SYSTEMATIC REVIEWS AND META-ANALYSES

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No Benefit of Covered vs Uncovered Self-Expandable Metal Stents in Patients With Malignant Distal Biliary Obstruction: A Meta-analysis

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BACKGROUND & AIMS: Self-expandable metal stents (SEMS) are used in patients with malignant distal biliary obstruction; trials that compared covered and uncovered SEMS reported different results because of heterogeneous designs and patient populations. These studies compared patency of uncovered SEMS and covered SEMS, along with rates of pancreatitis, cholecystitis, cholangitis, SEMS migration, bleeding, perforation, and recurrent biliary obstruction. **METHODS:** We performed a meta-analysis to compare the effects of covered and uncovered SEMS in patients with malignant distal biliary obstruction. We identified randomized controlled trials by using a literature search from 1980 through March 2012. We evaluated data from 5 full articles and 4 abstracts, comprising 1061 patients, and assessed statistical heterogeneity and publication bias. **RESULTS:** The weighted mean difference in the stent patency duration could only be calculated on the basis of 2 studies, but it was 67.9 days longer for covered SEMS than for uncovered SEMS (95% confidence interval [CI], 60.3–75.5). A summary analysis of data from 4 trials demonstrated no differences in patency of covered vs uncovered SEMS after 6 months (odds ratio [OR], 1.82; 95% CI, 0.62–5.25) or 12 months (OR, 1.25; 95% CI, 0.65–2.39). There were also no differences in the rates of pancreatitis, cholecystitis, perforation, bleeding, or cholangitis; length of hospital stay; or number of recurrent biliary obstructions. However, covered SEMS had a higher migration rate (OR, 7.13; 95% CI, 2.29–22.21). Patients with covered SEMS had a lower rate of tumor ingrowth (OR, 0.19; 95% CI, 0.07–0.55) but a higher rate of tumor overgrowth (OR, 1.88; 95% CI, 1.02–3.45). No summary calculations could be completed to confidently assess patient survival. **CONCLUSIONS: The use of covered SEMS, compared with uncovered SEMS, in patients with distal malignant biliary obstruction is of unclear benefit; covered SEMS have a higher rate of migration and do not appear to have longer patency.**

Keywords: Treatment; Surgery; Plastic Biliary Stents; Comparison.

Not uncommonly, distal malignant biliary obstruction is diagnosed at an advanced stage when the management is mainly palliative. In such instances the insertion of a plastic or an uncovered self-expandable metal stent (SEMS) helps to relieve jaundice and improves quality of life of patients.[1] Uncovered SEMS have a longer duration of patency when compared with polyethylene (plastic) stents,[2] a reduced number of stent-associated admissions, and reduced hospital stay.[3] In an attempt to prolong stent patency and limit tumor ingrowth, SEMS have been coated with a nonporous membrane that either completely or partially covers the whole length of the SEMS. The results of randomized controlled trials have been heterogeneous[4–12] in their conclusions, and it is especially unclear whether a prolonged duration of stent patency is at a cost of increased pancreatitis, cholecystitis, or stent migration. Moreover, although partially covered stents have been studied, fully covered stents have also been developed with limited comparative data.[13]

We therefore performed a meta-analysis to assess the efficacy of uncovered SEMS compared with covered SEMS and attempted to ascertain whether there are differences in both durations of stent patency and stent patency rates. We also assessed numerous clinically relevant secondary outcomes related to the possible complications associated with the use of both covered and uncovered SEMS. We also planned, where possible, to describe any differences between fully and partially covered SEMS.

Methods

Search Strategy

A computerized medical literature search was performed by using OVID MEDLINE, EMBASE, Cochrane Library, and the ISI Web of Knowledge from 1980 to March 2012. All abstracts from Digestive Disease Week, Canadian Digestive Diseases Week, and United European Gastroenterology Week were also searched, as were clinical trials databases (http://www.clinicaltrials.gov). A highly sensitive search strategy was used to identify reports of randomized controlled trials comparing patency duration and rates of covered vs uncovered SEMS with a combination of controlled vocabulary and text words related to (1) pancreatic neoplasms, (2) common bile duct neoplasms, (3) common bile duct diseases, (4) obstructive jaundice, (5) cholestasis, (6) stents, and (7) endoprosthesis (Supplementary Table 1). In addition, recursive searches and cross-referencing were performed, and hand searches of articles identified after the

Abbreviations used in this paper: CI, confidence interval; OR, odds ratio; SD, standard deviation; SEMS, self-expandable metal stents.

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initial search were also completed. An attempt to contact corresponding authors was made when critical information was not extractable from published potentially eligible full articles.

Trial Selection and Patient Population

We included all randomized controlled trials comparing patency duration and rates of covered vs uncovered SEMS, both fully published and those having appeared only in abstract form to date that compared covered with uncovered SEMS, including stents that were inserted endoscopically or percutaneously, in the setting of distal malignant biliary obstruction. We included all adult human studies published in English. We accepted broad inclusion criteria irrespective of their possible roles as confounders of outcome or effect modifiers.

Choice of Outcomes

The primary outcome measures were the duration of stent patency (defined as time to primary stent obstruction or patient's death if no obstruction occurred) and the proportion of patent stents at 6 and 12 months; recurrent biliary obstruction refers to the complete duration of follow-up during a trial. Stent survival was not chosen as an outcome because of its relative lack of clinical pertinence compared with that of stent patency. Secondary outcomes included patient survival, stent migration (whether after sphincterotomy or not), pancreatitis, cholecystitis, perforation, bleeding, cholangitis, length of hospital stay, recurrent biliary obstruction, the use of SEMS in the setting of pancreatic head tumors, tumor ingrowth (through the mesh of the stent), and tumor overgrowth (at the proximal and distal ends of the stent).

