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Efficacy of different stent types in post-liver-transplant anastomotic biliary strictures: a systematic review and meta-analysis

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Abstract

Background Stent selection in the endoscopic management of post-liver-transplant anastomotic biliary strictures remains controversial. This systematic review and meta-analysis aimed to evaluate the potential differences between available stents.

Methods MEDLINE, Cochrane, and Scopus databases were searched until April 2023 for comparative studies evaluating stricture management using multiple plastic stents (MPS) and self-expandable metal stents (SEMS), including fully-covered (FC)- and intraductal (ID)-SEMS. The primary outcome was stricture resolution, while secondary outcomes included stricture recurrence, stent migration and adverse events. Meta-analyses were based on a random-effects model and the results were reported as odds ratios (OR) with 95% confidence intervals (CI). Subgroup analyses by type of metal stent and a cost-effectiveness analysis were also performed.

Results Nine studies (687 patients) were finally included. Considering stricture resolution, SEMS and MPS did not differ significantly (OR 0.99, 95%CI 0.48-2.01; I^2=35%). Stricture recurrence, migration rates and adverse events were also comparable (OR 1.71, 95%CI 0.87-3.38; I^2=55%, OR 0.73, 95%CI 0.32-1.68; I^2=56%, and OR 1.47, 95%CI 0.89-2.43; I^2=24%, respectively). In the subgroup analysis, stricture resolution and recurrence rates did not differ for ID-SEMS vs. MPS or FC-SEMS vs. MPS. Migration rates were lower for ID-SEMS compared to MPS (OR 0.28, 95%CI 0.11-0.70; I^2=0%), and complication rates were higher after FC-SEMS compared to MPS (OR 1.76, 95%CI 1.06-2.93; I^2=0%). Finally, ID-SEMS were the most cost-effective approach, with the lowest incremental cost-effectiveness ratio: 3447.6 £/QALY.

Conclusion Stent type did not affect stricture resolution and recurrence; however, ID-SEMS placement was the most cost-effective approach compared to the alternatives.

Keywords Post-liver-transplant biliary strictures, self-expandable metal stents, intraductal, fully covered, plastic stents

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Introduction

Anastomotic biliary strictures post liver transplantation (LT) represent a particular category of benign biliary strictures, impacting the survival of both graft and patient [1]. They are primarily diagnosed within 12 months post-transplantation with a prevalence of 6.6-35.5%, associated with recurrent cholangitis, transplant failure or rejection, prolonged admissions, graft survival reduction, portal hypertension, re-transplantation, and a healthcare and cost burden [1-4].

Endoscopic retrograde cholangiopancreatography (ERCP) has been the mainstay intervention to manage these strictures, as the alternative percutaneous approach is associated with higher rates of allograft failure and prolonged hospitalization [2]. Biliary stenting is the suggested strategy for stricture remodeling; however, the type

of stent selected remains controversial. The European Society of Gastrointestinal Endoscopy (ESGE) recommends multiple plastic stents (MPS), based on evidence implying higher recurrence and complication rates after using self-expandable metal stents (SEMS) [5]. Conversely the American College of Gastroenterology (ACG) and the American Society of Gastrointestinal Endoscopy (ASGE) support the use of fully covered (FC)-SEMS over MPS, albeit based on low to moderate evidence [6-8].

During the last decade, a new type of SEMS has been developed to overcome the increased migration rates of SEMS and MPS, and to prevent the incomplete resolution of post-transplant strictures [9,10]. Intraductal (ID)-SEMS are fully-covered stents with shorter length and a central waist, offering a theoretical anti-migration mechanism by anchoring into the bile duct, and bearing a long string deployed in the duodenum that allows stent retrieval [9]. Although a few meta-analyses evaluated the efficacy of SEMS and MPS in post-LT biliary strictures, none of them compared the potential differences in the results between these stents and ID-SEMS [7,11-13]. Moreover, given the fact that the previous reports imply equivalent performance between SEMS and MPS, data on cost-effectiveness could assist in decision making [7,11-13]. This systematic review with meta-analysis aimed to evaluate the potential differences in the performance of SEMS and MPS, focusing on the various commercially available types of stents and their cost-effectiveness.

Materials and methods

This study was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Supplementary Table 1) [14]. A predefined protocol was registered in the international prospective platform for systematic reviews (PROSPERO Registration Number: CRD42023429536) (Supplementary Document).

Inclusion and exclusion criteria

The PICO (population, intervention, control, and outcomes) framework was used to structure the study's question, which included the evaluation of the available stents in treating post-LT anastomotic biliary strictures [15]. Comparative studies and randomized control trials (RCT) assessing the existing types of stents were included when the following prerequisites were met: (A) Patients: adult patients (≥18 years old), with post-LT anastomotic biliary stricture and indication for ERCP and stricture remodeling, using (B) Interventions: SEMS placement (FC-SEMS or ID-SEMS); (C) Comparators: patients who received treatment with MPS; (D) Outcomes: stricture resolution after completion of therapy. Stricture recurrence during the follow-up period, stent migration rates and adverse events (AEs) were also assessed. Studies with missing data for analysis, without clear presentation of the results per type of stent, not written in the English language, case reports or series, single arm cohorts, as well as animal studies were excluded.

Search strategy

A literature search was conducted using the MEDLINE/PubMed, Cochrane, and Scopus databases through 15th April 2023. The search algorithm was adjusted to the prerequisites of each database and included the following Boolean search terms: "*post-transplant biliary strictures*", "*Kaffes stent*", "*intraductal SEMS*", "*metal stent*", "*SEMS*", "*plastic stents*". Other relevant publications were found by hand-searching the reference lists of the retrieved articles and by using the "similar article" function within PubMed. Unpublished works and congress presentations were excluded. In the event of missing data, the first and/or corresponding authors were contacted. Two investigators (AP, DR) independently selected articles of interest based on the pre-defined inclusion and exclusion criteria, and any disagreements were resolved after consensus with the senior author (PG).

Data extraction and quality assessment

Data relating to study-, demographics-, intervention- and stent- related parameters were entered into a form by 2 investigators (AP and GT), and a third author (DR) controlled the datasets for any discrepancies. Disagreements were resolved after consulting a senior investigator (PG).

Quality assessment was carried out independently by 2 authors (DR and GT), using the ROBINS-I tool, which can be applied to both randomized and non-randomized studies.

Outcomes

The primary outcome was the rate of stricture resolution after completion of therapy, documented by cholangiogram or cross-sectional imaging, and the comparison between the SEMS and MPS groups.

Clinical and biochemical relapse with imaging confirmation, defined as stricture recurrence, was considered as a secondary outcome. AE rates were estimated and compared between the arms, while stent migration rates were calculated and compared separately. The mean number of ERCPs until stricture remodeling was assessed per stent type and included in the cost-effectiveness analysis, which provided results with regard to the

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primary outcome, the number of ERCPs needed, the alternative approaches in case of failure, and the expenditures on each arm.

Finally, subgroup analyses were performed with regard to the different available stent types (FC-SEMS vs. MPS, and ID-SEMS vs. MPS).

Cost-effectiveness analysis

A decision analysis model was constructed, incorporating ERCP with different stent types (ID-SEMS, FC-SEMS, MPS), anastomotic stricture outcomes, and management after failure (Supplementary Fig. 1). Outcomes included quality-adjusted life years (QALY) and institution-derived procedure/device costs, according to the UK National Health Service (NHS) reference prices. Complications were extracted from our meta-analysis. The main outcome measure was the incremental cost-effectiveness ratio (ICER), with a willingness-to-pay threshold of 50000 £/QALY. Net monetary benefit was also calculated. A probabilistic sensitivity analysis was then performed based on 1000 Monte Carlo simulations, generating a cost-effectiveness acceptability curve for competing strategies.

Statistical analysis

The pooled odds ratios (OR) and 95% confidence intervals (CI) of the outcomes were calculated using the DerSimonian and Laird random-effects model that incorporated both between- and within-study variations [16]. Subgroup analyses by type of SEMS and sensitivity analysis including only RCTs were performed to explore and explain the diversity among the results. To avoid a unit-of-analysis error, which can occur when a multi-arm study is included in a meta-analysis, we combined the intervention groups with different modalities into 1 large group, as recommended in the Cochrane Book for Systematic Reviews of Interventions [17]. Because of the low number of studies included in the meta-analysis, meta-regression analysis was not performed and publication bias was assessed using visual inspection of the funnel plot [18]. For all analyses, a P-value of <0.05 was considered statistically significant. All statistical analyses were performed using RevMAN Software (Review Manager, Version 5.4, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) [19].

Quality of evidence

The included studies were assessed for the quality of the provided evidence according to the GRADE criteria [20,21]. Following a structured assessment, including risk of bias (RoB), inconsistency, indirectness, imprecision and publication bias, the evidence was graded using the GRADEpro GDT tool (GRADEpro Guideline Development Tool. McMaster University and Evidence Prime, 2024. Available from gradepro.org). Following the initial grading and the results of our meta-analysis, the primary researchers (AP, PG) arrived at a consensus concerning the overall effect of the accumulated evidence [21].

Results

Characteristics of included studies

The literature search yielded 1873 results. After applying the inclusion criteria, 9 studies [22-30] (687 patients) were eligible (Fig. 1). Table 1 summarizes the main characteristics of the included studies. Five studies were retrospective [22,24,25,27,29], 3 RCTs [26,28,30], and the remaining 1 was a non-randomized prospective study [23], Three studies compared ID-SEMS with MPS [23,24,30] and 5 FC-SEMS with MPS [25-29], whereas 1 included all 3 approaches [22].

