/82)	18.8% (15/80)	.701

ERCP, endoscopic retrograde cholangiopancreatography; FCSEMS, fully covered self-expanding metal stent; ITT, intention to treat; MPS, multiple plastic stents; SAE, serious adverse event.
[a]One had prior biliary sphincterotomy, and 1 had biliary sphincterotomy at time of procedure.
[b]Other SAEs for MPS: recurrent cholestasis, mobile cholelithiasis; for FCSEMS: bacterial blood infection, duodenal edema.

showed that the candidate clinical risk factors were not associated with stent- or procedure-related SAEs (*P* value range .15–.86).

Overall, 18 (21.4%) MPS patients and 15 (18.8%) FCSEMS patients had at least 1 stent migration during the study, which was not significantly different between groups ($P = .701$, ITT analysis). The most frequent type of migration was CDM (11 patients in each group, $P = .999$, ITT), followed by partial distal (6 vs 5 for MPS vs FCSEMS, $P = .999$, ITT) and proximal migration (3 vs 4, $P = .715$, ITT). Of 60 patients treated with MPS only during the study, 9 were observed to have CDM after a median of 101 days (IQR 86–141.5 days) after baseline or last MPS exchange. Of 53 patients treated with an FCSEMS only, 4 were observed to have CDM after a median of 339 days (IQR 324.5–344.5 days) after baseline, and 1 of those 4 was restented.

Discussion

This open-label, multicenter randomized noninferiority clinical trial demonstrated that in patients with CP-associated BBS, 12-month treatment with MPS vs FCSEMS led to similar rates of stricture resolution and adverse events, with fewer numbers of ERCPs over the 24-month study period in the FCSEMS arm.

CP-associated BBS is the most common non–surgery-related type of BBS, usually involving the distal third of the common bile duct as a late consequence of progressive fibrosis of the pancreatic parenchyma due to recurrent acute or chronic inflammation.[21,22] Compared with BBS from other causes, CP-associated strictures may be more resistant to treatment because of the chronic nature of the insult and to the fibrotic nature of the strictures in calcifying CP.[23,24] Uncovered SEMS is not an acceptable alternative to plastic stenting to treat BBS because of stent-associated endoluminal hyperplastic tissue ingrowth and difficulty of removal.[24] Thus, partially and fully covered SEMS have been studied despite their higher risk of stent migration compared with uncovered SEMS.[25] A systematic review of endotherapy for BBS reported respective clinical stricture resolution rates of 77% and 33% for covered SEMS (partially covered in 3 studies, fully covered in 9 studies) and plastic stents at 12 months of follow-up, whereas no difference was seen between the 2 methods for strictures related to liver transplantation or other causes.[23] The rate of stricture resolution for FCSEMS in our trial is similar to this study, but our rate for MPS was substantially higher. This might reflect that our trial was conducted at centers with high levels of experience and high case volumes of endotherapy for the treatment of BBS secondary to CP, including the placement of MPS, which can be technically challenging.

In contrast to several previous studies that used FCSEMS removal or exchange at 6 months or less,[7,12,26,27] our RCT evaluated 12-month FCSEMS indwell in patients with CP-associated BBS. We chose 12-month treatment duration because this was on the higher end of published stent indwell duration, and because low stricture recurrence rates have been reported after 10- to 12-month FCSEMS indwell in the CP patient population.[6] Although longer duration of stent indwell has been associated with lower stricture recurrence,[28] the longer FCSEMS indwell time might also have led to a higher rate of SAEs and migration than seen in other studies. Rates of adverse events were higher for both FCSEMS and MPS (17.9% vs 23.8%) in our study compared with the rate reported for BBS of any etiology in the previously mentioned systematic review (covered SEMS and PS groups 13% vs 14%, 95% confidence interval 7%–19% vs 8.1%–19%, $P = .9$).[23] We did not observe a lower rate of adverse events for FCSEMS compared with MPS, as was seen in this systematic review. Approximately 20% of patients experienced stent migration within both arms of our study, which was somewhat higher than past single-arm studies of MPS (10.2%–13%)[12,13] and FCSEMS (5%–16.2%)[14,15,17] that informed our statistical hypothesis. In 7 cases, FCSEMS removal failed with conventional techniques and required insertion of an inner FCSEMS to obtain

pressure necrosis of the proximal and/or distal hyperplastic tissue embedding stent edges. Following FCSEMS removal, there were no reports of deficiencies in the covering of the FCSEMS in all 7 cases, and tissue overgrowth was possibly related to the 12-month stent indwelling period.