Validity Assessment

The eligibility and quality of the studies were assessed independently by 2 investigators (M.A. and A.N.B.), with discrepancies resolved after discussion and reaching a consensus. The quality of the studies was graded by using the Jadad score.[14]

Sources of Possible Clinical Heterogeneity

Comparative qualitative analyses were performed to assess the homogeneity of patient populations, interventions, and outcomes across studies, guiding possible subgroup analyses by identifying sources of clinical heterogeneity. We performed sensitivity analyses according to study quality scores, route of stent insertion (comparing percutaneously with endoscopically inserted SEMS), and extent of covering (fully covered and partially covered SEMS vs uncovered SEMS).

Statistical Methods

For each outcome and in every comparison, effect size was calculated as odds ratios (ORs) for categorical variables and weighted mean differences for continuous variables. The Mantel–Haenszel method for fixed-effect models was applied to determine corresponding overall effect sizes and their confidence intervals (CIs), except when statistical heterogeneity was noted, in which case a random-effects model was used according to the method of DerSimonian and Laird.[15] Weighted mean differences were handled as continuous variables by using the inverse variance approach. The presence of heterogeneity across studies was defined by using a χ^2 test of homogeneity with a 0.10 significance level.[16] The Higgins I^2 statistic[17] was calculated to quantify the proportion of variation in treatment effects attributable to between-study heterogeneity; values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. To identify possible sources of statistical heterogeneity, sensitivity analyses were performed, excluding studies one by one; in addition, if at least 10 trials were selected for analysis, we also planned to perform meta-regression by using a mixed-effects model according to predefined relevant variables. For all comparisons, publication bias was evaluated by using the Begg adjusted rank correlation test[18] and the Egger regression asymmetry test.[19] Summary statistics were expressed as means and standard deviations (SDs).

To ensure that zero event trials did not significantly affect the heterogeneity or P value, a continuity correction was added to each trial with zero events by using the reciprocal of the opposite treatment arm size.[20] All statistical analyses were done by using Meta package in R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria).

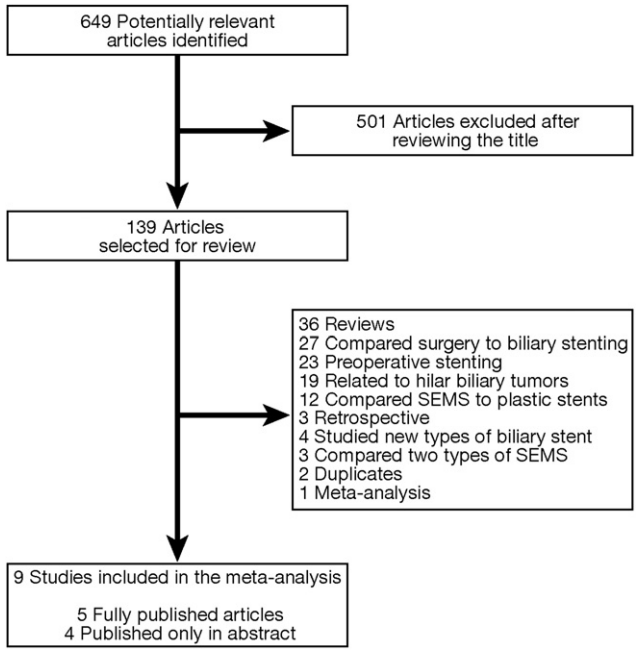

Figure 1. QUORUM diagram.

Results

Study Selection

From a total of 649 citations identified through the systematic review, 501 articles were excluded because they did not address the topic under study, 36 articles were reviews, 27 studies compared surgery with biliary stenting, 23 addressed preoperative stenting, 19 were related to patients with hilar biliary tumors, 12 studies compared SEMS with plastic stents, 3 were retrospective in nature, 4 studied new types of biliary stents, 3 compared 2 types of SEMS, 2 were duplicates, and 1 study was a meta-analysis. Two abstracts by Dhondt et al[21,22] were excluded because of limited available information and because the studies included patients with obstruction at the hilar level. We did not find any relevant additional trials with cross-referencing or hand searching. The corresponding QUORUM diagram is shown in Figure 1.

Five fully published articles[5–9] and 4 studies[4,10–12] published only in abstract form were included. Attempts to contact all authors for further details yielded no additional information. A total of 1061 patients (522 randomized to uncovered SEMS and 347 to partially covered SEMS; it was not clear in 192 whether the stents used were fully or partially covered SEMS) were included in the 9 selected studies. Partially covered SEMS were assessed in 3 fully published trials[7–9] and 1 abstract,[12] and a mixture of fully covered and partially covered SEMS were used in 2 fully published articles[5,6]; it was unclear in the remaining 3 articles, all in abstract form, whether the covered SEMS were partially or completely covered.[4,10,11] We were able to compare partially covered SEMS with uncovered SEMS only as a subgroup analysis but were unable to compare completely covered SEMS with uncovered SEMS because of incomplete data presentation in the studies.

Stent patency definitions varied across trials, and caution must be used to include the correct outcome (Table 1).

For the numbers of patients analyzed in the studies by Isayama et al[9] and Cho et al,[4] the numbers of patients were calculated values that were based on the respective published proportions reported.

Study Quality, Heterogeneity, and Publication Bias

The Jadad quality scores for each trial are shown in Table 2. They ranged from 1–5 out of a maximum of 5 points.

On the basis of the presence of heterogeneity, random-effect models were used for the following outcomes analyses: proportion of stent patency at 6 and 12 months, recurrent biliary obstruction, and tumor ingrowth.

Fixed-effect models were used to analyze the following outcomes: pancreatitis, stent migration, stent migration with prior sphincterotomy, stent migration with prior plastic stent, cholecystitis, perforation, perforation from stent migration, bleeding, and cholangitis.