The male-to-female ratio was 2.5:1 and the age ranged between 23 and 69 years. Indications for transplantation included viral hepatitis-related cirrhosis (n=276, 40.2%), hepatocellular carcinoma (n=108, 15.7%), alcoholic cirrhosis (n=68, 9.9%), non-alcoholic fatty liver disease (n=47, 6.8%), and autoimmune disorders (n=39, 5.7%). The remaining patients underwent transplantation for rare or undiagnosed liver diseases. The mean time from transplantation to stricture diagnosis was 1.3-26 months. The time the SEMS remained in place ranged from 3-6 months, whereas the plastic stents were exchanged every 3-4 months during an overall 12-month period. SEMS were placed in 251 patients, including 82 with ID-SEMS and 169 with FC-SEMS, and MPS in 436 cases. Stent diameter for ID-SEMS was 8-10 mm, except for 1 study where 6-8-mm stents were inserted [23]. Two studies provided detailed information about FC-SEMS and both used 8-10-mm diameter stents [28,29]. The MPS used were mainly 10 Fr in diameter and the mean number of maximum stents per patient ranged between 7.5 and 10. Two ERCPs were required for treatment in the SEMS group, whereas patients with MPS needed a median of 3-4.9 procedures until stricture resolution. After the completion of stricture calibration, patients were followed up for 12-64 months.

Quality assessment

All 3 RCTs were found to have a low RoB. However, the non-RCTs had an *a priori* RoB due to patient selection, which was serious in retrospective studies. The retrospective design did not allow the assessment of potential confounding factors affecting the outcomes. Supplementary Figure 13 presents the results of the RoB assessment, including the RCTs, the 1 prospective study with a low RoB, and the retrospective ones with a moderate RoB.

Primary outcome

SEMS resolved post-transplant biliary anastomotic strictures in 89.7% (95%CI 84.9-94.6) of cases, while the respective rates for the MPS approach was 88.5% (95%CI 83.1-94.0). The comparative assessment of stricture resolution rates between metal and plastic stents did not reveal any statistically significant difference (OR 0.99, 95%CI 0.48-2.01; I^2=35%) (Fig. 2).

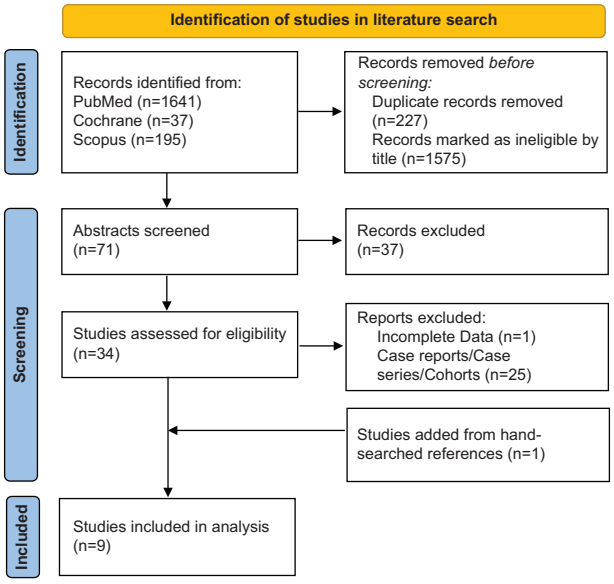


Figure 1 Study flowchart

Secondary outcomes

Stricture recurrence was recorded in 24.3% (95%CI 17.2-31.5%) of patients after SEMS and in 14.8% (95%CI 8.2-21.5) after MPS; the difference was not significant (OR 1.71, 95%CI 0.87-3.38; I^2=55%) (Supplementary Fig. 2). The time of recurrence ranged from 5.8-20 months following the completion of treatment and removal of the stent, and from 5-13.75 months after initial stricture resolution.

The pooled migration rate for SEMS was 14% (95%CI 6.4-21.5) and for MPS 18.5% (95%CI 12.8-24.3) with no difference between the 2 arms (OR 0.73, 95%CI 0.32-1.68; I^2=56%) (Supplementary Fig. 3).

The pooled rates of overall AEs were 29.6% (95%CI 14.7-44.5) after SEMS placement, and 27.6% (95%CI 15.4-39.9) after MPS, with a non-significant difference (OR 1.47, 95%CI 0.89-2.43; I^2=24%) (Supplementary Fig. 4). Cholangitis was diagnosed in 14.3% (95%CI 5.9-22.7) post-SEMS and in 11.0% (95%CI 4.7-17.4) post-MPS; their comparison gave an OR of 1.27 (95%CI 0.70-2.3; I^2=0%). Interestingly, only 3 studies mentioned antibiotic use as a standard of care measure [24,28,30]. Post-ERCP pancreatitis (PEP) was recorded in 27 cases (8.8%, 95%CI 3.1-14.4) in the SEMS group and 23 (5.5%, 95%CI 2.8-8.2) in the MPS group, with an OR of 2.27 (95%CI 0.97-5.31; I^2=29%). Three patients (1.2%) of the SEMS group and 12 (2.8%) of the MPS group presented with bleeding. One death, of a patient in the MPS group, was recorded in 1 study; however, no clear connection with the procedure was identified [22].

Subgroup analysis

Moderate heterogeneity was identified in all outcomes, except for overall AEs and cholangitis rates, where I^2 (24% and 0%, respectively) reflected low heterogeneity.

Regarding the primary outcome, ID-SEMS provided higher complete resolution rates compared to MPS (95.6%, 95%CI 91.3-100 vs. 80.9%, 95%CI 63.3-98.6, respectively), although the difference was marginally non-significant (P=0.07; OR 3.48, 95%CI 0.89-13.62; I^2=5%). The subgroup analysis comparing FC-SEMS and MPS also achieved reduction in heterogeneity, with FC-SEMS achieving comparable stricture resolution with MPS (84.2%, 95%CI 78.7-89.6 vs. 88.5%, 95%CI 82.7-94.3, respectively. OR 0.76, 95%CI 0.42-1.39; I^2=11%) (Supplementary Fig. 5).

The subgroup analysis for stricture recurrence did not reveal any significant difference between subgroups. ID-SEMS (25.6%, 95%CI 11.5-39.7) and MPS (29%, 95%CI 19.2-38.8) provided equivalent results (OR 1.01, 95%CI 0.51-2.03; I^2=0%), whereas FC-SEMS (22.2%, 95%CI 14.3-30.0) were associated with higher recurrence rates compared to MPS (10.6%, 95%CI 4.3-16.8), though the difference did not reach significance (P=0.09) or show homogeneity (OR 2.39, 95%CI 0.87-6.56; I^2=66%) (Supplementary Fig. 6).

On the other hand, migration rates were significantly lower for ID-SEMS compared to MPS, with an OR of 0.28 (95%CI 0.11-0.70; I^2=0%), and pooled rates of 9.4% (95%CI 2.3-16.5) and 18.5% (95%CI 12.8-24.3), respectively. However, FC-SEMS and MPS migrated with similar rates (OR 1.25, 95%CI 0.54-2.88; I^2=40%) (Supplementary Fig. 7).

Overall complication rates were similar for ID-SEMS and MPS (OR 0.90, 95%CI 0.28-2.84; 27.9%, 95%CI 0.0-57.7; and 32.2%, 95%CI 13.8-50.6, respectively), but with a high level of heterogeneity (I^2=47%). Interestingly, FC-SEMS placement resulted in a significantly higher rate of AEs compared to MPS (OR 1.76, 95%CI 1.06-2.93; 25%, 95%CI 10.5-39.5; and 21.2%, 95%CI 8.4-34.1) with null heterogeneity (I^2=0%) (Supplementary Fig. 8), probably reflecting the odds of PEP (OR 2.27, 95%CI 0.97-5.31); I^2=29%), with this complication occurring in 13.7% (95%CI 3.7-23.8) after FC-SEMS and in 7.0% (95%CI 2.5-11.5) after MPS. Regarding ID-SEMS, only 3 cases of PEP were recorded. Cholangitis rates were similar in all compared stent subtypes: ID-SEMS vs. MPS OR 1.23 (95%CI 0.62-2.44; I^2=17%); FC-SEMS vs. MPS: OR 0.89 (95%CI 0.35-2.28; I^2=0%). The main results are also presented in a graphical abstract.

Sensitivity analysis

Given the methodological advantages of RCTs over non-randomized studies, we elected to perform sensitivity analyses to assess the impact of study design on all of our outcomes. All estimates remained unchanged (Supplementary Fig. 9).

Cost-effectiveness analysis

In our base-case analysis, ID-SEMS was the most cost-effective strategy, with an ICER of 3447.6 £/QALY. Probabilistic sensitivity analysis demonstrated that ID-SEMS was cost-effective at a willingness-to-pay threshold of £50,000. A cost-effectiveness acceptability curve and a graph of net monetary benefit across a range of willingness-to-pay thresholds are shown in Supplementary Fig. 10 and 11, respectively. MPS was found to be the least cost-effective strategy.

