Covered self-expandable metal stents for pancreatic duct stricture: a systematic review and meta-analysis

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Authors
Alberto Tringali[1], Deborah Costa[1], Matteo Rota[2], Douglas G. Adler[3], Guido Costamagna[4]

Institutions
1 Endoscopy Unit, Department of Medicine, ULSS 2 Marca Trevigiana, Conegliano Hospital, Italy
2 Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy
3 Center for Advanced Therapeutic Endoscopy (CATE), Centura Health, Denver, Colorado, United States
4 Digestive Endoscopy Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Rome, Italy

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Corresponding author
Alberto Tringali, MD , Endoscopy Unit – Department of Medicine, Ulss 2 Marca Trevigiana, Conegliano Hospital, Conegliano (TV), Italy
Fax: +39 0438663404
alberto.tringali@aulss2.veneto.it

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ABSTRACT

Background and study aims Placement of a covered (C)-self-expandable metal stent (SEMS) has been recently investigated as an alternative endoscopic treatment for main pancreatic duct stricture (MPDS) in chronic pancreatitis. Our aim was to carry out a systematic review and meta-analysis of studies quantifying efficacy and safety of C-SEMSs in the management of MPDS.

Methods A multiple database search was performed, including MEDLINE, Embase and Cochrane Library, from January 2000 to September 2020, to identify studies reporting the efficacy and safety of C-SEMSs in patients with MPDS. Stricture and pain resolution were investigated. Other outcomes included technical success, stent migration, stricture recurrence and need for repeated stent placement. Pancreatitis, severe abdominal pain requiring stent removal and de-novo stricture were recorded as complications.

Results Nineteen studies were identified, which included a total of 300 patients. C-SEMSs showed a pooled stricture resolution rate of 91 % [95 % confidence interval (CI), 85 %–96 %] and a pooled pain resolution rate of 92 % (95 % CI, 85 %–98 %). The pooled proportion for stricture recurrence was equal to 6 % (95 % CI, 1 %–14 %), while stent migration occurred in 33 of 300 patients, the pooled proportion being 7 % (95 % CI 1 %–15 %). The pooled mean stent duration was 133 days (95 % CI, 100–166 days). The most common complication was pancreatitis (3 %, 95 % CI 0 %–8 %), while de-novo stricture pooled proportion was 2 % (95 % CI, 0 %–5 %).

Conclusions C-SEMSs are effective and safe in the treatment of MPDS. However, there is a significant need for further high-quality, well-designed studies to produce evidence-based data on short and long-term efficacy, safety, costs of C-SEMSs, and also optimal stent duration.

Introduction

Main pancreatic duct strictures (MPDS) occur in almost half of patients with chronic pancreatitis (CP), and can lead to increased pressure within the pancreatic ductal system and pancreatic-type pain [1].

In the majority of cases, treatment of MPDS is based on placement of a single plastic stent (PS) for 1 year in case of initial successful pancreatic drainage, with the aim of dilating and decompressing the MPD to reduce patients' pain [2]. However, the insertion of a single PS is not universally effective, with stricture resolution rates ranging from 9 % to 50 % and long-

term pain relief achieved in 67.5 % of patients, as quantified in a meta-analysis of nine studies [3–8]. As shown in long-term follow-up studies [9, 10], endoscopic treatment with multiple side-by-side PSs was effective, but it had a not-negligible reintervention rate [10].

Persistence or recurrence of MPDS after a 1-year treatment with PS could potentially be treated by surgery, multiple side-by-side PS or self-expandable metal stents (SEMS) [2]. Surgical treatment has resulted in better results when compared to endoscopic treatment [11], but this approach is more invasive and not all patients are willing to undergo pancreatic surgery. Temporary placement of a covered (C)-SEMS, either fully (FC-SEMS) or partially (PC-SEMS), has been investigated as an alternative endoscopic treatment. A systematic review published in 2014, including five studies, showed pain improvement in 85 % of patients treated with FC-SEMSs [12]. More recently, Li et colleagues performed an updated meta-analysis of 10 studies, showing a 93 % MPD stricture resolution in 163 patients [13]. Nevertheless, this latter meta-analysis did not consider data from abstracts nor carried out a quantitative synthesis of complications.

The aim of our study, therefore, was to systematically review and quantify pain, stricture resolution rates and complications of C-SEMSs in management of MPDS, and to further assess whether there was a trend over time through a cumulative meta-analysis.

Methods

This systematic review and meta-analysis has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42021225136. Results are reported based on the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [14] (**Supplementary material 1**).

Search strategy

We performed a computerized literature search in MEDLINE, Embase and Cochrane Library aimed to identify studies, published from January 2000 to September 2020, assessing the role of C-SEMSs in the management of pancreatic duct strictures in CP. The key words “endoprosthesis,” “metal stent,” “endoscopic stent,” “self-expandable metal stent,” “covered SEMS,” “pancreatic duct stricture,” “pancreatic duct stenosis” and “chronic pancreatitis” were associated in different combinations using the Boolean terms AND/OR. No language or publication status restrictions were imposed. The full search strategy is provided in the appendix (**Supplementary material 2**).