The Begg adjusted rank correlation test and the Egger regression asymmetry test demonstrated potential publication bias for the outcomes of SEMS migration, SEMS migration with prior sphincterotomy, SEMS migration with prior insertion of plastic biliary stents, perforation from SEMS migration, and bleeding from SEMS migration (Table 3).

Meta-regression was not performed because fewer than 10 trials were included in the analyses.

Primary Outcomes

Stent patency duration. The only studies that could be analyzed for these end points were the 2 trials by Krokidis et al,[5,6] which included 140 patients. The weighted mean difference in the stent patency was 67.9 days (95% CI, 60.3–75.5), favoring the covered SEMS. We could not determine this outcome from other studies because of reporting as ranges,[4,9,11] interquartile ranges,[8] or first quartile[7] that did not allow us to reach a summary value.

Stent patency proportion at 6 and 12 months. Four fully published trials[6–9] reported patency rates at 6 and 12 months in a total of 718 patients (Table 2). There were no differences in the patency rates of covered SEMS compared with uncovered SEMS at 6 months (OR = 1.82; 95% CI, 0.63–5.25) or 12 months (OR = 1.25; 95% CI, 0.65–2.39] (Table 2, Figure 2).

One fully published study[5] and 4 abstracts[4,10–12] did not report patency rates at 6 or 12 months.

When performing the sensitivity analysis according to study quality, no differences were noted among the trials with a Jadad scale score of 3 or more[7–9] with regard to stent patency rates at 6 months (OR = 1.36; 95% CI, 0.45–4.13) or 12 months (OR = 1.03; 95% CI, 0.54–1.95).

Secondary Outcomes

Patient survival. Five studies[5–9] provided durations of survival in a total of 781 patients; 2 abstracts[10,11] only stated that there was no difference in survival between both groups; 1 abstract reported on the number of deaths during a time period of 12–165 days,[12] and 1 abstract did not report on patient survival.[4] Three studies provided survival data only as ranges[9] and interquartile ranges,[7,8] showing no differences individually but not allowing for a summary calculation.[7–9] In the 2010 trial, Krokidis et al[5] reported not a mean but rather a median survival duration of 180.5 days (SD, 82.6) and 243.5 days (SD, 141.1) for the uncovered SEMS and covered SEMS groups, respectively ($P = .039$) (Table 3); in their 2011 trial, Krokidis et al[6] published that the mean duration of survival was 203.2 days (SD, 74.8) for the uncovered SEMS group vs 247 days (SD, 126.7) for the covered SEMS group ($P = .06$) (Table 3).

Stent migration. Three fully published studies reported on the incidence of SEMS migration in the setting of prior sphincterotomy,[5,6,8] with a total of 269 patients, and 4 fully published studies reported on SEMS migration in those with a prior plastic biliary stent,[5,6,8,9] with a total of 381 patients.

Only migration of covered SEMS, as a combined outcome, was found to be significantly increased (OR = 7.13; 95% CI, 2.29–22.21). Neither covered SEMS migration rates in those with a prior sphincterotomy (OR = 1.64; 95% CI, 0.21–12.79) nor rates in those with a prior plastic biliary stent (OR = 2.02; 95% CI, 0.36–11.25) were significant (Figure 3).

Pancreatitis. Five fully published studies[5–9] and one in abstract form[10] reported the incidence of pancreatitis in 895 patients. There was no difference in the rate of pancreatitis when comparing covered with uncovered SEMS (OR = 1.07; 95% CI, 0.44–2.59) (Table 3). Early pancreatitis (<72 hours) was reported by Gonzalez-Huix et al,[10] occurring in 2 patients in the uncovered SEMS group and in 1 patient in the covered SEMS group. Post–endoscopic retrograde cholangiopancreatography pancreatitis also occurred in 3 patients in the covered SEMS group and in 4 in the uncovered SEMS group in the study by Kullman et al.[7] In the week after SEMS insertion, 1 patient in the uncovered SEMS group developed pancreatitis in the study by Telford et al.[8]

Cholecystitis. Five fully published studies reported the incidence of cholecystitis after the insertion of SEMS[5–9] in a total of 781 patients, yielding no increased incidence (OR = 1.34; 95% CI, 0.48–3.77) for covered SEMS.

Perforation. Perforation rates associated with the placement of the SEMS were reported in 5 fully published articles[5–9] and 1 abstract,[10] with a total of 895 patients. When comparing covered SEMS with uncovered SEMS, the OR of perforation was 1.84 (95% CI, 0.49–6.87). Perforation from SEMS migration was reported in 4 fully published articles,[5,6,8,9] with a total of 381 patients, with OR = 2.00 (95% CI, 0.36–11.17) in the covered SEMS group. In the trial by Kullman et al[7]