Table 1 Main characteristics of included studies

Author, year [ref.]	Country	Study design	Recruitment period	Total patients	Age [mean ± SD, median (range)]	Female, n (%)	Stent type			Median (or mean) onset time post-transplant (months) ID-SEMS/ SEMS/ MPS	Stent width (mm) ID-SEMS/ SEMS/ MPS
							ID-SEMS	FC-SEMS	MPS		
Kaffes *et al* 2014 [30]	Australia	RCT	2008-2011	20	56.5 (38-67) /49.5 (23-69)	5 (50%)/ 5 (50%)	10	0	10	11.8/NA/26	8-10/NA/10 Fr
Sung *et al* 2020 [23]	South Korea	Prospective comparative	2014-2017	36	57.5±6.1/54.2±6.3	3 (18.7%)/ 3 (15.0%)	16	0	20	9.8/NA/6	6-8/NA/7-10 Fr
Sissingh *et al* 2023 [24]	Netherlands	Retrospective comparative	2010-2019	80	58 (50.8-64)/52 (31-59.8)	12 (27.3%)/ 18 (50%)	44	0	36	3.8/NA/4.5	8-10/NA/10 Fr
Zeair *et al* 2017 [22]	Poland	Retrospective comparative	2010-2017	39	50.17±13.46/ 51.36 ±15.14/ 46.69±13.74	4 (33.3%)/ 1 (9.09%)/ 3 (18.75%)	12	11	16	2.6/1.3/1.4	8-10/NA/10 Fr
Cantu *et al* 2018 [29]	Italy	Retrospective multi-center comparative	2013	181	61 (38-68)/59 (20-76)	8 (30%)/ 17 (17%)	0	26	101	NA/8/4	NA/8-10/10 Fr
Cantu *et al* 2021 [28]	Italy	RCT	NA	30	59 (50–67)/53 (22–68)	3 (21%)/ 1 (7%)	0	15	15	NA	NA/8-10/10 Fr
Jang *et al* 2020 [27]	USA	Retrospective comparative	2008-2017	158	58.0±8.1/ 56.6±10.8	11(22.4)/ 42(38.5)	0	49	109	NA	NA
Martins *et al* 2018 [26]	Brazil	RTC	2009-2014	64	52.9/ 50.4	8 (26.7%)/ 9 (31.0%)	0	30	29	NA/7.7/ 9.3	NA
Martins *et al* 2015 [25]	Brazil	Retrospective cohort	2006-2014	157	54.5 (± 12.9) /48.8 (± 14.5)	12 (25.0%)/ 33 (30.3%)	0	38	100	NA/7.4/7.1	NA

FC-SEMS, fully covered self-expandable metal stents; ID-SEMS, intraductal SEMS; MPS, multiple plastic stents; RCT, randomized controlled trial; NA, not available; SD, standard deviation

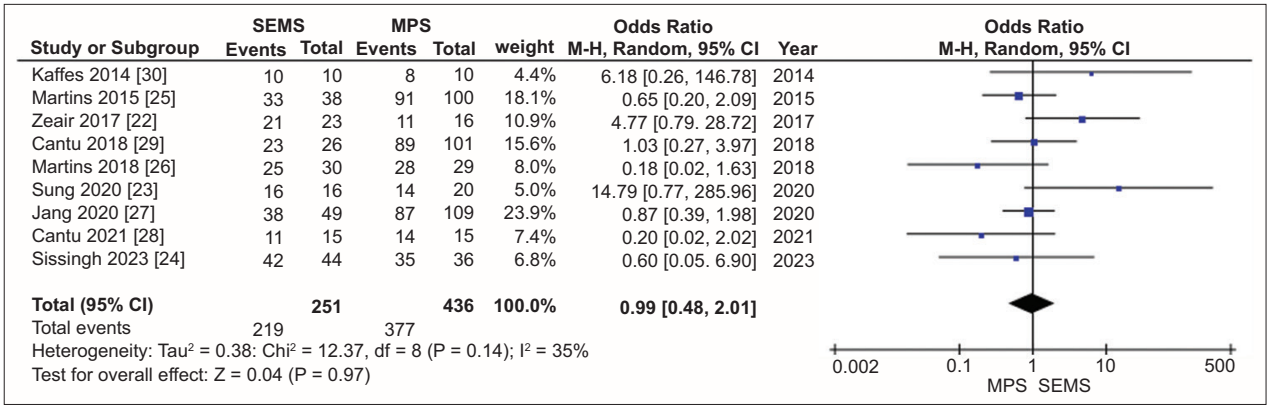


Figure 2 Forest plot reporting the odds ratios of stricture resolution rates between self-expandable metal stents (SEMS) and multiple plastic stents (MPS) *M-H, Mantel-Haenszel; CI, confidence interval*

Quality of evidence

Following the assessment of the respective variables per outcome, the level of evidence was graded as moderate for the primary outcome and low for the secondary outcomes. More specifically, the inclusion of both RCTs and non-randomized, observational studies in our study downgraded the level of evidence *a priori*, thus creating a serious RoB. The funnel plot for the primary outcome (Supplementary Fig. 12) indicated an absence of publication bias, whereas the respective plots for the secondary outcomes created suspicion of potential publication bias, thus downgrading the level of evidence to low. No reasons for further downgrading were recognized (Supplementary Table 3). After combining the meta-analysis outcomes and the GRADE results, we arrived at a final estimation of the effect and the overall certainty of evidence (Supplementary Table 4). With regard to the SEMS vs. MPS comparison, the presented evidence provides a small effect, which is likely to be important in terms of stricture recurrence and AEs.

Publication bias

The funnel plot considering the primary outcome presents with symmetry, indicating the absence of publication bias (Supplementary Fig. 12).

Discussion

This systematic review with meta-analysis is the first to assess the performance of the commercially available types of stents in terms of therapeutic efficacy, AEs and cost-effectiveness. The comparison between SEMS and MPS did not reveal any significant difference in stricture resolution, recurrence, migration rates or AEs, with the 2 main arms achieving high rates of stricture resolution: 89.7%, 95%CI 84.9-94.6 vs. 88.5%, 95%CI 83.1-94.0. A cost-effectiveness analysis indicated that ID-SEMS was the most cost-effective approach, followed by FC-SEMS, whereas the MPS strategy was the least cost-effective choice, probably because the lower stent cost of using MPS compared to SEMS is offset by the procedural cost of requiring more ERCPs. The main strength of this meta-analysis is that the results are based on high-quality, comparative studies with clear outcomes per stent subtype in relation to post-LT strictures. The presentation of cost-effectiveness analysis provides a practical answer to the reasonable query of which approach is the most affordable.

The subgroup analysis, focusing on the individual ID-SEMS and FC-SEMS compared with MPS, did not change the results for the primary outcome and stricture recurrence. However, ID-SEMS treated anastomotic strictures successfully in 95.6% (95%CI 91.3-100) of cases compared to 80.9% (95%CI 63.3-98.6) for MPS in this subgroup, though the comparison marginally failed to achieve significance. ID-SEMS have been used in clinical practice since 2014 [30], when an RCT compared them with MPS for anastomotic biliary strictures after LT. Three subsequent studies included patients with refractory strictures on other stents, either MPS or SEMS, where the success rates of ID-SEMS was not affected by the refractoriness of the stricture, implying a potential role as rescue treatment [10,24,31]. Their anti-migration technology leads to significantly lower migration rates compared to MPS (OR 0.28, 95%CI 0.11-0.70). However, this finding is not accompanied by higher clinical success. The cumulative number of cases having ID-SEMS (n=82) may have affected this outcome, and a larger sample size would be necessary to clarify whether this superiority could be significant. Moreover, as with every SEMS, the number of ERCPs required to treat the strictures was significantly lower in all studies compared to the MPS groups; however, this parameter was not associated with more AEs in the MPS group, given the repeated ERCPs [22-24,30].

Traditionally, FC-SEMS and MPS have been considered as the main approaches to calibrate benign biliary strictures, including those post-LT. Interestingly, the ACG recommends FC-SEMS over MPS, based on the lower number of procedures required, whilst this statement is of conditional strength [6]. On the other hand, the ESGE stratified stent selection based on the type and location of the stricture, the anatomy of the bile duct and the endoscopist's preference, as SEMS deployment depends on the level of the stricture and the distance from the liver hilum, which is not a concern for MPS [5]. The absence of cumulative evidence until now did not allow guidelines to incorporate the role of ID-SEMS separately. Although all comparative studies include ID-SEMS and MPS arms, only one of them compared

the conventional FC-SEMS with ID-SEMS, retrospectively [22]. Their rates of successful stricture resolution, recurrence and complications were equivalent, achieving stricture remodeling in 90.9% and 91.7% of cases, respectively. In our study, FC-SEMS had comparable rates with MPS for the primary outcome and migration rates, whereas recurrence was detected in 22.2% (95%CI 14.3-30.0) of cases after FC-SEMS, compared to 10.6% (95%CI 4.3-16.8) after MPS, with their difference not being significant. ID-SEMS achieved marginally non-significant higher stricture resolution rates, and significantly fewer migrations compared to MPS; however, the assumption that ID-SEMS are superior to FC-SEMS for these variables cannot be justified, given the absence of direct comparisons.

Apart from migration, AEs are an important parameter, given the fragility of the transplanted patients. The overall frequency of complications was similar in the SEMS (29.6%) and MPS (27.6%) groups, with FC-SEMS resulting in a significantly higher rate (OR 1.76, 95%CI 1.06-2.93) compared to MPS, even though the pooled rates were 25% (95%CI 10.5-39.5) and 21.2% (95%CI 8.4-34.1), respectively. Cholangitis represents a dangerous condition for patients with previous LT, and is recognized as an independent risk factor for early and late graft loss, and need for re-transplantation [32,33]. According to the collected studies, cholangitis was the most common AE, with equivalent rates between the compared stents. Three studies [24,28,30] documented antibiotic prophylaxis to prevent cholangitis. Although there are reports indicating that antibiotic prophylaxis has no benefit on post-ERCP cholangitis in transplanted patients [34], the ESGE recommends antibiotics in deeply immunocompromised patients undergoing ERCP, probably including post-LT patients under immunosuppressives [35]. Another interesting aspect is the rate of PEP in these patients undergoing FC-SEMS placement. Martins *et al* [25] reported higher rates of PEP after FC-SEMS (17.1%) compared to MPS (4.1%). The authors noticed the greater incidence of this AE in the first few cases, hypothesizing that the absence of sphincterotomy could result in pancreatic outflow obstruction, as implied by the reduction in its prevalence after routinely performing sphincterotomy. Our results confirmed the significantly higher prevalence of PEP in the FC-SEMS subgroup, compared to MPS (OR 2.27, 95%CI 0.97-5.31; I^2=29%); however, the effect of performing sphincterotomy or not prior to FC-SEMS could not be proven. On the other hand, the rate of PEP after ID-SEMS placement may represent an advantage over the alternatives, as the stent is not deployed across the sphincter.