For the sake of completeness, we also reviewed reference lists of potentially eligible articles to identify any articles not found through the computerized literature search.

Inclusion criteria

Full text articles and abstracts were included in the systematic review and meta-analysis if they reported results of randomized or controlled clinical trials, observational studies or cross-sectional studies, including case series, assessing the efficacy and safety of endoscopic retrograde cholangiopancreatography (ERCP) placed C-SEMSs in patients with chronic benign pancreatic stricture. Studies investigating the role of C-SEMSs in patients previously treated with PS were considered eligible.

Reviews, guidelines, single case reports, editorials or commentaries, studies on pediatric populations, studies investigating pancreatic duct stones without strictures, studies investigating PS only, as well as studies with biliary, endoscopic ultrasound, percutaneous or surgical SEMS placement, were excluded.

Outcomes

Pain resolution was defined as pain relief or at least reduction in the visual analog scale pain score of > 50 % compared with that before SEMS placement and stricture resolution was defined as satisfactory flow of the contrast medium after stent withdrawal. Other outcomes included technical success, stent migration, stricture recurrence, need for repeated stent placement and complications such as pancreatitis, severe abdominal pain requiring stent removal and de-novo stricture. Technical success was defined as exact placement of the stent along the entire length of the stricture with free flow of contrast medium. Stricture recurrence was stated as the redevelopment of MPDS after initial stricture resolution. Stent migration was considered as dislocation of the stent above or below the stricture site, regardless stricture resolution. After stent removal, occurrence of a new pancreatic ductal stricture at the ends of the stent was described as de-novo stricture.

Identification, selection of studies, and data extraction

Each article was read and analyzed by two members of the research team (A.T. and D.C.), and eligibility assessment was performed independently in an unblinded standardized manner. Any differences were resolved by discussion.

Data were extracted using a standardized form, including: first author, year and type of publication (full text or abstract), study country, study design, number of patients, age and sex of patients, alcohol abuse, stent type, stent diameter, stent length, stent covering material, stricture localization, stricture length, diameter of pancreatic duct dilation, presence of pancreatic duct stone, stent placed across major or minor papilla, need of dilation before stenting, need for extracorporeal shock wave lithotripsy (ESWL), and follow-up time. The following outcomes data were extracted: stricture and pain resolution, technical success, stricture recurrence, need for repeated stent placement, stent migration, severe pancreatitis, severe pain requiring stent removal, de-novo stricture and cholangitis.

Two investigators (A.T. and D.C.) and a biostatistician (M.R.) extracted data from the eligible publications independently.

Quality appraisal

Each study was evaluated through the Cochrane Risk of Bias in Non-randomized Studies of Interventions I (ROBINS-I) tool (15), which is based on confounding, selection bias, bias in measurement classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in meas-

urement of outcomes and bias in selection of the reported results.

Statistical analysis

All the outcomes were evaluated in terms of proportion and corresponding 95 % CI. To avoid the use of continuity correction factors to estimate study variances in studies with proportions close to the margins (i. e. 0 or 1), the Freeman-Tukey double arcsine transformation was used. Pooled estimates were computed using the random effect model using the Der Simonian and Laird moment estimator of the between-study variance component [15]. Finally, study-specific and pooled proportions with their corresponding 95 % CIs were back transformed on the original scale of proportions and graphically represented through forest plots. Duration of stent placement was synthesized in terms of mean days and its standard deviation.

The 95 % prediction intervals, which estimate the expected effect in future studies, were also computed.

Between-study heterogeneity was assessed through the Q test and the I^2 statistic [16].

Sensitivity analyses by omitting one study at a time were performed in order to assess the influence that each individual study had on the final pooled estimates.

For pain and stricture resolution rates, a cumulative meta-analysis in which studies were added one at a time according to publication year (earliest to the most recent), was carried out to assess the presence of a trend over time.

To investigate potential sources of heterogeneity, we carried out stratified analyses according to year of study publication, geographical area of the study, study design (retrospective vs prospective), publication type (original article vs congress abstract), stent diameter (6–8 vs 8–10 mm), duration of stent placement and study follow-up duration (≤ 1 vs > 1 year).

Publication bias was initially assessed by visual inspection for the presence of the asymmetry of the funnel plot and Egger test was carried out to evaluate the presence of asymmetry [17].

Statistical analyses were performed using the "metafor" package under the R version 4.0.2 (R Foundation for statistical computing, Vienna, Austria).