Table 1. Description of Continuous Variables of Trials

Primary outcomes	No. of fully published articles that reported on the outcome	No. of articles that reported on the outcome in abstract form	Study	USEMS	CSEMS	Definition of stent patency
Stent patency duration (*days*)	5	2	Krokidis et al[6]	Mean: 166.0 (SD 13.11)	Mean: 234.0 (SD 20.87)	Primary patency of endoprosthesis was defined as the time interval between initial placement and recurrence of obstruction. If there was no evidence of obstruction during the patient's life, the patency period was considered to be equal to the survival period.
			Krokidis et al[5]	Mean: 166.0 (SD 87.7)	Mean: 227.3 (SD 139.7)	Primary patency of endoprosthesis was defined as the time interval between initial placement and recurrence of obstruction. If there was no evidence of obstruction during the patient's life, the patency period was considered to be equal to the survival period.
			Isayama et al[9a]	Mean: 161 (range: 1–548)	Mean: 304 (range: 90–649)	The authors considered the duration of stent patency as the period between stent insertion and death of patients, whereas mean period of obstruction was the period between stent insertion and obstruction or patient death with patent stent. The latter better fit the definition of our primary outcome selection, although this was analyzed in a subgroup of patients with stent obstruction or patient death.
			Telford et al[8a]	Median: 711 (IQR: 283–NA)	Median: 357 (IQR: 264–1302)	Patients not experiencing recurrent biliary obstruction were censored at the date of last follow-up or date of death.
			Kullman et al[7]	First quartile stent patency: 199	First quartile stent patency: 154	Uneventful follow-up for 12 months, death with a patent stent, and confirmed stent failure.
			Lee et al[11a]	Median: 127 (range: 25–447)	Median: 216 (range: 76–760)	No definition
			Cho et al[4a]	Median: 195	Median: 227	No definition
Patient duration of survival (*days*)	5	0	Krokidis et al[6]	Mean: 203.2 (SD 74.8)	Mean: 247 (SD 126.7)	
			Krokidis et al[5]	Median: 180.5 (SD 82.6)	Median: 243.5 (SD 141.1)	
			Isayama et al[9a]	Mean: 237 (range: 12–810)	Mean: 255 (range: 11–1155)	
			Telford et al[8a]	Median: 239 (IQR: 84–401)	Median: 227 (IQR: 99–365)	
			Kullman et al[7a]	Median: 174 (IQR: 284)	Median: 116 (IQR: 242)	

Table 1. Continued

Primary outcomes	No. of fully published articles that reported on the outcome	No. of articles that reported on the outcome in abstract form	Study	USEMS	CSEMS	Definition of stent patency
Duration of follow-up (*days*)	1	1	Telford et al[8]	Mean: 217 (SD 208)	Mean: 244 (SD 231)	
			Smits et al[12a]	Median: 71	Median: 76	
Duration of hospital stay (*days*)	2	0	Krokidis et al[6]	Mean: 5.05 (SD 1.1)	Mean: 4.8 (SD 1.0)	
			Krokidis et al[5]	Mean: 6 (SD 1.8)	Mean: 5.6 (SD 2.3)	

CSEMS, covered or partially covered SEMS; IQR, interquartile range; USEMS, uncovered SEMS.
[a]Data not usable for analysis.

both perforations (one case in each study arm) were retroperitoneal and were treated conservatively. In the trial by Telford et al[8] two duodenal perforations (both in the partially covered stent group) occurred because of migration of the stents distally; 1 patient underwent a laparoscopic gastrojejunostomy and died 10 months later. The second patient was managed endoscopically with enteral stent placement across the perforation and a gastrostomy tube because the patient was not a surgical candidate; the patient died 3 weeks later. In the trial by Gonzalez-Huix et al[10] there was one reported perforation in the covered stent group; the trial did not specify the location of perforation, the method of management, or the outcome.

Bleeding. The incidences of bleeding from stent migration and bleeding in general were reported in 4 fully published articles,[5–7,9] totaling 452 patients. None were more frequent in one group compared with the other; bleeding from covered SEMS migration yielded OR = 1.52 (95% CI, 0.25–9.22), whereas bleeding in general from these was associated with OR = 0.46 (95% CI, 0.13–1.66).

Cholangitis. Cholangitis associated with the use of SEMS was reported in 3 fully published articles[7–9] and 1 abstract,[10] totaling 755 patients. The OR was 1.07 (95% CI, 0.57–2.01).

Length of hospital stay. The duration of hospitalization was reported as means and SDs in the 2 trials by Krokidis et al[5,6] for a total of 140 patients. There was no difference in the mean durations of hospital stay between covered or uncovered SEMS; weighted mean difference equals 0.28 days (95% CI, −0.70 to 0.15).

Recurrent biliary obstruction. The incidence of recurrent biliary obstruction associated with the use of SEMS was reported in 5 fully published trials[5–9] and in an article in abstract form.[10] The OR (random-effect model) was found to be 0.98 (95% CI, 0.49–1.95).

Pancreatic head tumors. The only trial that looked at the use of SEMS in pancreatic head tumors exclusively was the trial by Krokidis et al.[6] The mean patency for uncovered SEMS was 166.0 ± 13.11 days compared with 234.0 ± 20.87 days for the covered SEMS ($P = .007$). The median survival was 203.2 ± 11.8 days for the uncovered SEMS group and 247.0 ± 20 days for the covered SEMS group ($P = .06$).

Tumor ingrowth. The incidence of tumor ingrowth was reported in 6 trials[5–9,12] that included 817 patients and was less in the covered SEMS group when compared with the uncovered group (OR = 0.19; 95% CI, 0.07–0.55) (Figure 3).

Tumor overgrowth. The incidence of tumor overgrowth was reported in 6 trials[5–9,12] that included 817 patients and was higher in the covered SEMS group when compared with the uncovered group (OR = 1.88; 95% CI, 1.02–3.45) (Figure 3).

Subgroup Analyses

Partially vs fully covered self-expandable metal stents. When trying to compare partially covered with uncovered SEMS, we assessed the subgroup of 4 studies that exclusively used partially covered SEMS.[7–9,12] Indeed, other studies either did not specify the type of covered SEMS that they had used[4,10,11] or stated that they had used a mixture of partially and fully covered SEMS.[5,6] Thus, we could not describe an analysis specifically comparing fully covered SEMS with either partially or uncovered SEMS. Table 3 shows no differences in the results