Cost-effectiveness is a variable with special interest, and our findings indicate that the ID-SEMS strategy is the most cost-effective. Although stricture resolution did not differ significantly, the calculation of costs and QALYs revealed the inferiority of MPS. The costs of ID-SEMS and FC-SEMS are considerable (£1050 and at least £767.04, respectively); however, only 2 ERCPs are needed with these approaches, compared to a mean number of 4 using MPS, which increases the overall cost of the latter. These results are in agreement with those of Kaffes *et al* [30], who reported that ID-SEMS represented a more affordable approach, costing $10,830 compared to $23,580 for MPS. Cantu *et al* [28] calculated the costs of FC-SEMS and MPS without detecting any difference; however, they performed a plain calculation of the expenditures, instead of a cost-effectiveness analysis [28]. Although the costs in our study are based on UK prices, the differences are probably applicable to other countries and currencies. The fact that the results of 2 cost-effectiveness analyses support ID-SEMS use provides enhanced evidence for clinical decision making; however, it would be reasonable for this issue to be reassessed based on local financial policies and costs.

This study, although it provides original and high-quality results, had some limitations. First, not all of the included studies were RCTs, which reduced the quality of evidence. To estimate this risk, we performed a sensitivity analysis, which confirmed that the results remained unaffected. Moreover, all studies but one did not provide comparisons between ID-SEMS and FC-SEMS, thus precluding a direct comparison of these approaches. Overall, only 82 patients were included in the ID-SEMS group, and this limited sample size could affect the resulting significance of some outcomes, especially when we consider that the stricture resolution rates compared to MPS were marginally non-significant. Further studies demonstrating this comparison, including a direct comparison between FC-SEMS and ID-SEMS, might provide a clearer picture. Finally, potential variables impacting on stricture development or recurrence (e.g., indication for transplantation) were not assessed by the included studies, and hence were not included in this meta-analysis.

To conclude, post-LT anastomotic biliary strictures can be treated with comparable efficiency using SEMS and MPS. SEMS probably do not reduce stricture resolution after completion of therapy compared to MPS, and may result in little or no difference in stent migration rates; however, they may have slightly higher rates of stricture recurrence and AEs. ID-SEMS provide lower migration rates than MPS, albeit not clearly reflected by resolution rates. However, the assessment of cost-effectiveness suggests superior results for the ID-SEMS approach over FC-SEMS and MPS.

Summary Box

What is already known:

- Post-liver-transplant (LT) anastomotic biliary strictures are pose a challenge to treatment and are associated with significant burden
- There is a discrepancy between endoscopic societies as to the recommended stent types to treat post-LT biliary strictures
- Intraductal self-expandable metal stents (SEMS) were designed to prevent stent migration

What the new findings are:

- SEMS and multiple plastic stents (MPS) show similar efficacy for stricture resolution
- Intraductal SEMS provide lower migration rates than MPS; however, this does not clearly impact on stricture resolution rates
- Intraductal SEMS are more cost-effective compared to fully covered-SEMS and MPS

References

1. Han JW, Choi JY, Lee SK, et al. Long-term clinical outcomes and predictive factors for living-donor liver transplant recipients with biliary strictures. *Transplantation* 2022;**106**:1990-1999.
2. Kohli DR, Desai MV, Kennedy KF, Pandya P, Sharma P. Patients with post-transplant biliary strictures have significantly higher rates of liver transplant failure and rejection: a nationwide inpatient analysis. *J Gastroenterol Hepatol* 2021;**36**:2008-2014.
3. Guirguis RN, Nashaat EH, Yassin AE, et al. Biliary complications in recipients of living donor liver transplantation: a single-centre study. *World J Hepatol* 2021;**13**:2081-2103.
4. Fasullo M, Patel M, Khanna L, Shah T. Post-transplant biliary complications: advances in pathophysiology, diagnosis, and treatment. *BMJ Open Gastroenterol* 2022;**9**:.
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**:910-930.
6. Elmunzer BJ, Maranki JL, Gómez V, et al. ACG Clinical Guideline: diagnosis and management of biliary strictures. *Am J Gastroenterol* 2023;**118**:405-426.
7. Visconti TAC, Bernardo WM, Moura DTH, et al. Metallic vs plastic stents to treat biliary stricture after liver transplantation: a systematic review and meta-analysis based on randomized trials. *Endosc Int Open* 2018;**6**:E914-E923.
8. Kohli DR, Amateau SK, Desai M, et al; (ASGE Standards of Practice Committee Chair). American Society for Gastrointestinal Endoscopy guideline on management of post-liver transplant biliary strictures: summary and recommendations. *Gastrointest Endosc* 2023;**97**:607-614.
9. Aepli P, St John A, Gupta S, et al. Success and complications of an intra-ductal fully covered self-expanding metal stent (ID-FCSEMS) to treat anastomotic biliary strictures (AS) after orthotopic liver transplantation (OLT). *Surg Endosc* 2017;**31**:1558-1563.
10. Ahmed W, Kyle D, Khanna A, et al. Intraductal fully covered self-expanding metal stents in the management of post-liver transplant anastomotic strictures: a UK wide experience. *Therap Adv Gastroenterol* 2022;**15**:17562848221122473.
11. 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**:407-415.
12. Facciorusso A, Rosca EC, Ashimi A, et al. Management of anastomotic biliary stricture after liver transplantation: metal versus plastic stent. *Ann Gastroenterol* 2018;**31**:728-734.
13. 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**:131-151.
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71.
15. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. *AMIA Ann Symp Proc* 2006;**2006**:359-363.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177-188.
17. Higgins J, Thomas J, Chandler J, et al (Editors). Cochrane handbook for systematic reviews of interventions, 2nd ed. John Wiley & Sons, Chichester (UK), 2019.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-560.
19. R Core Team. R: a language and environment for statistical computing. (Version 4.0) [Computer software]. Available from: https://cran.r-project.org/[Accessed 24 May 2024].
20. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol* 2011;**64**:1303-1310.
21. Santesso N, Glenton C, Dahm P, et al; GRADE Working Group. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol* 2020;**119**:126-135.
22. Zeair S, Butkiewicz F, Butkiewicz J, Stasiuk R. 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**:719-724.
23. Sung MJ, Jo JH, Lee HS, et al. Optimal drainage of anastomosis stricture after living donor liver transplantation. *Surg Endosc* 2021;**35**:6307-6317.
24. Sissingh NJ, de Vries BA, Inderson A, van Hoek B, van der Heide F, van Hooft JE. Intraductal fully covered self-expandable metal stent versus multiple plastic stents for treating biliary anastomotic strictures after liver transplantation. *Gastrointest Endosc* 2023;**97**:704-712.
25. Martins FP, Kahaleh M, Ferrari AP. Management of liver transplantation biliary stricture: Results from a tertiary hospital. *World J Gastrointest Endosc* 2015;**7**:747-757.
26. Martins FP, De Paulo GA, Contini MLC, Ferrari AP. Metal versus plastic stents for anastomotic biliary strictures after liver transplantation: a randomized controlled trial. *Gastrointest Endosc* 2018;**87**:131.e1-e131.e13.
27. Jang S, Stevens T, Lopez R, et al. Self-expandable metallic stent is more cost efficient than plastic stent in treating anastomotic biliary stricture. *Dig Dis Sci* 2020;**65**:600-608.
28. 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**:825-834.
29. Cantù P, Tarantino I, Baldan A, et al. Endo-therapies for biliary duct-to-duct anastomotic stricture after liver transplantation: Outcomes of a nationwide survey. *Liver Int* 2019;**39**:1355-1362.
30. 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.
31. Jang SI, Sung SY, Park H, Lee KH, Joo SM, Lee DK. Salvage therapy using self-expandable metal stents for recalcitrant anastomotic strictures after living-donor liver transplantation. *Therap Adv Gastroenterol* 2017;**10**:297-309.
32. Lafont E, Roux O, de Lastours V, et al. Pyogenic liver abscess in liver transplant recipient: a warning signal for the risk of recurrence and retransplantation. *Transpl Infect Dis* 2020;**22**:e13360.
33. Yao S, Yagi S, Nagao M, et al. Etiologies, risk factors, and outcomes of bacterial cholangitis after living donor liver transplantation. *Eur J Clin Microbiol Infect Dis* 2018;**37**:1973-1982.
34. Kohli DR, Shah TU, BouHaidar DS, Vachhani R, Siddiqui MS. Significant infections in liver transplant recipients undergoing endoscopic retrograde cholangiography are few and unaffected by prophylactic antibiotics. *Dig Liver Dis* 2018;**50**:1220-1224.
35. Dumonceau JM, Kapral C, Aabakken L, et al. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2020;**52**:127-149.