Results

Study selection and characteristics of included studies

A total of 1091 unique articles were identified through the systematic review of the literature. We assessed 128 articles for eligibility, 19 of which were finally included in the meta-analysis (**Supplementary figure 1**). Six studies were published as abstracts [18–23], while the remaining were full articles [24–36]. All included studies were observational in nature and there were no randomized or controlled clinical trials (▶ **Table 1**). There were six prospective [26–28, 31, 33, 36] and 13 retrospective [18–25, 29, 30, 32, 34, 35] studies, with a median follow-up of 20 months (range 3–47 months), including a total of 300 patients with CP treated with C-SEMS, 296 of whom had FC- and four PC-SEMS. The majority of the studies (11 of 19) were conducted in Asia [18, 20, 22, 26, 27, 31–36], with the rest being performed in Western nations, including three studies conducted in the United States [19, 25, 29] and five studies conducted in Europe [21, 23, 24, 28, 30]. The majority of the included patients were men (213 out of 300, 71 %) with a median age of 53 years (range 15–87). The etiology of CP was alcohol for 183 of 300 patients (61 %). Only 18 of the included patients (6 %) were naïve to pancreatic stenting while the remaining 282 (94 %) failed a previous ESWL and/or endoscopic treatment with PS. Inclusion criteria in eligible studies are reported in ▶ **Table 2**.

Stricture and pain resolution

Mean duration of stent placement (133 days, 95 % CI, 100–166 days) was highly heterogeneous across studies, as shown in **Supplementary figure 2**. Stricture resolution was achieved in 264 of 300 patients, with a pooled stricture resolution rate of 91 % (95 % CI, 85 %-96 %). Moderate between-studies heterogeneity emerged (I^2 = 52 %, P < 0.01), although no single study significantly influenced the pooled estimate (▶ **Fig. 1a**). The cumulative meta-analysis did not reveal a significant trend over time (P = 0.28), although there was a slight tendency toward a decrease in the stricture resolution rate over time (▶ **Fig. 1a**).

The rate of pain resolution was reported in 18 of 19 included studies (▶ **Fig. 1b**). The pooled rate was 92 % (95 % CI, 85 %-98 %), and was similar to that observed for stricture resolution, in the presence of significant between-study heterogeneity (I^2 = 64 %, P < 0.01). The cumulative meta-analysis did not show a statistically significant difference in pain resolution rate over the time of the published studies (P = 0.75).

Visual inspection of funnel plots for stricture resolution and pain resolution showed no evidence of asymmetry (**Supplementary figure 3**). The Egger's test gave a P of 0.14 and 0.09, respectively, showing no potential publication bias.

Stratified analyses

Results of stratified analyses on stricture resolution are shown in ▶ **Table 3**. Retrospective studies showed a significantly (P = .02) lower stricture resolution rate (85 %, 95 % CI, 78 %-92 %) as compared to prospective studies (98 %, 95 % CI, 91 %-100 %). The pooled stricture resolution rate was lower when considering the six congress abstracts (83 %, 95 % CI, 71 %-93 %). The diameter of the stent was not significantly related to the stricture resolution rate (P = .61), although studies using 8–10 mm diameter stents showed a pooled stricture resolution rate of 83 % (95 % CI, 71 %-93) as compared to 93 % (95 % CI, 87 %-98) in two studies using 6–8 mm stents. Duration of stent placement (P = .82) and study follow-up duration (P = .56) did not influence the stricture resolution rate.

Other outcomes

The technical success rate for SEMS placement was 100 %. The pooled proportion for stricture recurrence (▶ **Fig. 2a**) was 6 % (95 % CI, 1 %-14 %), with a significant between-study heterogeneity (I^2 = 62 %, P < 0.01). The sensitivity analysis revealed that the study by Cho et al. [18], published as an abstract, significantly influenced the pooled estimate. Its exclusion reduced the pooled estimate by one-third to 4 % (95 % CI, 1 %-10 %), and

▶ **Table 1** Characteristics of studies included in the meta-analysis.