Table 2. Methodological Details of Trials Included in the Analysis

	Smits et al[12]	Isayama et al[9]	Lee et al[11]	Gonzalez–Huix et al[10]
Type of publication	Abstract	Fully published	Abstract	Abstract
Year of publication	1995	2004	2004	2008
Number of centers involved	NA	4	NA	5
Duration of follow-up (*days*) (mean/range)	Median CSEMS 71 USEMS 76	246 (11–1155)	Median 5.3 months (0.8–29)	NA
Total number of patients	46	112	43	114
CSESM/USEMS	22/24	57/55	22/21	61/53
Age (*y*) (mean/range)	Median 77/51–92	Reported for the subgroups only	70/49–87	77 (SD 12)
Sex (male/female)	26/20	66/46	26/17	54/60
CSESM	NA	35/22	NA	NA
USEMS	NA	31/24	NA	NA
Type of tumor				
Pancreas (CSEMS/USEMS)	34	34/32	17	63
Bile duct (CSEMS/USEMS)	5	6/5	17	42
Metastatic nodes (CSEMS/USEMS)	0	12/11	0	0
Gallbladder (CSEMS/USEMS)	0	3/6	5	0
Papillary (CSEMS/USEMS)	7	2/1	4	9
Method of insertion of stent				
Endoscopic (CSEMS/USEMS)	46	45/50	43	NA
Transhepatic (CSEMS/USEMS)	0	12/5	0	NA
Combined technique (CSEMS/USEMS)	0	4/4	0	NA
Type of stent				
Covered SEMS	Partially covered Wallstents	Partially polyurethane covered Ultraflex Diamond stent (Microvasive; Boston Scientific Corporation, Natick, MA)	Membrane-CSEMS (Shim-Hanarostent, M.I. Tech, Seoul, Korea)	Covered Wallstent
Uncovered SEMS	Uncovered Wallstents	Original Diamond stent	USEMS (Hanarostent)	Uncovered Wallstent
Patency of SEMS (*%*)				
3 months (CSEMS/USEMS)	NA	100/81	NA	NA
6 months (CSEMS/USEMS)	NA	91/68	NA	NA
12 months (CSEMS/USEMS)	NA	74/55	NA	NA
Jadad score	1	3	2	1

CSEMS, covered or partially covered SEMS; ePTFE/FEP, expanded polytetrafluoroethylene/fluorinated-ethylene-propylene; NA, not available; USEMS, uncovered SEMS.

when identifying only partially covered SEMS compared with the uncovered SEMS group for all outcomes assessed.

Percutaneous vs endoscopic self-expandable metal stent insertion. The data did not allow us to compare percutaneous[5,6] vs first intent of endoscopic[4,7–12] insertion routes because there were no head-to-head trials, but we did describe results in the distinct subgroups undergoing either a percutaneous or an endoscopic approach separately.

A subgroup analysis for the studies that inserted SEMS endoscopically[4,7–12] demonstrated there were no differences in outcomes except for a greater rate of stent migration for covered SEMS (OR = 9.74; 95% CI, 2.58–36.72) (more detailed data available on request).

A subgroup analysis for the studies that inserted SEMS percutaneously[5,6] showed increased stent patency and survival rates for covered stents without differences in lengths of hospital stay, as mentioned above, and decreased tumor ingrowth. There were also no differences in stent migration, bleeding, recurrent biliary obstruction, or tumor overgrowth, with no reported cases of pancreatitis, cholecystitis, perforation, cholangitis, or death at 30 days (more detailed data available on request).

Discussion

The use of SEMS in the management of distal malignant biliary obstruction has become common practice in

Table 2. Continued

Cho et al[4]	Telford et al[8]	Kullman et al[7]	Krokidis et al[5]	Krokidis et al[6]
Abstract	Fully published	Fully published	Fully published	Fully published
2009	2010	2010	2010	2011
6	4	10	2	2
NA	CSEMS244 (SD 231) USEMS217 (SD 208)	Unclear	212 (45–675)	Median 192 (104–603)
77	129	400	60	80
39/38	68/61	200/200	30/30	40/40
NA	66 (SD 14)	NA	65.3/46–78	62.7/41–79
NA	61/68	179/221	36/24	53/27
NA	30/38	88/112	20/10	17/23
NA	31/30	91/109	16/14	36/4
NA	106	152/155	0/0	40/40
NA	NA	12/10	30/30	0/0
NA	NA	16/18	0/0	0/0
NA	NA	8/3	0/0	0/0
NA	NA	8/9	0/0	0/0
NA	129	400	0	0
NA	0	NA	60	80
NA	0	NA	0	0
Covered Bonastent (Standard Scitech, Seoul, Korea), or covered Wallstent	Partially covered Wallstent	Polycarbonate-polyurethane covered nitinol stent (Nitinella; ELLA-CS, Hradec Kralove, Czech Republic); distal 5 mm of the covered stent was uncovered	ePTFE/FEP–covered stent grafts (Viabil biliary stent; Gore, Flagstaff, AZ)	ePTFE/FEP–covered stent grafts (Viabil biliary stent)
Uncovered Bonastent or Hanarostent	Uncovered Wallstent	Uncovered nitinol stent (Nitinella)	Uncovered Wallstent	Bare nitinol stents (Luminexx nitinol biliary stent; Bard, Murray Hill, NJ)
NA	NA	83/87	NA	97.5/77.5
NA	87/90	74/78	NA	92.2/69.8
NA	47/55	50/56	NA	87.6/69.8
1	5	3	2	2

cases of unresectable tumors. SEMS have the advantage of a larger inner diameter when compared with plastic biliary stents and thus a longer duration of patency, requiring fewer repeat insertions.[2,23–26] Nonetheless, the use of SEMS is associated with dysfunction caused by tumor ingrowth, overgrowth, blockage by debris, and migration. Covered SEMS were introduced to prevent ingrowth of tumors. Whether the use of covered SEMS, partially or completely covered, has resulted in an advantage over the use of uncovered SEMS has remained unclear.