Supplementary material

Supplementary Table 1 PRISMA 2020 checklist of the presented objects in this review

Section and Topic	Item #	Checklist item	Reported (Yes/No)
		TITLE	
Title	1	Identify the report as a systematic review.	YES/p1
		BACKGROUND	
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	YES/p3
		METHODS	
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	YES/p3
Information sources	4	Specify the information sources (e.g., databases, registers) used to identify studies and the date when each was last searched.	YES/p3
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	YES/p3
Synthesis of results	6	Specify the methods used to present and synthesise results.	YES/p3
		RESULTS	
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	YES/p3
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	YES/p3
		DISCUSSION	
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g., study risk of bias, inconsistency and imprecision).	YES/p3
Interpretation	10	Provide a general interpretation of the results and important implications.	YES/p3

Study checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review.	Page 1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 6
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pages 6-7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Pages 6-7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7

Section and Topic	Item #	Checklist item	Location where item is reported
		METHODS	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7-8
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 7-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	Page 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pages 8-9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pages 8-9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages 8-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 8-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	Page 9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Pages 9-10, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Pages 10-11 and suppl Table 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Page 11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 10, suppl table 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 11-12, figure 2 and suppl fig 1-11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 12, suppl fig 5-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 13, suppl fig 9

Section and Topic	Item #	Checklist item	Location where item is reported
		RESULTS	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Suppl fig 12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 13-16
	23b	Discuss any limitations of the evidence included in the review.	Page 16
	23c	Discuss any limitations of the review processes used.	Page 16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 17

Supplementary Table 3 Quality of evidence assessment according to the GRADE system and the precision of overall evidence effect and certainty

Certainty assessment							Summary of findings					Overall effect
Participants (studies) Follow up	Risk of bias	In consistency	In directness	Im precision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects		Comments
							With MPS	With SEMS		Risk with MPS	Risk difference with SEMS	
Stricture resolution after completion of therapy												
687 (9 non-randomized studies)	serious[a]	not serious	not serious	not serious	none	⨁◯◯◯ Very Low	377/436 (86.5%)	219/251 (87.3%)	OR 0.99 (0.48 to 2.01)	865 per 1.000	1 fewer per 1.000 (from 111 fewer to 63 more)	SEMS have no additional effect on stricture resolution after completion of therapy compared to MPS but the evidence is very uncertain.
Stricture recurrence during the follow-up period												
687 (9 non-randomized studies)	serious[a]	not serious	not serious	not serious	publication bias strongly suspected[b]	⨁◯◯◯ Very Low	67/436 (15.4%)	64/251 (25.5%)	OR 1.71 (0.87 to 3.38)	154 per 1.000	83 more per 1.000 (from 17 fewer to 227 more)	SEMS may increase stricture recurrence during the follow-up period compared to the MPS but the evidence is very uncertain.
Stent migration rates												
264 (7 non-randomized studies)	serious[a]	not serious	not serious	not serious	publication bias strongly suspected[b]	⨁◯◯◯ Very Low	319/62 (514.5%)	35/202 (17.3%)	OR 0.73 (0.32 to 1.68)	5.145 per 1.000	1.000 fewer per 1.000 (from 1.000 fewer to 1.000 fewer)	SEMS may have little to no effect on stent migration rates compared to MPS but the evidence is very uncertain.
Adverse events rates												
560 (8 non-randomized studies)	serious[a]	not serious	not serious	not serious	publication bias strongly suspected[b]	⨁◯◯◯ Very Low	77/335 (23.0%)	77/225 (34.2%)	OR 1.47 (0.89 to 2.43)	230 per 1.000	75 more per 1.000 (from 20 fewer to 191 more)	SEMS may increase adverse events rates compared to MPS but the evidence is very uncertain.

a. Study design. Non-RCTs mixed with RCTs included

b. Large CIs, crossing 1

c. Relative asymmetry in the Funnel plot

CI, confidence interval; OR, odds ratio

Supplementary Table 4 The precision of overall evidence effect and certainty

Patient or population: Post-liver transplant anastomotic biliary strictures

Intervention: SEMS

Comparison: MPS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with MPS	Risk with SEMS				
Stricture resolution after completion of therapy	865 per 1.000	863 per 1.000 (754 to 928)	OR 0.99 (0.48 to 2.01)	687 (9 non-randomised studies)	⊕⊕⊕◯ Moderate[a]	SEMS likely do not reduce stricture resolution after completion of therapy compared to MPS.
Stricture recurrence during the follow-up period follow-up: range 3 months to 64 months	154 per 1.000	237 per 1.000 (136 to 380)	OR 1.71 (0.87 to 3.38)	687 (9 non-randomised studies)	⊕⊕◯◯ Low[a,b]	SEMS may result in a slight increase in stricture recurrence during the follow-up period.
Stent migration rates follow-up: range 3 months to 64 months	5.145 per 1.000	-1000 per 1.000 (-659 to 1.000)	OR 0.73 (0.32 to 1.68)	264 (7 non-randomised studies)	⊕⊕◯◯ Low[a,b]	SEMS may result in little to no difference in stent migration rates.
Adverse events rates follow-up: range 3 months to 064 months	230 per 1.000	305 per 1.000 (210 to 420)	OR 1.47 (0.89 to 2.43)	560 (8 non-randomised studies)	⊕⊕◯◯ Low[a,b]	SEMS may result in a slight increase in adverse events rates compared to MPS.

**The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval; OR, odds ratio*

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

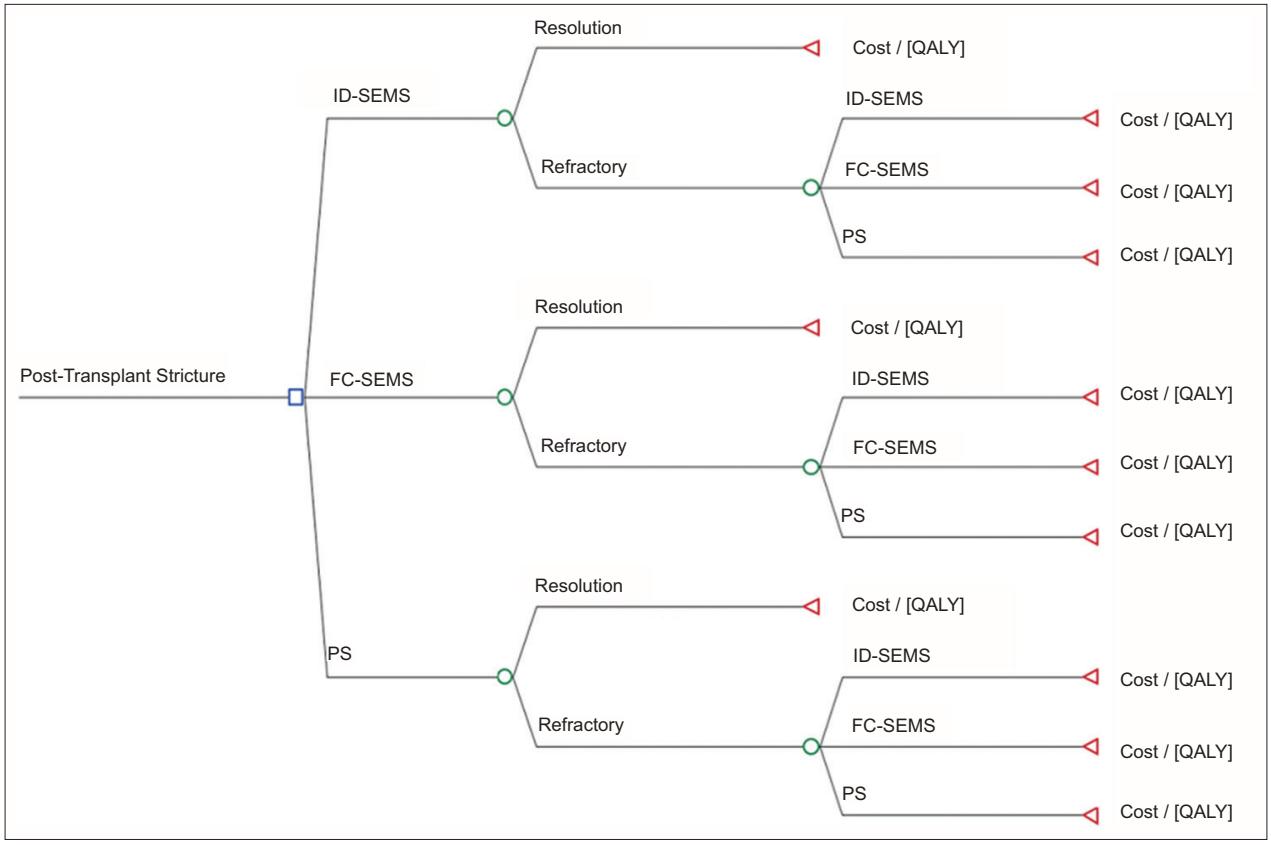
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Study design. Non-RCTs mixed with RCTs included

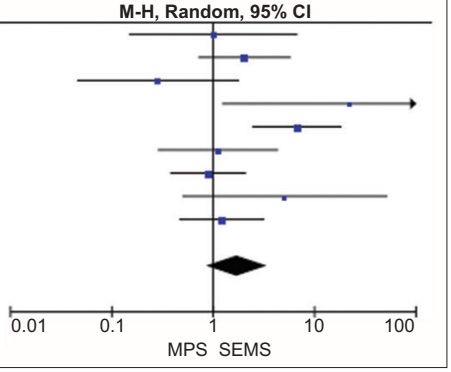
b. Relative asymmetry in the Funnel plot