Study	Country	Study design	Stent type, diameter, and length	No. patients	Median age (range)	Sex (M/F)	Alcohol abuse	Study follow-up (months)
Okushima et al. 2005 [35]	Japan	Retrospective	Diamond (PC-SEMSs), 8–10 mm*, 4 cm	3	51 (39–59)	3/0	2/3	24 (18–25)
Park et al. 2008 [26]	South Korea	Prospective	Niti D, 6–8 mm*, 5–7 cm	13	49 (32–68)	9/4	8/13	5 (2–10)
Sauer et al. 2008 [25]	United States	Retrospective	VIABIL, 8–10 mm*, 4–10 cm	6	54 (42–64)	4/2	4/6	3 (1–8)
Moon et al. 2010 [27]	South Korea	Prospective	Niti-S Bumpy, 6–10 mm*, 4–10 cm	32	48 (17–73)	27/5	27/32	5 (3–7)
Giacino et al. 2012 [24]	France	Retrospective	WallStent (PC–SEMS, 1 patient), WallFlex (9 patients), 8–10 mm*, 4–8 cm	10	53 (31–84)	8/2	6/10	20 (13–34)
Sangwaiya et al. 2015 [21]	United Kingdom	Retrospective	FC-SEMSs, not otherwise specified	8	58 (41–68)	3/5	4/6	9 (2–15)
Matsubara et al. 2016 [36]	Japan	Prospective	Niti-S D/Bumpy, 8–10 mm*, 5–10 cm	10	50 (36–71)	6/4	8/13	35 (19–57)
Ogura et al. 2016 [32]	Japan	Retrospective	Niti-S biliary S, 6 mm*, 6–8 cm	13	54 (36–81)	6/7	19/32	8 (6–18)
Patel et al. 2017 [19]	United States	Retrospective	FC-SEMSs, not otherwise specified	20	43 (15–75)	9/11	NA	NA
Korpela et al. 2018 [30]	Finland	Retrospective	Niti-S Bumpy, Hanaro, VIABIL, 8–10 mm*, 3–6 cm	17	58 (19–68)	16/1	10/17	29 (8–80)
Oh et al. 2018 [34]	South Korea	Retrospective	Bonastent, 6 mm*, 5–8 cm	18	43 (35–62)*	7/11	7/18	47 (7–57)*
Traini et al. 2018 [23]	Italy	Retrospective	Niti-S biliary, variable diameter and length	5	57 (± 14 SD)	4/1	3/5	NA
Tringali et al. 2018 [28]	Italy	Prospective	Niti-S Bumpy, 6–8 mm*, 3–5 cm	15	60 (19–85)	10/5	4/15	39 (5–55)
Yamada et al. 2018 [33]	Japan	Prospective	Dumbbell, 8–10 mm*, 3–7 cm	22	66 (15–80)	17/5	20/22	14 (9–16)
Cho et al. 2019 [18]	South Korea	Retrospective	FC-SEMSs, not otherwise specified, 8–10 mm*, 4–8 cm	23	48 (NA)	21/2	23/23	17 (11–35)*
Jain et al. 2019 [20]	India	Retrospective	FC-SEMSs, not otherwise specified	23	42 (22–65)	17/6	NA	42 (6–78)*
Sharaiha et al. 2019 [29]	United States	Retrospective	Wallflex, 8–10 mm*, variable length	33	54 (18–87)	25/8	19/33	14 (6–24)
Shen et al. 2019 [22]	China	Retrospective	FC-SEMSs, not otherwise specified	4	NA	NA	NA	33 (23–39)
Lee et al. 2020 [31]	South Korea	Prospective	Dumbbell, 8–10 mm*, 3–5 cm	25	53 (46–56)*	21/4	19/25	34 (25–56)*

* IQR was reported.

▶ **Table 2** Inclusion criteria for each study included in the meta-analysis.

Study	Inclusion criteria
Okushima et al. 2005 [35]	Stone recurrence after ESWL and/or endoscopic treatment 3–6 times.
Park et al. 2008 [26]	Refractory strictures defined as stricture of the pancreatic duct during follow-up after previous placement of single or double plastic stents (10 F or double 7 F) with regular intervals of stent change for at least 12 months.
Sauer et al. 2008 [25]	Refractory strictures defined as failure of conventional placement of a plastic stent in the PD to relieve pain.
Moon et al. 2010 [27]	Recurrent painful stricture after initial stricture resolution or persistent stricture despite plastic stenting for at least 2 months.
Giacino et al. 2012 [24]	Recurrent typical pain which required daily analgesics and at least one dominant pancreatic duct stricture at endoscopic retrograde pancreatography. Eight patients had undergone one or two plastic pancreatic stents (7–11.5 Fr) and biliary stents for 4–12 months. The other two patients proceeded directly to treatment with an FC-SEMS.
Sangwaiya et al. 2015 [21]	Main pancreatic duct stricture due to chronic pancreatitis. 5 patients had prior placement of plastic stents and 3 had no prior endoprostheses. Stents were inserted through Santorini's duct.
Matsubara et al. 2016 [36]	Refractory strictures defined as recurrent pain or pancreatitis after plastic stent removal caused by unresolved stricture or requirement for continuous plastic stents placement for symptomatic unresolved stricture; previous placement of a single PS with regular intervals of stent exchange for at least 3 months.
Ogura et al. 2016 [32]	Symptomatic chronic pancreatitis with abdominal pain and a main pancreatic head duct stricture. All 13 patients were native of pancreatic stenting.
Patel et al. 2017 [19]	Refractory MPDS (no definition).
Korpela et al. 2018 [30]	Refractory dominant stricture defined as a definite narrowing of the pancreatic duct creating obstruction to pancreatic flow, with persistence of contrast medium in the dilated duct of the body and tail for more than 5 minutes after stent removal (*Costamagna G, Bulajic M, Tringali A* et al. Multiple stenting of refractory pancreatic duct strictures in severe chronic pancreatitis: long-term results. Endoscopy 2006; 38: 254–259).
Oh et al. 2018 [34]	Refractory strictures defined as presence of pain relapse or pancreatitis occurring within 6 months after plastic stent removal, which had been in place for at least 12 months.
Traini et al. 2018 [23]	Strictures that persisted after repeated plastic stenting.
Tringali et al. 2018 [28]	Persistent strictures defined as the persistence of the MPDS after initial treatment with pancreatic sphincterotomy and single plastic stent insertion.
Yamada et al. 2018 [33]	Painful CP with MPDS and upstream ductal dilation (>6 mm), prior deployment of a plastic stent for 6 months and symptomatic after stent deployment.
Cho et al. 2019 [18]	Refractory MPDS (no definition).
Jain et al. 2019 [20]	Refractory MPDS (no definition).
Sharaiha et al. 2019 [29]	Refractory strictures defined as refractory pain despite prior treatment with a conventional therapy that included at least three balloon dilations, repeat plastic stent placements with upsizing of the stents, or stone lithotripsy.
Shen et al. 2019 [22]	Refractory strictures defined as MPDS refractory to conventional pancreatic plastic stent implantation.
Lee et al. 2020 [31]	Refractory strictures defined as persistence of the MPDS after initial treatment with pancreatic sphincterotomy and single plastic stent insertion (recurrence of a painful stricture within 6 months or stricture persistence after plastic stent removal).