This meta-analysis that includes all randomized controlled trials that compared stent patency duration and rates of covered vs uncovered SEMS published to date demonstrates that there are no differences in the rates of patency at 6 or 12 months between uncovered SEMS or covered SEMS. However, covered SEMS migrated significantly more frequently than uncovered SEMS (OR = 7.13; 95% CI, 2.29–22.21), presumably because of the membrane covering of the former. There were no differences in the rates of pancreatitis, cholecystitis, perforation, bleeding, cholangitis, or recurrent biliary obstruction, as well as no differences in durations of survival or hospital stay. There was, however, a decrease in tumor ingrowth but an increased risk of tumor overgrowth in the covered SEMS group when compared with the uncovered SEMS group. Because fully covered SEMS appear to cause minimal tissue overgrowth and fibrosis in normal biliary tissue as suggested in animal studies,[27] the increased rate noted in the trials may be related to the tumor rather the reaction to the stent, although the rate of ingrowth is less in covered SEMS because of the membranous covering of the mesh of the stent; this benefit is offset by the increased rate of overgrowth at the edges of covered SEMS. We could not perform a subgroup analysis between fully covered SEMS and uncovered SEMS because the trials were not explicit about the type of covered SEMS used. In addition, there were no head-to-head trials that compare partially with completely covered SEMS.

However, it is pertinent and important to discuss the limitations of the trials and this meta-analysis before reviewing in

Table 3. Measures of Effect for Outcomes of Interest

Outcome	Comparison groups	No. of studies	OR	95% CI	*P* value for heterogeneity	Measure of heterogeneity	Publication bias (*P* value)
Proportion of stent patency at 6 months	CSEMS vs USEMS	4	1.82	0.63–5.25	.0016	I^2 = 80%	Begg = .73 Egger = .26
	Partially CSEMS vs USEMS	3	1.36	0.45–4.13	.0068	I^2 = 80%	
Proportion of stent patency at 12 months	CSEMS vs USEMS	4	1.25	0.65–2.39	.02	I^2 = 71%	Begg = .31 Egger = .22
	Partially CSEMS vs USEMS	3	1.03	0.54–1.95	.04	I^2 = 69%	
Pancreatitis	CSEMS vs USEMS	6	1.07	0.44–2.59	.65	I^2 = 0%	Begg = 1.00 Egger = .89
	Partially CSEMS vs USEMS	3	1.29	0.48–3.61	.24	I^2 = 29%	
SEMS migration	CSEMS vs USEMS	7	7.13	2.29–22.21	.81	I^2 = 0%	Begg = .04 Egger = .003[a]
	Partially CSEMS vs USEMS	4	8.30	1.87–36.78	.83	I^2 = 0%	
SEMS migration with prior sphincterotomy	CSEMS vs USEMS	3	1.64	0.21–12.79	.89	I^2 = 0%	Begg = 1.00 Egger = .01[a]
	Partially CSEMS vs USEMS	1	2.94	0.11–78.12	NA	NA	
SEMS migration with prior plastic stent	CSEMS vs USEMS	4	2.02	0.36–11.25	.95	I^2 = 0%	Begg = .30 Egger < .001[a]
	Partially CSEMS vs USEMS	2	3.06	0.31–30.49	.97	I^2 = 0%	
Tumor ingrowth	CSEMS vs USEMS	6	0.19	0.07–0.55	.05	I^2 = 56%	Begg = 1.00 Egger = .16
	Partially CSEMS vs USEMS	4	0.30	0.17–0.53	.12	I^2 = 49%	
Tumor overgrowth	CSEMS vs USEMS	6	1.88	1.02–3.45	.83	I^2 = 0%	Begg = .71 Egger = .65
	Partially CSEMS vs USEMS	4	2.15	1.09–4.26	.86	I^2 = 0%	
Cholecystitis	CSEMS vs USEMS	5	1.34	0.48–3.77	.88	I^2 = 0%	Begg = .22 Egger = .56
	Partially CSEMS vs USEMS	3	1.41	0.46–4.28	.55	I^2 = 0%	
Perforation	CSEMS vs USEMS	6	1.84	0.49–6.87	.97	I^2 = 0%	Begg = .71 Egger = .62
	Partially CSEMS vs USEMS	3	2.18	0.48–9.94	.87	I^2 = 0%	
Perforation from SEMS migration	CSEMS vs USEMS	4	2.00	0.36–11.17	.89	I^2 = 0%	Begg = .31 Egger = .002[a]
	Partially CSEMS vs USEMS	2	3.02	0.30–30.19	.56	I^2 = 0%	
Bleeding	CSEMS vs USEMS	4	0.46	0.13–1.66	.82	I^2 = 0%	Begg = .73 Egger = .11
	Partially CSEMS vs USEMS	2	0.30	0.03–2.60	.71	I^2 = 0%	
Bleeding from SEMS migration	CSEMS vs USEMS	4	1.52	0.25–9.22	.97	I^2 = 0%	Begg = .31 Egger = .003[a]
	Partially CSEMS vs USEMS	2	2.04	0.18–23.11	.72	I^2 = 0%	
Cholangitis	CSEMS vs USEMS	4	1.07	0.57–2.01	.50	I^2 = 0%	Begg = .73 Egger = .99
	Partially CSEMS vs USEMS	1	0.65	0.26–1.63	NA	NA	
Recurrent biliary obstruction	CSEMS vs USEMS	6	0.98	0.49–1.95	.004	I^2 = 71%	Begg = .46 Egger = .81
	Partially CSEMS vs USEMS	3	0.84	0.32–2.17	.01	I^2 = 80%	

CSEMS, covered SEMS; NA, not applicable; USEMS, uncovered SEMS.
[a]Asymmetry in the funnel plots that signifies publication bias.

more detail the results pertaining to stent patency duration/rates and patient survival.

