

Clinical outcomes of self-expandable stent placement for benign esophageal diseases: A pooled analysis of the literature

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Author contributions: van Halsema EE and van Hooft JE contributed to conception and design, analysis and interpretation of the data, drafting of the article and final approval of the article; van Hooft JE contributed to critical revision of the article.

Conflict-of-interest: Emo van Halsema had no conflict of interest. Jeanin van Hooft: consultancy work for Cook Medical, Boston Scientific, Abbott and Covidien.

Data sharing: All data in this systematic review were extracted from the original articles and are presented in the literature Tables 1 and 4. No additional data are available.

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Received: August 28, 2014

Peer-review started: September 3, 2014

First decision: November 19, 2014

Revised: December 4, 2014

Accepted: December 16, 2014

Article in press: December 17, 2014

Published online: February 16, 2015

METHODS: The PubMed, Embase and Cochrane databases were searched for relevant articles published between January 2000 and July 2014. Eight prospective studies were identified that analyzed the outcomes of stent placement for refractory benign esophageal strictures. The outcomes of stent placement for benign esophageal leaks, perforations and fistulae were extracted from 20 retrospective studies that were published after the inclusion period of a recent systematic review. Data were pooled and analyzed using descriptive statistics.

RESULTS: Fully covered self-expandable metal stents (FC SEMS) ($n = 85$), biodegradable (BD) stents ($n = 77$) and self-expandable plastic stents (SEPS) ($n = 70$) were inserted in 232 patients with refractory benign esophageal strictures. The overall clinical success rate was 24.2% and according to stent type 14.1% for FC SEMS, 32.9% for BD stents and 27.1% for SEPS. Stent migration occurred in 24.6% of cases. The overall complication rate was 31.0%, including major (17.7%) and minor (13.4%) complications. A total of 643 patients were treated with self-expandable stents mainly for postsurgical leaks (64.5%), iatrogenic perforations (19.6%), Boerhaave's syndrome (7.8%) and fistulae (3.7%). FC SEMS and partially covered SEMS were used in the majority of patients. Successful closure of the defect was achieved in 76.8% of patients and according to etiology in 81.4% for postsurgical leaks, 86.0% for perforations and 64.7% for fistulae. The pooled stent migration rate was 16.5%. Stent-related complications occurred in 13.4% of patients, including major (7.8%) and minor (5.5%) complications.

CONCLUSION: The outcomes of stent placement for refractory benign esophageal strictures were poor. However, randomized trials are needed to put this into perspective. The evidence on successful stent placement for benign esophageal leaks, perforations

Abstract

AIM: To analyze the outcomes of self-expandable stent placement for benign esophageal strictures and benign esophageal leaks in the literature.

and fistulae is promising.

Key words: Self-expandable stents; Benign esophageal strictures; Esophageal perforation; Esophageal fistula; Anastomotic leak; Systematic review

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Core tip: After a systematic search of the literature, we performed a pooled analysis on the clinical outcomes of self-expandable stent placement for benign esophageal diseases. We analyzed the clinical success, adverse events and removal outcome of stent placement in 232 patients with refractory benign esophageal strictures and 643 patients with benign esophageal leaks, perforations and fistulae. Additional analyses were performed for clinical outcomes according to stent type and etiology.

van Halsema EE, van Hooft JE. Clinical outcomes of self-expandable stent placement for benign esophageal diseases: A pooled analysis of the literature. *World J Gastrointest Endosc* 2015; 7(2): 135-153 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v7/i2/135.htm> DOI: <http://dx.doi.org/10.4253/wjge.v7.i2.135>

INTRODUCTION

Esophageal self-expandable stent placement is a well-established, evidence-based treatment for the palliation of malignant dysphagia. By the end of the 90's self-expandable metal stents have replaced the traditional rigid plastic tubes, because of their superiority in safety and cost-effectiveness^[1-6]. Ever since the stent designs have evolved in order to improve their efficacy, durability and safety, and to expand their use for different clinical indications.