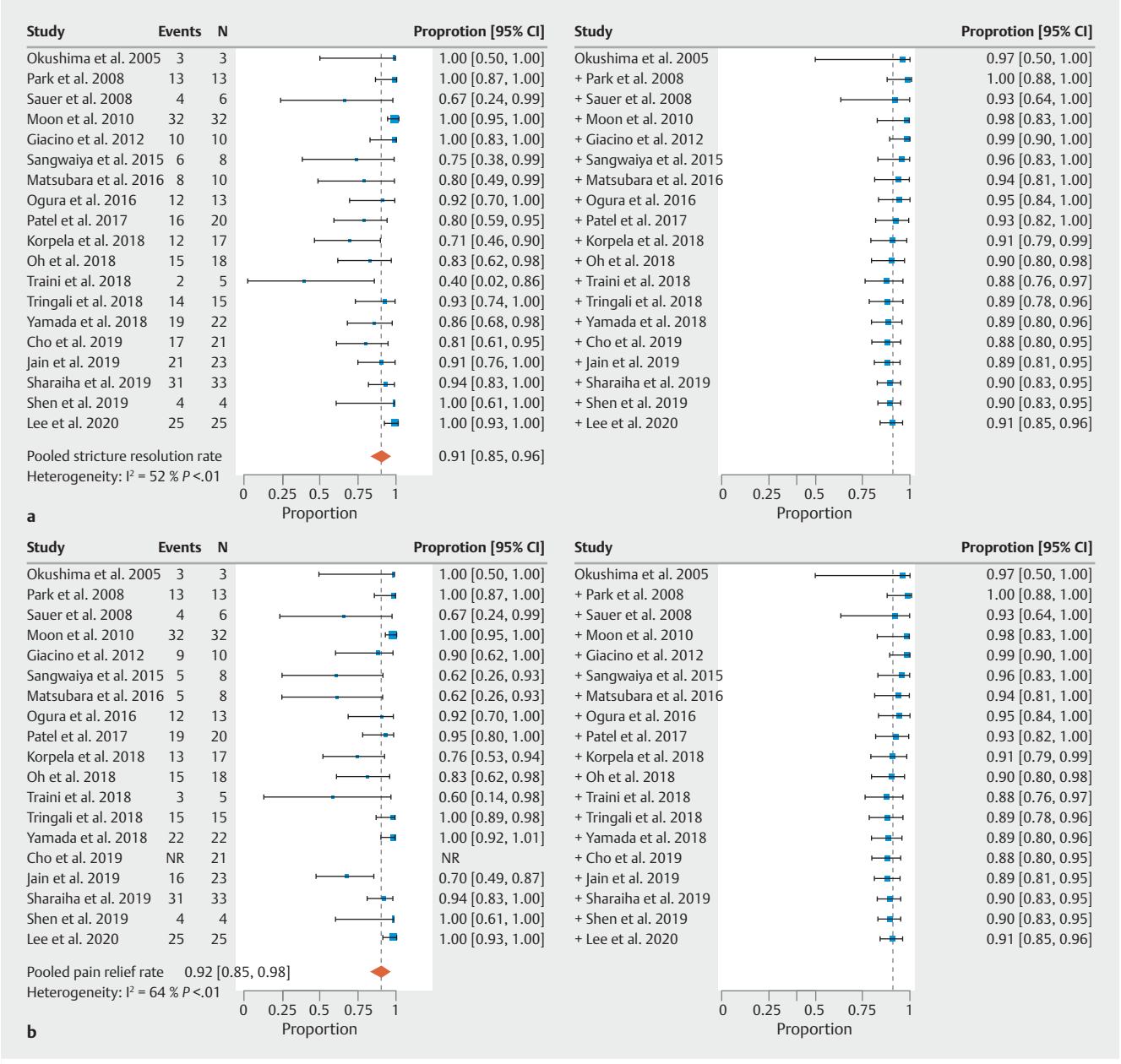
the amount of between-study heterogeneity was reduced, too (I^2 = 45 %, P = .02).