Definitions of stent patency was not uniform across trials, and the patient selection with disparate inclusion and exclusion criteria such as type of tumor, the presence of metastases, previous plastic stent insertion, the method of stent insertion, type of SEMS, etc, was not uniform either. Moreover, both irresolvable study heterogeneity and publication bias were noted for a number of the studied outcomes.

For instance, the study by Gonzalez-Huix et al[10] and the 2 trials by Krokidis et al[5,6] excluded those with metastatic disease, whereas the study by Isayama et al[9] excluded those with an Eastern Cooperative Oncology Group score of 3 or more. Many of the patients with advanced disease would have a poorer prognosis and thus a shorter duration of follow-up and may not have sufficient time to develop SEMS dysfunction, let alone exhibiting differences in survival. Isayama et al[9] had a uniquely structured partially covered stent; instead of being covered in

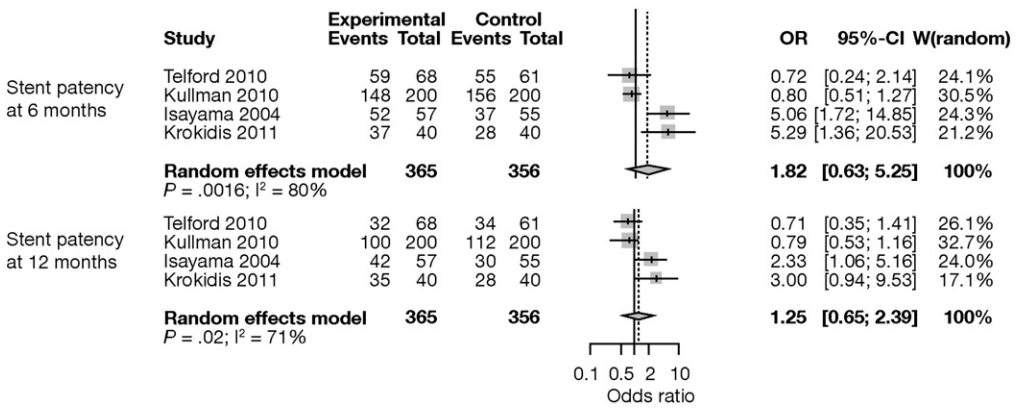

Figure 2. Forest plot of stent patency proportion at 6 and 12 months.

Figure 3. Forest plot of tumor ingrowth, tumor overgrowth, and stent migration.

the mid portion of the stent and uncovered at the ends, the stent had pores within the mid portion. This stent is not widely available. The stent used by Kullman et al[7] only had the distal 5 mm of the stent uncovered as opposed to some that have both distal and proximal uncovered ends. The 2 studies by Krokidis et al inserted SEMS through a transhepatic route, whereas Isayama et al included endoscopically inserted SEMS with the use of the transhepatic with rendez-vous approach only after endoscopic failure. Selective management might have influenced the complications reported by investigators. In the study by Isayama et al, caution was used not to overlap the cystic duct, and in the studies by Krokidis et al when the cystic duct was potentially occluded by the SEMS, a partially covered SEMS with side holes was used. These interventions might have potentially decreased the incidence of cholecystitis. Also the periprocedural management differed; some investigators administered antibiotics before the procedure,[5–7] whereas others did not.[8,9] Methodological differences may also have been at the source of some heterogeneity. The definition of early and late complications varied between studies; for instance in the studies by Lee et al[11] and Gonzalez–Huix et al, early complications were those that occurred <72 hours after stent insertion, whereas in the study by Isayama et al, early complications included those occurring in the first 30 days.

In the 3 studies of initially endoscopically inserted SEMS that reported patency rate, the trials by Telford et al[8] and Kullman et al[7] showed no added advantage when using a covered SEMS, whereas the study of Isayama et al[9] did; our summary analysis, however, showed no prolonged patency rate at 6 or 12 months. In contrast, both studies that used initial percutaneous insertion of SEMS measured stent patency as duration, showing a significantly more prolonged patency in the covered SEMS group. Although biological explanations are lacking, perhaps bacterial exposure or positioning angle at insertion of the stents may have impacted on these findings; statistical issues may also explain this discrepancy as discussed further. In the study by Telford et al[8] after controlling for many variables, there was a higher probability of obstruction with pancreatic cancer (hazard ratio = 4.96; 95% CI, 1.68–14.59), whereas the prior insertion of a plastic biliary stent was associated with a lower probability of recurrent biliary obstruction (hazard ratio = 0.39; 95% CI, 0.17–0.93). This was not the case in the trial by Krokidis et al[6] that exclusively assessed patients with pancreatic head tumors. We could not perform a subgroup analysis for comparing pancreatic cancer with other types of cancer because of the lack of patient-level data.

When further assessing the stent patency duration findings, a number of additional methodological issues need to be considered. Indeed, this meta-analysis was limited by the form of data reporting in the trials and the absence of some information across studies, despite our attempts to contact the authors. Indeed, the duration until stent obstruction was reported in a variety of formats such as median and interquartile ranges as well as medians and SDs. In addition, there were discrepancies in the use of the terms *stent patency* and *stent survival* as applied to reported proportions, depending on whether patients dying with a patent stent were included. Sensitivity analysis suggested no differences when reviewing the interpretation of stent patency durations across studies. The outcome of stent survival reflected a subgroup of patients in most trials and was not chosen as an outcome of interest because of its lesser clinical pertinence. Such variability in reporting prevents obtaining a summary measure of effect.[20] Furthermore, subgroup analysis of the effect of prior sphincterotomy and prior plastic biliary stenting is limited by the fact that most studies reported these variables collectively, not for each arm. Also we could not use a composite measure for all complications in the absence of individual patient-level data. The small number of patients and studies further limits any summary analyses, also precluding meta-regression. Of note, some of the studies that were published in abstract form are old, with one of them dating back to

1995.[12] Why these studies have not been fully published is unclear and needs to be considered when interpreting the data.