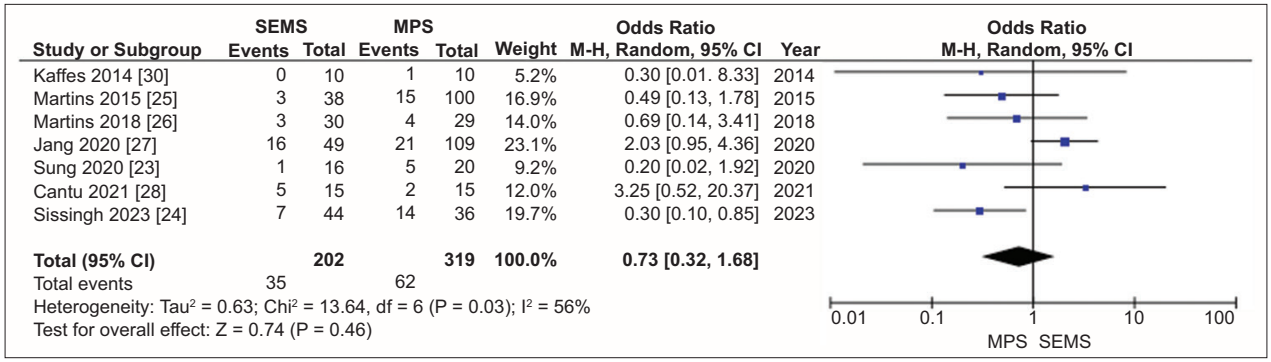
Supplementary Figure 1 Decision tree of the cost-effectiveness analysis
FC-SEMS, fully covered self-expandable metal stents; ID-SEMS, intraductal SEMS; PS, plastic stents; QALY, quality-adjusted life years

Study or Subgroup	SEMS Events	SEMS Total	MPS Events	MPS Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Kaffes 2014 [30]	3	10	3	10	8.0%	1.00 [0.15, 6.77]	2014
Martins 2015 [25]	7	38	10	100	14.6%	2.03 [0.71, 5.80]	2015
Zeair 2017 [22]	2	23	4	16	8.5%	0.29 [0.05, 1.80]	2017
Martins 2018 [26]	8	30	0	29	4.4%	22.29 [1.22, 406.89]	2018
Cantu 2018 [29]	11	26	10	101	14.9%	6.67 [2.42, 18.43]	2018
Sung 2020 [23]	6	16	7	20	11.7%	1.11 [0.28, 4.37]	2020
Jang 2020 [27]	9	49	22	109	16.4%	0,89 [0.38, 2.11]	2020
Cantu 2021 [28]	4	15	1	15	6.1%	5.09 [0.50, 52.29]	2021
Sissingh 2023 [24]	14	44	10	36	15.4%	1.21 [0.46, 3.19]	2023
Total (95% CI)		**251**		**436**	**100.0%**	**1.71 [0.87, 3.38]**	
Total events	64		67				

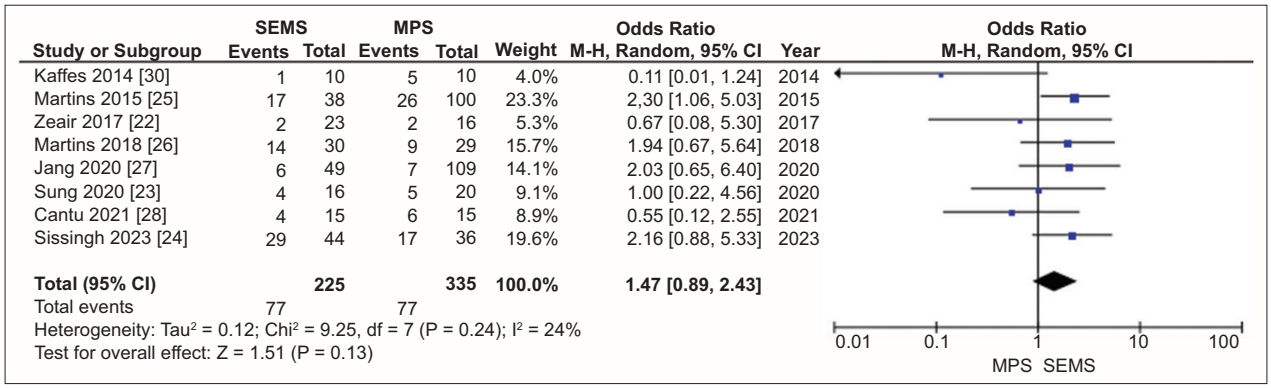
Heterogeneity: Tau² = 0.54; Chi² = 17.87, df = 8 (P = 0.02); I² = 55%
Test for overall effect: Z = 1.56 (P = 0.12)



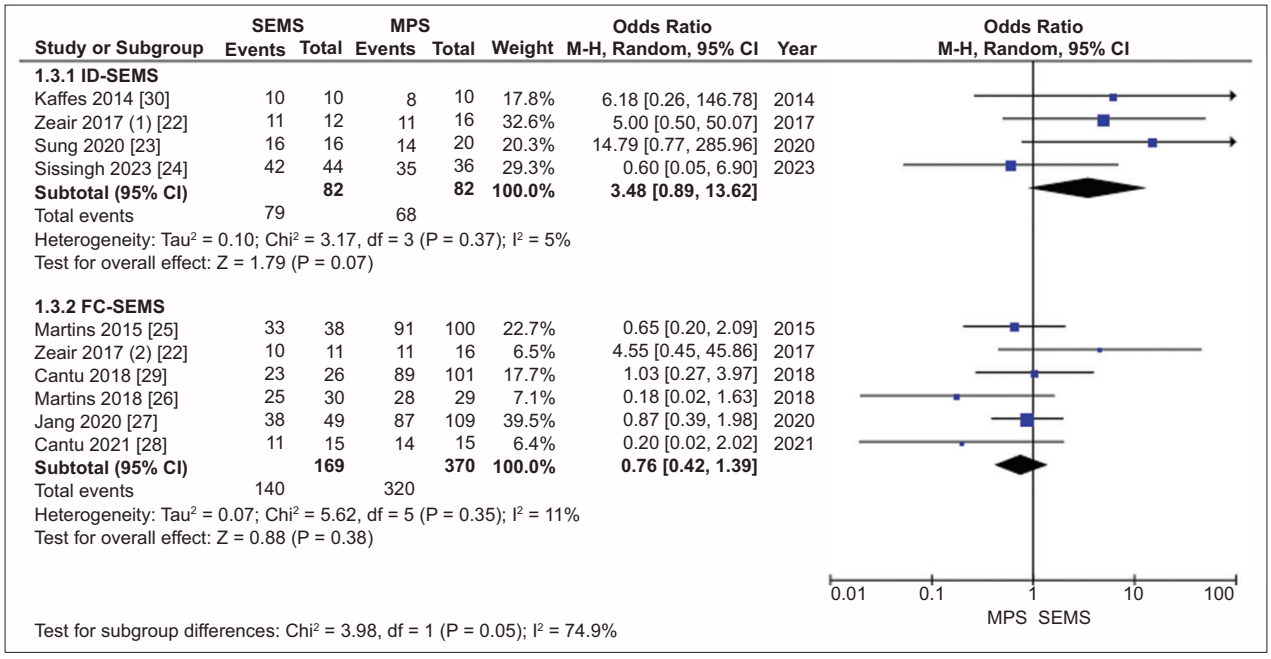
Supplementary Figure 2 Forest plot reporting the odds ratios of recurrence rates between SEMS and MPS
SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stents; CI, confidence interval; M-H, Mantel-Haenszel



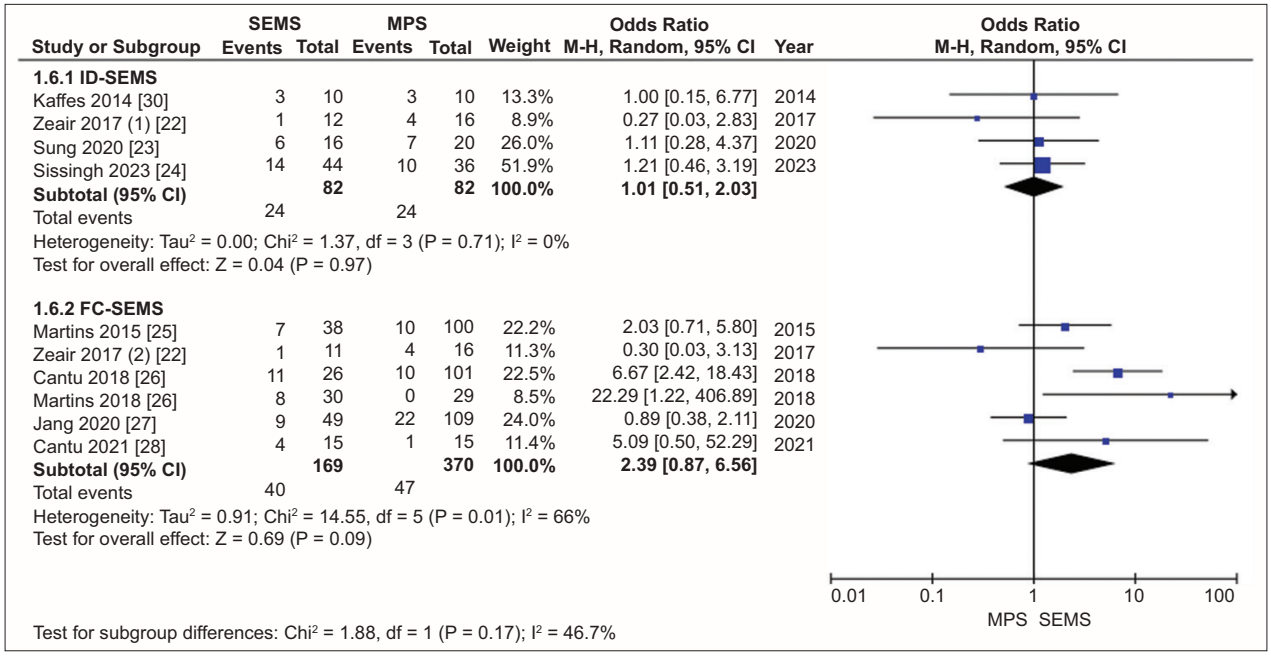
Supplementary Figure 3 Forest plot reporting the odds ratios of migration rates between SEMS and MPS
SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stents; CI, confidence interval; M-H, Mantel-Haenszel