Regarding complications (▶ **Fig. 2b**), 10 of 300 patients experienced severe pain requiring stent removal (**Supplementary figure 4**), with a pooled proportion equal to 1 % (95 % CI, 0 %–3 %). Acute pancreatitis (**Supplementary figure 5**) was experienced by 21 patients (3 %, 95 % CI, 0 %–8 %). The pooled proportion of de-novo stricture (**Supplementary figure 6**) was equal to 2 % (95 % CI, 0 %–5 %). Only three patients experienced cholangitis.

Stent migration (**Supplementary figure 7**) was heterogenous across studies (I^2 = 73 %, P < .01), with a total of 33 cases in 300 patients, the pooled proportion being 7 % (95 % CI, 1 %–15 %). Although a sensitivity analysis revealed that no single study appeared to influence the pooled proportion, the three studies by Park et al. [26], Korpela et al. [30] and Tringali et al. [28] showed migration rates at or above 40 %. Only 15 patients needed repeated stent placement (**Supplementary figure 8**), the pooled proportion being 3 % (95 % CI, 1 %–7 %).

Risk of bias evaluation

Risk of bias evaluation according to the ROBINS-I tool is reported in ▶ **Fig. 3**. There was no useful information for risk of bias evaluation in six studies published as abstracts [18–23], while



▶ **Fig. 1** Forest plots showing the results of **a** conventional and cumulative meta-analysis of the stricture resolution and **b** pain relief rate of C-SEMSs for the treatment of MPDS. The pooled odds ratio (OR) is represented through a diamond and its tips represents the 95 % confidence interval (CI), whereas the prediction interval is represented through a dashed thin line.

nine studies [24, 25, 27, 29, 30, 32–35] were evaluated to have a moderate overall risk of bias. The remaining ones [26, 28, 31, 36] were evaluated to have a low risk of bias.

Discussion

The results of this meta-analysis showed that C-SEMSs are an effective and safe endoscopic treatment for patients with MPDS in CP. Nineteen studies were included in the meta-analysis, leading to a total of 300 patients, 296 of whom treated with FC- and four with PC-SEMSs (three Diamond [35] and one WallStent [24], Boston Scientific Co., Natick, Massachusetts, United States, described as FC-SEMSs in the original publications [24, 35]). In line with a recently published meta-analysis [13], our results, which included additional studies not previously considered [18–23, 29, 31, 34, 35], showed that stricture and pain resolution were respectively achieved in 91 % and 92 % of patients with MPDS in CP, with low rates of stricture recurrence and procedure-related complications. Of note, the cumulative meta-analysis revealed a slight tendency toward a decrease in the stricture resolution rate over time, without a statistically significant trend. This result was in contrast to our expectations according to which factors, such as better selection of candidate patients, technological improvements and acquisition of

▶ **Table 3** Results of stratified analyses on stricture resolution.

Strata	No. studies	Pooled estimate (95% CI)	I^2, *P* value for heterogeneity	*P* value for subgroup differences
Publication year				.22
▪ Before 2018	9	0.93 (0.83–1.00)	55%, .02	
▪ After 2018	10	0.89 (0.80–0.96)	54%, .02	
Geographic area				.22
▪ America	3	0.86 (0.68–0.98)	51%, .13	
▪ Asia	11	0.95 (0.89–0.99)	44%, .06	
▪ Europe	5	0.82 (0.61–0.97)	62%, .03	
Study design				.02
▪ Retrospective	13	0.85 (0.78–0.92)	29%, .16	
▪ Prospective	6	0.98 (0.91–1.00)	53%, .06	
Publication type				.07
▪ Original article	13	0.94 (0.87–0.99)	52%, .01	
▪ Congress abstract	6	0.83 (0.71–0.93)	25%, .25	
Stent diameter (mm)[1]				.61
▪ 6–8	2	0.93 (0.87–0.98)	0%, .36	
▪ 8–10	8	0.83 (0.71–0.93)	56%, .03	
Duration of stent placement (months)[1]				.82
▪ ≤3	6	0.92 (0.75–1.00)	63%, .02	
▪ >3	10	0.93 (0.86–0.98)	39%, .10	
Study follow-up duration (years)[1]				.56
▪ ≤1	5	0.94 (0.78–1.00)	65%, .02	
▪ >1	12	0.92 (0.86–0.97)	32%, .14	