One recommendation for future trials in this area might be to adopt a more comprehensive outcome measure such as "recurrent biliary obstruction" because an event of "stent occlusion" (or loss of stent patency) may actually be due to stent migration.

In the only published meta-analysis on the topic to date, Saleem et al[28] imputed data from the standard errors of the means, CIs, interquartile ranges, or ranges to be able to amalgamate more trials together with regard to the primary outcomes. Even with such imputations, Saleem et al were only able to base their analysis of mean differences in stent patency on 3 randomized trials,[5,6,9] two of which had exclusively inserted the SEMS through a percutaneous route.[5,6] The discrepancy between our conclusions and those of Saleem et al might be due to differing methodological approaches, with the limitations of imputation having been previously described by the Cochrane group.[29] Saleem et al also used the stent survival definition for both Isayama et al[9] and Telford et al,[8] in which this outcome is more properly defined as stent patency (see Table 2 for stent patency definition). Telford et al found no difference in the stent patency duration, whereas Isamaya et al reported a significant difference favoring covered stents. Both trials were not included in our analysis because of the adopted reporting format. The largest trial by Kullman et al[7] that did not find a difference in the stent patency between covered and uncovered SEMS was not included in both meta-analyses because no ranges or distribution were provided. Furthermore, our interpretation of stent patency definitions varied with theirs because of poorly standardized reporting across the different trials. We included an additional 4 trials, all in abstract form, that were not included in the meta-analysis by Saleem et al, but none could be used for the main outcome analysis. These additional studies, as well as adding double zero events, resulted in a bigger, perhaps more generalizable sample size for analyzable outcomes. One potential cause of stent obstruction is reflux of food material into the stent; from the data available, we cannot determine whether the position of the distal-most portion of the stent in relation to the papilla (above or below) would alter stent occlusion.

The findings relating to survival are also worthy of discussion. We were unable to provide summary data on this important outcome because of lack of statistical reporting, as described above. Interestingly, 3 trials documented improved survival with covered stent insertion, only one significantly.[6] Two of the three trials reported on percutaneous stenting. It is unclear why survival may be prolonged in the percutaneously inserted covered SEMS group, but this observation may relate at least in part to subclinical differences in biliary contamination at insertion. Alternately, this observation might reflect, in part, differences in patient selection. Unfortunately, the data did not allow us to directly compare percutaneous vs endoscopic methods of insertion. Although the literature on malignant biliary stenting almost uniformly reports no survival benefits, such an advantage has been noted for SEMS compared with plastic stents in a retrospective study (6.5 vs 4 months, $P < .05$)[30] and was also shown in an as yet unpublished older meta-analysis of 3 randomized controlled trials (OR = 0.69; 95% CI, 0.49–0.97).[31] Saleem et al[28] reported an improvement in survival after imputation of some of the trial data also reported in our current meta-analysis. Although promising, we believe more data are required to substantiate this finding, considering the aforementioned methodological limitations.

The majority of indications are in a palliative setting, but biliary stenting has also increasingly been performed in other clinical scenarios such as in the preoperative biliary drainage of patients with pancreatic head cancer. Studies have mainly used plastic biliary stents and have been associated with increased complications.[32] It is not clear, although feasible,[33] whether the use of SEMS before surgery in those with symptoms related to biliary obstruction, those requiring neoadjuvant therapy, or when surgery is delayed would result in long-term better outcomes; the use of short SEMS before surgery in patients who are thought to be resectable might avoid a second palliative endoscopic retrograde cholangiopancreatography in patients found to be unresectable.[34]

In conclusion, the current meta-analysis demonstrates that the use of covered SEMS does not alter stent patency rates at 6 or 12 months or mortality when compared with uncovered SEMS in patients with distal malignant biliary obstruction. However, significant limitations exist with the available evidence; stent patency duration improved in an analysis of 2 trials that used an initial percutaneous approach. Covered SEMS resulted in decreased stent ingrowth but in increased stent migration and overgrowth; no other secondary outcomes differed. We believe that more trials that use standardized patient selection, technical approaches, outcome definitions, and statistical reporting methods are needed to clarify the optimal role of covered SEMS and to identify the patient population who may most benefit from this technology.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2012.10.019.

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Reprint requests

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Conflicts of interest

This author discloses the following: Dr Barkun is a consultant for Boston Scientific Inc, Olympus Canada Inc, and Cook Inc and has also received "at arms-length" grant funding from both Boston Scientific Inc and Cook Inc. The remaining authors disclose no conflicts.

Supplementary Table 1. Search String

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomized.ab.
4.	placebo.ab.
5.	randomly.ab.
6.	trial.ab.
7.	groups.ab.
8.	or/1−7
9.	exp Pancreatic Neoplasms/
10.	(pancrea$ adj5 neoplas$).tw.
11.	(pancrea$ adj5 cancer$).tw.
12.	(pancrea$ adj5 carcin$).tw.
13.	(pancrea$ adj5 tumo$).tw.
14.	(pancrea$ adj5 metasta$).tw.
15.	(pancrea$ adj5 malig$).tw.
16.	exp common bile duct neoplasms/
17.	(bile adj5 duct adj5 neoplas$).tw.
18.	exp bile duct neoplasms/
19.	exp cholestasis/
20.	(bile adj5 duct adj5 obstruct$).tw.
21.	cholestas$.tw.
22.	exp common bile duct diseases/
23.	exp jaundice, obstructive/
24.	(obstruct$ adj5 jaundice$).tw.
25.	(malig$ adj10 bil$ adj10 obstruct$).tw.
26.	(bil$ adj10 strictur$).tw.
27.	or/9-26
28.	exp stents/
29.	stent$.tw.
30.	endoprosthesis.tw.
31.	or/28-30
32.	8 and 27 and 31