Besides malignant indications, esophageal self-expandable stents are nowadays used for refractory benign strictures, benign perforations, postoperative anastomotic leaks and benign fistulae^[1,7]. To define the heterogeneous group of patients with refractory benign esophageal strictures Kochman *et al*^[8] have proposed a uniform definition that has been widely accepted. According to Kochman's criteria an esophageal stricture is refractory or recurrent when it cannot be remediated to a diameter of 14 mm over 5 dilatation sessions at 2-wk intervals, or when a satisfactory luminal diameter cannot be maintained for 4 wk once the target diameter of 14 mm has been achieved^[8]. The definition only applies in the absence of active inflammation and neuromuscular dysfunction. In this subgroup of patients with refractory strictures self-expandable stent placement is performed to extend the dysphagia-free period and to reduce the number of dilatations (Figure 1A and B).

There is a varied offer of esophageal self-ex-

pandable stents, that can be divided into four main groups: (1) removable fully covered metal stents (FC SEMS); (2) removable partially covered metal stents (PC SEMS); (3) removable covered plastic stents (SEPS); and (4) biodegradable stents (BD stents). In this literature review we aim to provide an overview of the clinical outcomes of self-expandable stent placement for benign esophageal diseases including a by clinical indication and by stent design breakdown.

MATERIALS AND METHODS

The PubMed, Embase and Cochrane databases were searched for publications from January 2000 to July 2014. Key words that were used included esophagus, stent and benign. Articles were screened by title and abstract for their relevance. Studies were considered for inclusion when they reported on the clinical outcomes of esophageal self-expandable stent placement for benign strictures, benign perforations, anastomotic leaks and/or benign fistulae. The exclusion criteria and search results are shown in Figure 2. The primary endpoint was clinical success, which was defined as the absence of dysphagia at end of follow-up after single stent placement in case of esophageal strictures and successful closure of the defect after single or multiple stent placements in case of an esophageal leak, perforation or fistula. Clinical failures were defined as recurrent dysphagia in case of esophageal strictures and persistent leak or death during stent therapy in case of esophageal leaks, perforations and fistulae. Secondary endpoints were the technical success rates of esophageal stent placement, morbidity rates, mortality rates and stent removal outcome. Technical success was defined as stent placement across the lesion at the end of the procedure, including successful stent repositioning after immediate migration. Successful stent removal was defined as uneventful endoscopic stent extraction without the need for additional interventions or procedures. So stent removal by the stent-in-stent procedure, which is used to induce pressure-necrosis of granulation tissue to facilitate the removal of an embedded stent, was considered an adverse event.

Statistical analysis

This manuscript contains descriptive statistics. Data were pooled and presented as frequency and percentage, so no biostatistical tests were used.

RESULTS

Refractory benign esophageal strictures

After searching the literature no randomized controlled trials (RCTs) were found that studied the outcomes of stent placement for refractory benign esophageal strictures. Twelve prospective, nonrandomized studies were identified that reported on the outcomes of esophageal stent placement for benign strictures

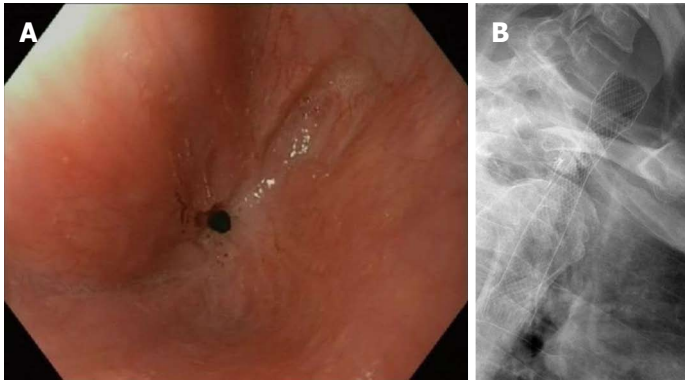


Figure 1 Refractory benign anastomotic stricture after esophagectomy (A) and fully covered self-expandable metal stent placement for a refractory benign esophageal anastomotic stricture (B).