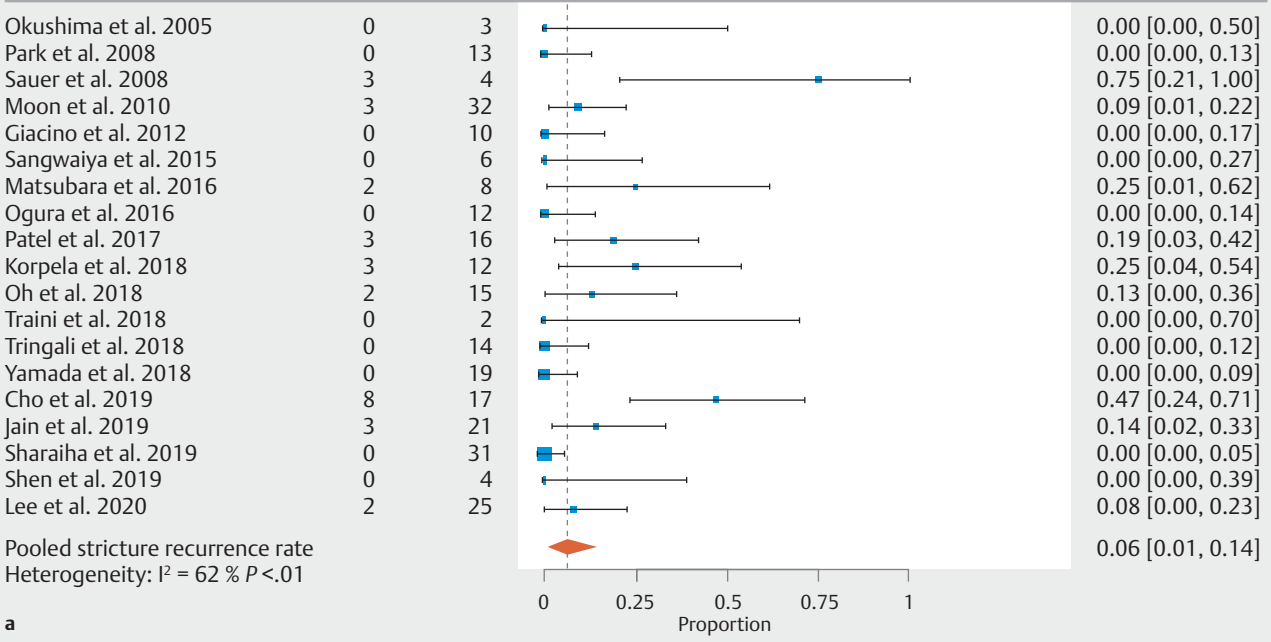
[1] The sum of number of studies does not add up to the total since some studies did not report such information.

expertise, may have had a positive impact on efficacy over the years. However, it should be pointed out that C-SEMS appeared to resolve pancreatic strictures and pain in over 90% of cases, a result similar to that obtained with multiple plastic stenting in an Italian retrospective long-term follow-up study [10].

The results of our meta-analysis were strengthened by quantification of complications. In particular, the severe acute pancreatitis rate was comparable to those emerging after post-ERCP pancreatitis performed for different indications [37–39]. On the other hand, stent migration was slightly lower compared to multiple plastic stenting (10.5%) [12], but in line with that observed for biliary benign stenosis due to CP [40]. The rate of cholangitis was too low to perform pooled analysis.

Stent size and stent characteristics may influence the stricture resolution rate. Our stratified analyses showed that stent diameter was not significantly related to the stricture resolution rate, although 8- to 10-mm diameter stents showed a lower stricture resolution when compared to 6- to 8-mm stents (83% vs 93%, respectively). The reason for which a narrower stent had a better impact on stricture resolution is unclear. Rather, the diameter and length of the stent must be tailored to the stricture anatomy and to the diameter of the MPD above and below the stricture. Due to heterogeneity and lack of data among the included studies, we were unable to carry out stratified analyses according to other stent characteristics, such as length, anti-migration properties, metal type, and covering material.

Our meta-analysis showed that leaving a stent in situ for more or less than 3 months did not significantly influence the stricture resolution rate. Efficacy and safety of C-SEMS placement for refractory MPDS has been compared with multiple PS treatment in a previous systematic review of five studies by Shen et al [12]. The authors documented no statistically significant differences in terms of functional success defined as successful drainage, reintervention rate, and pain improvement, but the included studies showed high heterogeneity and a meta-analysis was not performed. Indeed, additional studies are needed to better investigate whether stent placement



▶ **Fig. 2** Forest plots showing **a** stricture recurrence of C-SEMSs for the treatment of MPDS and **b** secondary endpoints. The pooled odds ratio (OR) is represented through a diamond and its tips represents the 95 % confidence interval (CI), whereas the prediction interval is represented through a dashed thin line.

duration could influence stricture resolution rate. A concern in our meta-analysis was substantial between-study heterogeneity. Although we carried out sensitivity and stratified analyses, we were not able to identify single influential studies nor potential sources of heterogeneity. If any, stratified analyses showed that retrospective studies had a significantly lower stricture resolution rate, in the absence of significant between-study heterogeneity, as compared to prospective studies, the results of which were more heterogeneous. This result may be only partly explained considering that six [18–23] of the 13 included retrospective studies were abstracts, which in turn reported a lower pooled stricture resolution rate (83 %). In fact, the statistically significant difference of stricture resolution rates across retrospective and prospective studies disappeared when removing abstracts [18–23] in a sensitivity analysis. As recommended by the Cochrane association, risk of bias evaluation of the included studies was carried out through the ROBINS-I tool (15). However, abstracts [18–23] did not report any useful information to quantify such risk of bias. We could argue that selection bias would be unlikely to explain such a result as typically affects retrospective studies, which conversely showed higher stricture resolution rates.