Comorbidities further complicate CP treatment issues. Patients with CP are often poor surgical candidates because of malnutrition, which is associated with increased morbidity, a higher rate of infectious complications, and longer intensive care unit stay compared with well-nourished patients with CP who undergo pancreatic surgery.[29] Most patients develop chronic pain that is multifactorial, thought to be caused by parenchymal and ductal hypertension and parenchymal inflammation.[30] A meta-analysis reported that 5 years after diagnosis, patients with CP have a nearly 8-fold increased risk of pancreatic cancer.[31] Consistent with this finding, 11 patients (6.7%) of the 164 patients who were randomized in our study were diagnosed with pancreatic cancer during follow-up. Noncompliance is common among heavy alcohol users, and vigilant gastroenterological follow-up is necessary because of ongoing risks of severe complications in these patients. For example, a retrospective study of 14 patients with chronic alcoholic CP who had stent placement for biliary stenosis reported no complications in 2 patients who attended follow-up visits for stent exchanges, compared with 16 observations of cholangitis and 3 diagnoses of biliary sepsis among the remaining 12 patients, who were admitted a mean 2.9 times per patient as emergency cases.[32] Patients such as these could benefit from the lower frequency of stent exchanges with comparable efficacy and safety seen for FCSEMS compared with MPS in our study. The incidence of pancreatic cancer was similar in the 2 groups, thus we believe that the lower frequency of repeated cholangiograms did not affect the possibility for an earlier cancer diagnosis. Importantly, before the start of long-term FCSEMS insertion to dilate a benign stricture, exhaustive investigations should be done to exclude an underlying malignancy.

Our study has several strengths and limitations. The randomized trial design ensured that the MPS and FCSEMS groups had similar distributions of clinical risk factors at baseline. Patients with past use of a metal stent or more than 1 plastic stent were excluded because their likelihood of stricture resolution could be lower due to ductal fibrosis at baseline. The study completion rate was high, with monitoring that continued for 1 year after the end of the 12-month treatment period. Limitations of the study included mis-randomization of 3 patients in each arm and crossover in 13% of patients during follow-up that might have altered the balance of baseline risk between arms. Data are not available on balloon dilation concurrent with stent placement at the index procedure. Results may not be generalizable to less experienced endoscopists or community gastroenterology practices. The rates of stricture resolution by 12 months after stent removal should not be considered definitive, because strictures are known to recur late. For example, a longitudinal study of 118 patients with CP-associated BBS who received 10- to 12-month FCSEMS treatment reported that at a median of 58 months post-FCSEMS indwell, the probability of remaining stent-free was 61.6%,[6] compared with approximately 75% for the FCSEMS arm at 1 year in the current trial that used the same device. This study was sponsored by the manufacturer of the metal stent used in the study.

In conclusion, endotherapy of BBS secondary to CP has similar effectiveness and safety when using a single FCSEMS compared with MPS for 1 year, with the FCSEMS option requiring fewer ERCPs over 2 years after initial stenting.

References

1. Costamagna G, Boskoski I. Current treatment of benign biliary strictures. Ann Gastroenterol 2013;26:37–40.
2. Deviere J, Nageshwar Reddy D, Puspok A, et al. Successful management of benign biliary strictures with fully covered self-expanding metal stents. Gastroenterology 2014;147:385–395; quiz e15.
3. Costamagna G. Covered self-expanding metal stents in benign biliary strictures: not yet a “new paradigm” but a promising alternative. Gastrointest Endosc 2008;67:455–457.
4. Issa Y, van Santvoort HC, Fockens P, et al. Diagnosis and treatment in chronic pancreatitis: an international survey and case vignette study. HPB (Oxford) 2017;19:978–985.
5. Draganov P, Hoffman B, Marsh W, et al. Long-term outcome in patients with benign biliary strictures treated endoscopically with multiple stents. Gastrointest Endosc 2002;55:680–686.
6. Lakhtakia S, Reddy N, Dolak W, et al. Long-term outcomes after temporary placement of a self-expanding fully covered metal stent for benign biliary strictures secondary to chronic pancreatitis. Gastrointest Endosc 2020;91:361–369.e3.
7. Haapamaki C, Kylanpaa L, Udd M, et al. Randomized multicenter study of multiple plastic stents vs covered self-expandable metallic stent in the treatment of biliary stricture in chronic pancreatitis. Endoscopy 2015;47:605–610.
8. 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;50:910–930.
9. ASGE Standards of Practice Committee, Chandrasekhara V, Chathadi KV, et al. The role of endoscopy in benign pancreatic disease. Gastrointest Endosc 2015;82:203–214.
10. ASGE Standards of Practice Committee, Chathadi KV, Chandrasekhara V, et al. The role of ERCP in benign diseases of the biliary tract. Gastrointest Endosc 2015;81:795–803.
11. Abdallah AA, Krige JE, Bornman PC. Biliary tract obstruction in chronic pancreatitis. HPB (Oxford) 2007;9:421–428.
12. Catalano MF, Linder JD, George S, et al. Treatment of symptomatic distal common bile duct stenosis secondary to chronic pancreatitis: comparison of single vs.