Supplementary Figure 4 Forest plot reporting the odds ratios of adverse events rates between SEMS and MPS
SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stents; CI, confidence interval; M-H, Mantel-Haenszel

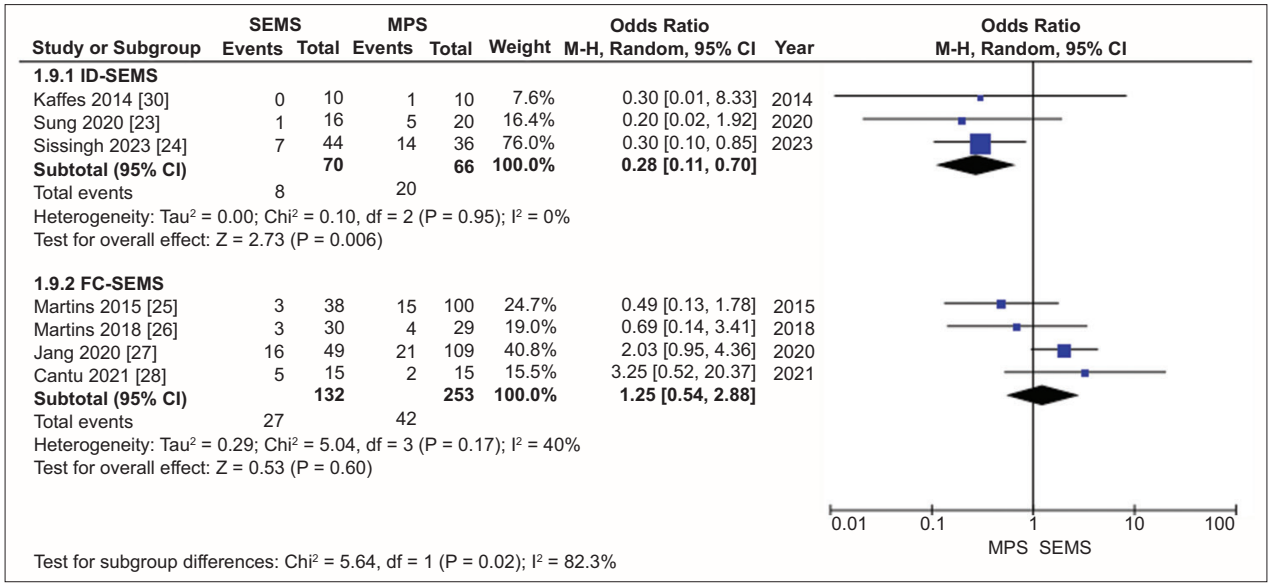


Supplementary Figure 5 Forest plot of the subgroup analysis (ID-SEMS and FC-SEMS) reporting the odds ratios of stricture resolution rates compared to MPS group
SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stents; CI, confidence interval; M-H, Mantel-Haenszel; FC, fully covered; ID, intraductal



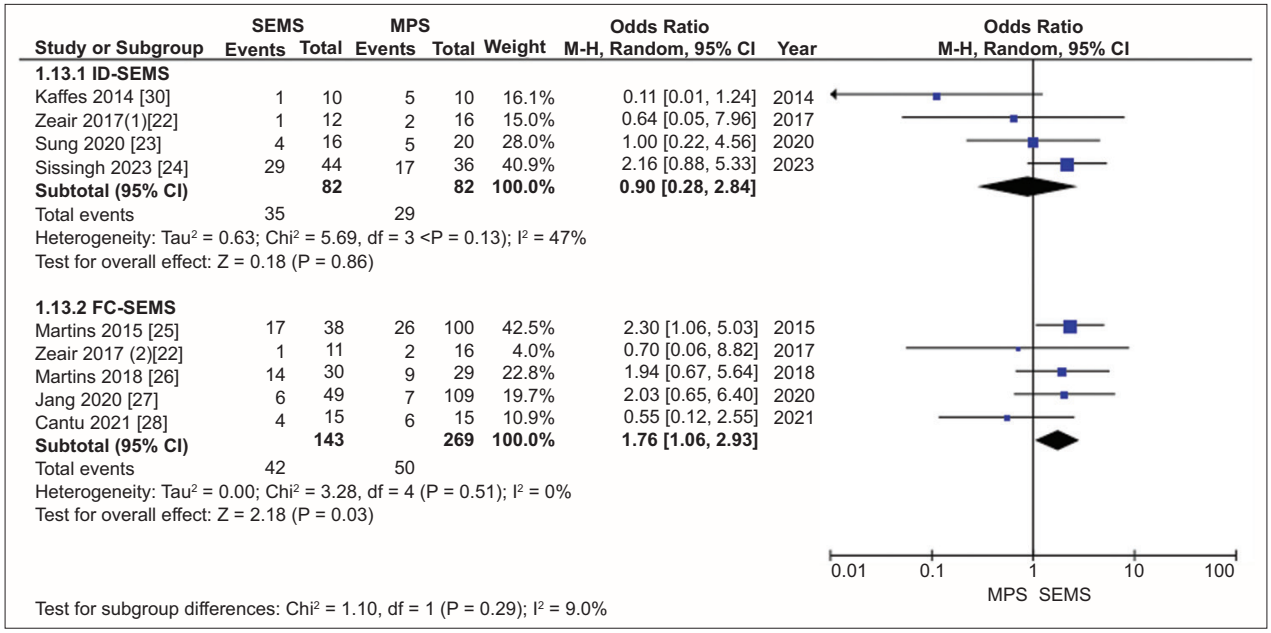
Supplementary Figure 6 Forest plot of the subgroup analysis (ID-SEMS and FC-SEMS) reporting the odds ratios of stricture recurrence rates compared to MPS group

SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stents; CI, confidence interval; M-H, Mantel-Haenszel; FC, fully covered; ID, intraductal



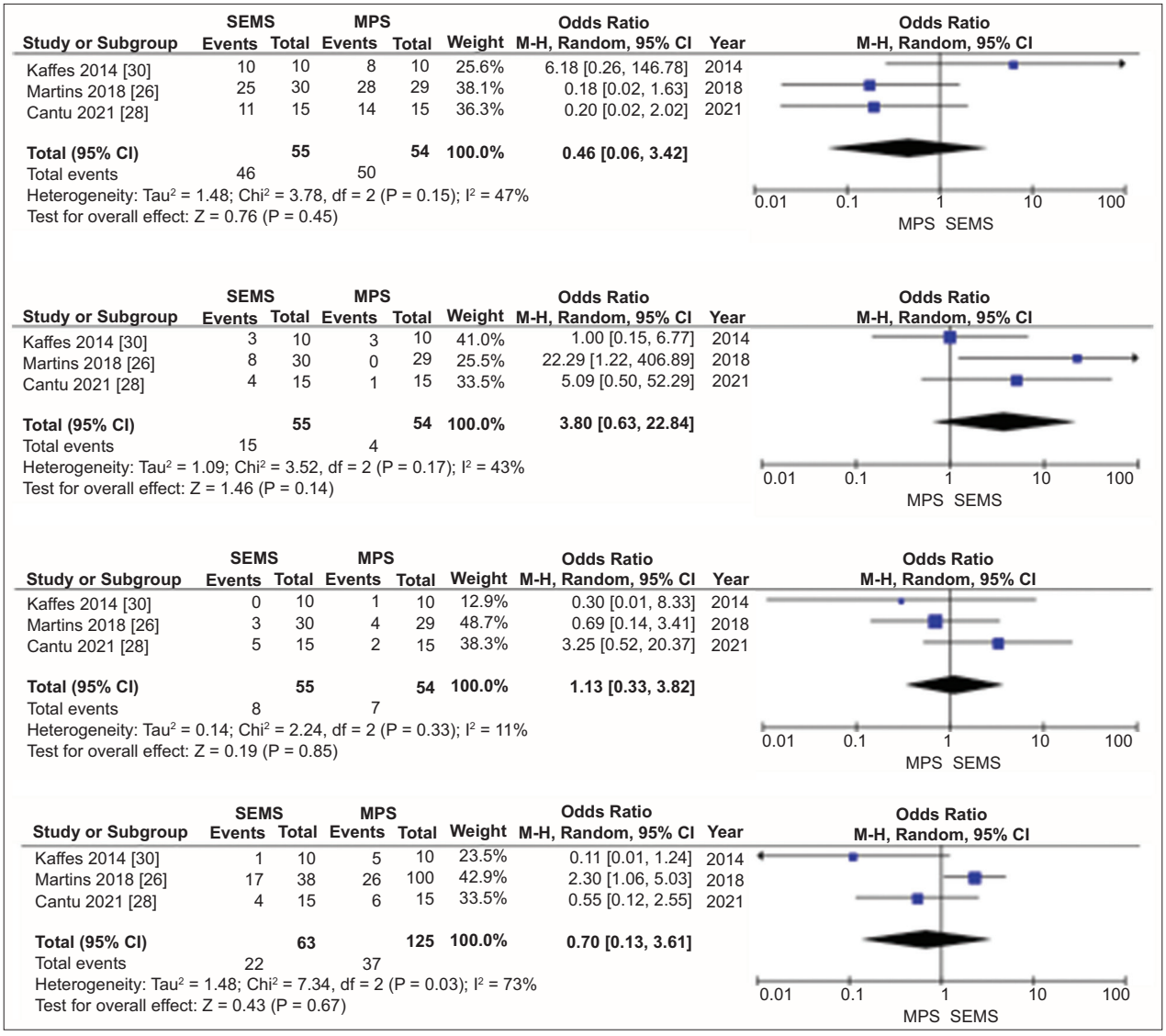
Supplementary Figure 7 Forest plot of the subgroup analysis (ID-SEMS and FC-SEMS) reporting the odds ratios of migration rates compared to MPS group

SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stents; CI, confidence interval; M-H, Mantel-Haenszel; FC, fully covered; ID, intraductal



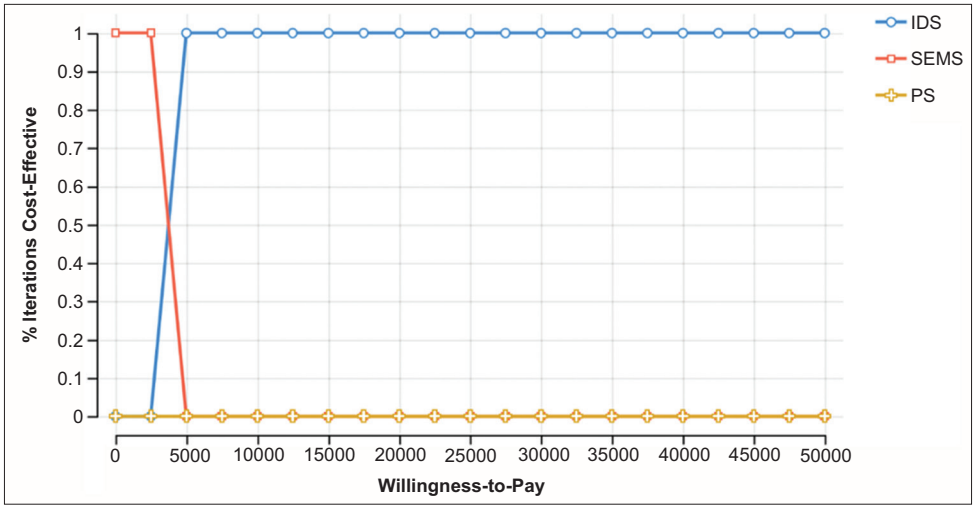
Supplementary Figure 8 Forest plot of the subgroup analysis (ID-SEMS and FC-SEMS) reporting the odds ratios of adverse event rates compared to MPS group

SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stents; CI, confidence interval; M-H, Mantel-Haenszel; FC, fully covered; ID, intraductal

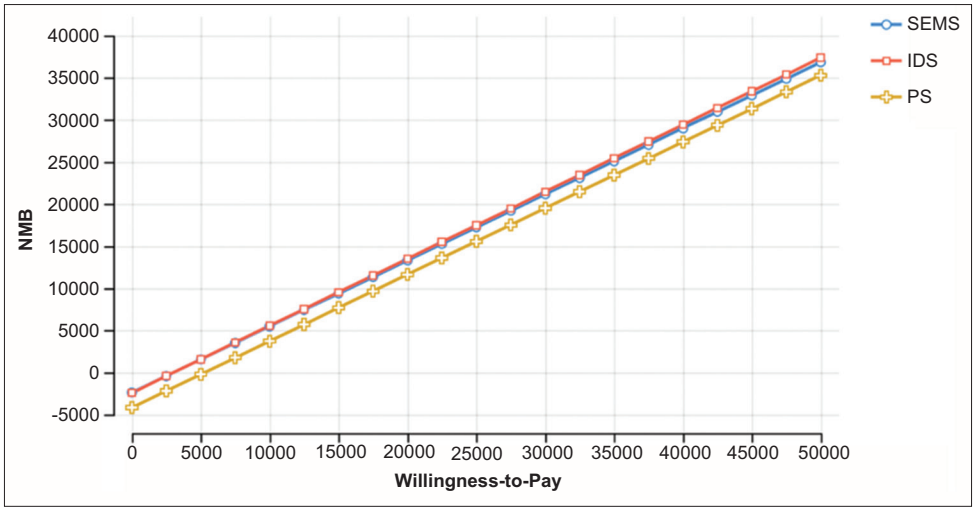


Supplementary Figure 9 Forest plots of the sensitivity analysis including RCTs and reporting the odds ratios of stricture resolution, recurrence, migration and adverse event rates between SEMS and MPS

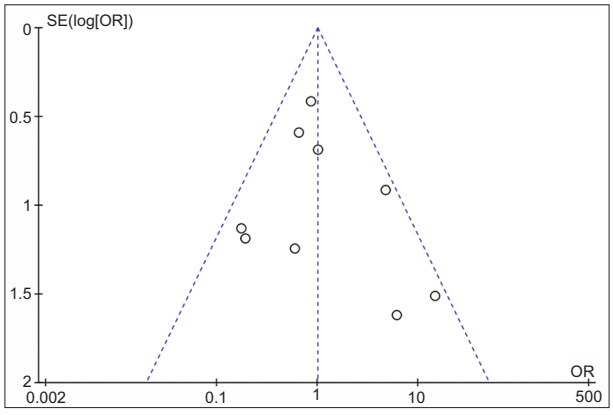
SEMS, fully covered self-expandable metal stents; MPS, multiple plastic stents; CI, confidence interval; M-H, Mantel-Haenszel



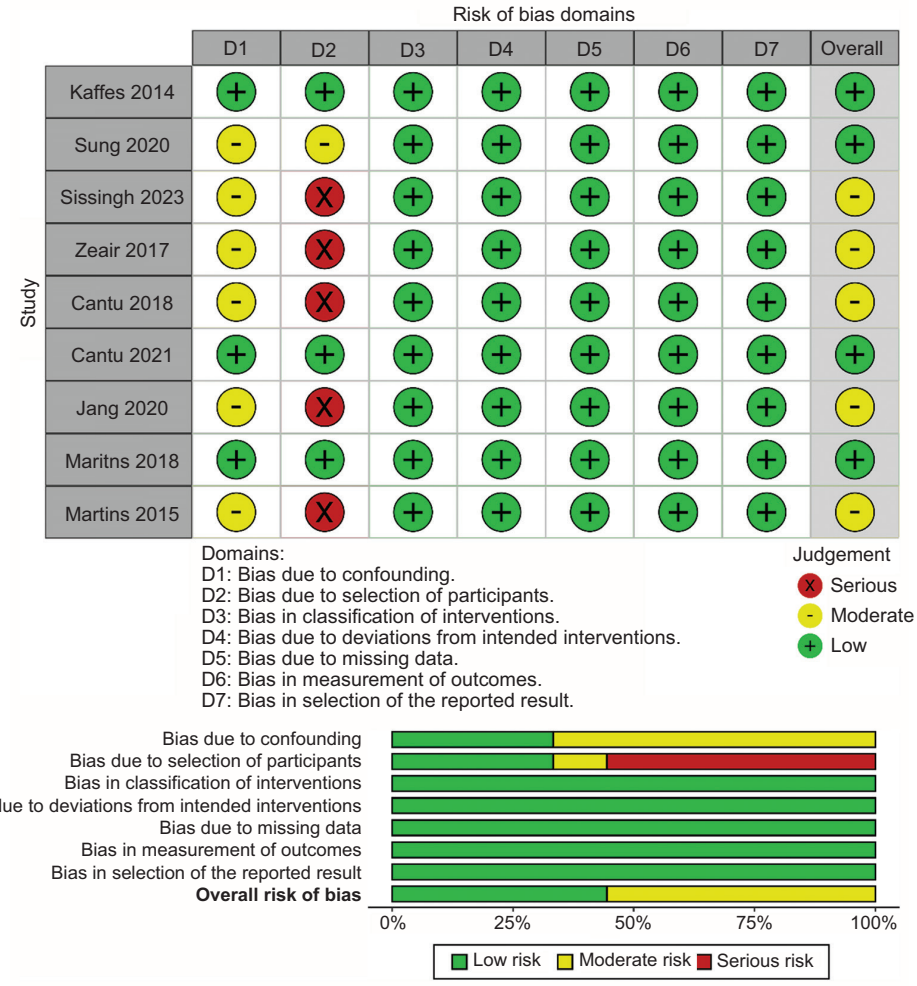
Supplementary Figure 10 The cost-effectiveness acceptability curve
SEMS, fully covered self-expandable metal stents; PS, plastic stents; IDS, intraductal stents



Supplementary Figure 11 Graph showing the net monetary benefit across a range of willingness-to-pay
SEMS, fully covered self-expandable metal stents; PS, plastic stents; IDS, intraductal stents



Supplementary Figure 12 Funnel plot illustrating the absence of publication bias of the analysis concerning the primary outcome
SE, standard error; OR, odds ratio



Supplementary Figure 13 Risk of bias assessment according to the ROBINS-I tool