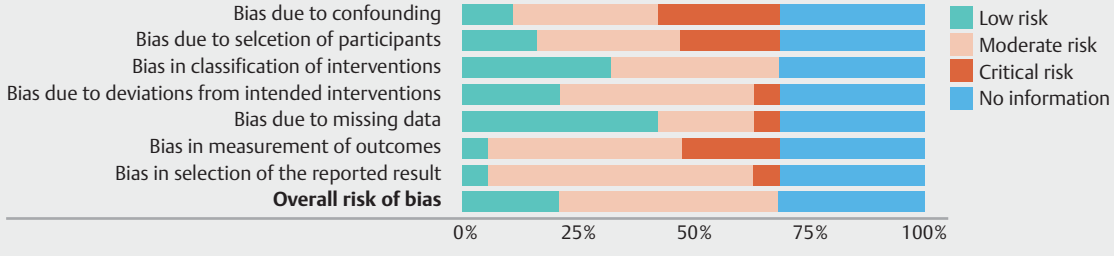
Heterogeneity could also be explained by the relatively low number of eligible studies and their limited sample size, ranging from 3 [35] to 33 [29] patients. In fact, all the included studies were single-center experiences with consecutive patients and were not powered on the basis of pre-specified study hypotheses. We showed in a stratified analysis that stricture resolution did not differ across studies with median follow-up durations ≤ 1 year as compared to those with longer durations (> 1 year). However, the different follow-up durations of the included studies hampered any evaluation of long-term stricture resolution. In addition, heterogeneity may also derive from the inclusion criteria for the eligible studies, which differed in terms

Study	Risk of bias domains							
	D1	D2	D3	D4	D5	D6	D7	Over-all
Okushima et al. 2005	!	!	+	−	+	!	−	−
Park et al. 2008	+	+	+	−	−	−	−	+
Sauer et al. 2008	−	−	+	+	!	!	!	−
Moon et al. 2010	!	!	+	+	−	!	−	−
Giacino et al. 2012	!	!	−	+	−	−	−	−
Sangwaiya et al. 2015	?	?	?	?	?	?	?	?
Ogura et al. 2016	−	−	−	−	+	−	−	−
Matsubara et al. 2016	−	+	+	−	+	−	−	+
Patel et al. 2017	?	?	?	?	?	?	?	?
Korpela et al. 2018	!	!	−	−	+	−	−	−
Oh et al. 2018	−	−	−	!	+	!	−	−
Traini et al. 2018	?	?	?	?	?	?	?	?
Tringali et al. 2018	−	−	+	+	+	−	+	+
Yamada et al. 2018	−	−	−	−	−	−	−	−
Cho et al. 2019	?	?	?	?	?	?	?	?
Jain et al. 2019	?	?	?	?	?	?	?	?
Sharaiha et al. 2019	!	−	−	−	+	−	−	−
Shen et al. 2019	?	?	?	?	?	?	?	?
Lee et al. 2020	+	+	−	−	+	+	−	+

Domains:
D1: Bias due to confounding
D2: Bias due to selcetion of participants
D3: Bias in classification of interventions
D4: Bias due to deviations from intended interventions
D5: Bias due to missing data
D6: Bias in measurement of outcomes
D7: Bias in selection of the reported result

Judgement:
! Critical
− Moderate
+ Low
? No information

a



b

▶ **Fig. 3** Risk of bias evaluation of the included studies according to the Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool. **a** Study-specific risk of bias. **b** Summary risk of bias.

of indications for C-SEMS placement, previous treatment with ESWL, previous placement of pancreatic stents with different indwelling time, number of naïve patients, and absence of a shared definition of refractory stricture. We carried out sensitivity analyses showing that the inclusion of four of 300 patients treated with PC-SEMS (Diamond [35] and WallStent [24], Boston Scientific Co., Natick, Massachusetts, United States) did not influence pooled estimates nor between-study heterogeneity. We also point out that this systematic review and meta-analysis was not designed to highlight potential differences between FC- and PC-SEMS, as this was not possible in the absence of published comparative studies.

Recently, a newly designed biodegradable non-covered SEMS has been used to treat pancreatic duct strictures in CP [41]. The stent resembles a metallic expandable stent, although it is made of polydioxanone fibers and is designed to degrade within 3 to 6 months. It was used in 19 patients whose previous endoscopic PS insertions failed, achieving stricture resolution in 58 % of cases. Such a study [41] did not meet the inclusion criteria for our meta-analysis. Future studies designed to test efficacy and safety of C-SEMSs for MPDS in CP should be randomized and have a multi-arm design, allowing comparisons between FC-SEMS, PC-SEMS, multiple plastic, and biodegradable stents.

Conclusions

Pancreatic C-SEMS appear effective and safe in patients with benign strictures due to CP. However, there is a significant need for further high-quality, well-designed studies to produce evidence-based data on short- and long-term efficacy, safety, costs, and optimal stent duration with pancreatic C-SEMSs, in comparison with multiple plastic and biodegradable stents.

Competing interests

The authors declare that they have no conflict of interest.

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