multiple simultaneous stents. Gastrointest Endosc 2004; 60:945–952.
13. Eickhoff A, Jakobs R, Leonhardt A, et al. Endoscopic stenting for common bile duct stenoses in chronic pancreatitis: results and impact on long-term outcome. Eur J Gastroenterol Hepatol 2001;13:1161–1167.
14. Behm B, Brock A, Clarke BW, et al. Partially covered self-expandable metallic stents for benign biliary strictures due to chronic pancreatitis. Endoscopy 2009;41:547–551.
15. Kahaleh M, Behm B, Clarke BW, et al. Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? (with video). Gastrointest Endosc 2008;67:446–454.
16. Mahajan A, Ho H, Sauer B, et al. Temporary placement of fully covered self-expandable metal stents in benign biliary strictures: midterm evaluation (with video). Gastrointest Endosc 2009;70:303–309.
17. Park DH, Lee SS, Lee TH, et al. Anchoring flap versus flared end, fully covered self-expandable metal stents to prevent migration in patients with benign biliary strictures: a multicenter, prospective, comparative pilot study (with videos). Gastrointest Endosc 2011;73:64–70.
18. Chan IS. Exact tests of equivalence and efficacy with a non-zero lower bound for comparative studies. Stat Med 1998;17:1403–1413.
19. Rehal S, Morris TP, Fielding K, et al. Non-inferiority trials: are they inferior? A systematic review of reporting in major medical journals. BMJ Open 2016;6:e012594.
20. Tringali A, Blero D, Boskoski I, et al. Difficult removal of fully covered self expandable metal stents (SEMS) for benign biliary strictures: the "SEMS in SEMS" technique. Dig Liver Dis 2014;46:568–571.
21. Familiari P, Boskoski I, Bove V, et al. ERCP for biliary strictures associated with chronic pancreatitis. Gastrointest Endosc Clin N Am 2013;23:833–845.
22. Ma MX, Jayasekeran V, Chong AK. Benign biliary strictures: prevalence, impact, and management strategies. Clin Exp Gastroenterol 2019;12:83–92.
23. Siiki A, Helminen M, Sand J, et al. Covered self-expanding metal stents may be preferable to plastic stents in the treatment of chronic pancreatitis-related biliary strictures: a systematic review comparing 2 methods of stent therapy in benign biliary strictures. J Clin Gastroenterol 2014;48:635–643.
24. Gupta R, Reddy DN. Stent selection for both biliary and pancreatic strictures caused by chronic pancreatitis: multiple plastic stents or metallic stents? J Hepatobiliary Pancreat Sci 2011;18:636–639.
25. Deviere J, Devaere S, Baize M, et al. Endoscopic biliary drainage in chronic pancreatitis. Gastrointest Endosc 1990;36:96–100.
26. Cahen DL, van Berkel AM, Oskam D, et al. Long-term results of endoscopic drainage of common bile duct strictures in chronic pancreatitis. Eur J Gastroenterol Hepatol 2005;17:103–108.
27. Cote 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;315:1250–1257.
28. Khan MA, Baron TH, Kamal F, et al. Efficacy of self-expandable metal stents in management of benign biliary strictures and comparison with multiple plastic stents: a meta-analysis. Endoscopy 2017;49:682–694.
29. Schnelldorfer T, Adams DB. The effect of malnutrition on morbidity after surgery for chronic pancreatitis. Am Surg 2005;71:466–472; discussion 472–473.
30. Strate T, Yekebas E, Knoefel WT, et al. Pathogenesis and the natural course of chronic pancreatitis. Eur J Gastroenterol Hepatol 2002;14:929–934.
31. Kirkegard J, Mortensen FV, Cronin-Fenton D. Chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. Am J Gastroenterol 2017; 112:1366–1372.
32. Kiehne K, Folsch UR, Nitsche R. High complication rate of bile duct stents in patients with chronic alcoholic pancreatitis due to noncompliance. Endoscopy 2000; 32:377–380.

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Conflict of interest

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