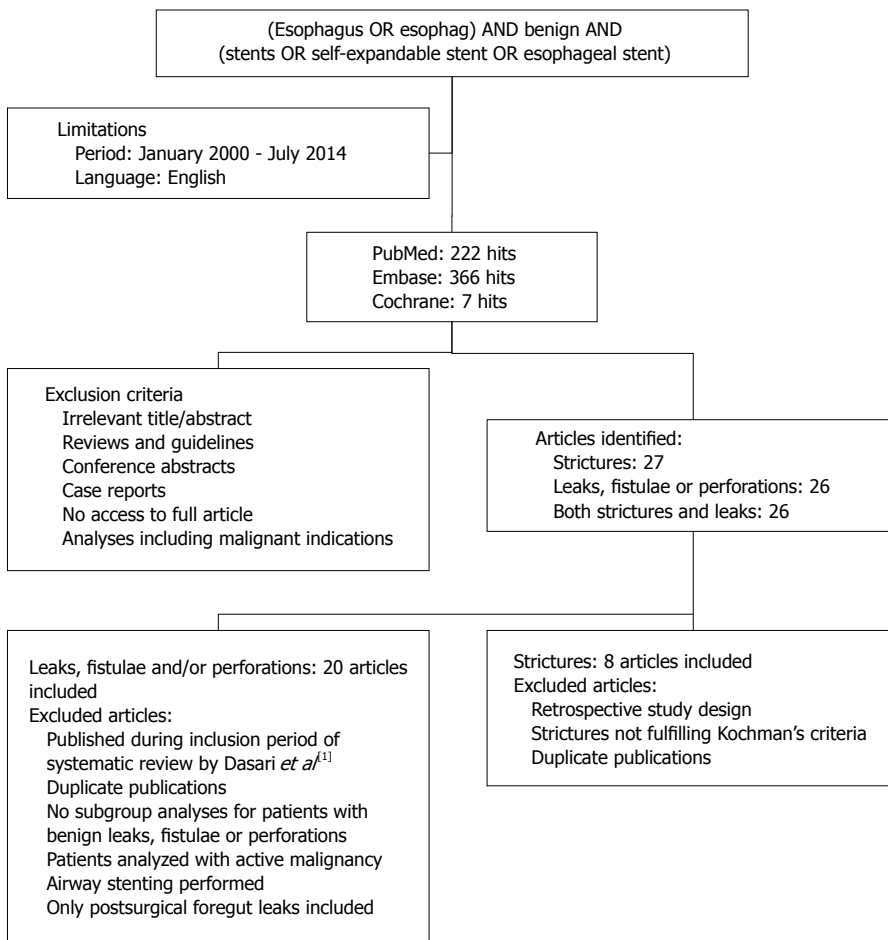


Figure 2 Literature search.

(Table 1)^[9-20]. One was excluded because of a duplicate publication^[20]. To create a homogeneous population only the studies were analyzed that included patients with refractory benign esophageal strictures according to Kochman's criteria^[8]. A total of eight prospective cohort series were included that reported on 232 patients with refractory benign esophageal strictures^[9-16]. In 85 patients a FC SEMS was placed, 77 patients received a BD stent and a SEPS was inserted in 70 patients. No PC SEMS were used in any of the included articles. The overall pooled technical success rate of esophageal stent placement was 98.7%. De-

tails on stricture etiology, stent type and clinical outcomes are summarized in Table 2. Analyses by stricture etiology were not possible due to lacking data.

Clinical success: The overall clinical success rate after single stent placement was 24.2%. The clinical success rates per type of stent are presented in Table 2. The time to recurrence of dysphagia after failed stent therapy varied widely. Stricture recurrence after FC SEMS removal was reported by three studies after median periods ranging from 15 d to 1.7 mo^[9,10,12]. Recurrence of dysphagia after SEPS removal was re-

Table 1 Literature on self-expandable stent placement for refractory benign esophageal strictures

Ref.	Study design	Patients, indications	Stent type, technical success rate, scheduled removal	Follow-up median (range)	Complications	Successful stent removal	Clinical success (dysphagia-free)
Prospective cohort studies including patients with RBES according to Kochman's criteria Chaput <i>et al</i> ^[9] 2013	Prospect	Patients with recurrent benign strictures after more than 3 dilations to more than 15 mm during the previous 12 mo: <i>n</i> = 41 1 Anastomotic stricture: 29% (12/41) 2 Peptic stricture: 39% (16/41) 3 Caustic stricture: 7% (3/41) 4 Radiation stricture: 20% (8/41) 5 Others: 5% (2/41)	Standard FC SEMS: 100% (24/24) - 4 wk Multilayer silicone FC SEMS: 100% (17/17) - 3 mo	24 mo	Overall complications: Stent migration: 29.3% (12/41) Chest pain requiring stent removal or repositioning: 9.8% (4/41) Chest pain resolved with conservative management: 2.4% (1/41) Vomiting: 2.4% (1/41) Pneumonia: 2.4% (1/41)	FC SEMS: 100% (41/41)	Overall clinical success: 9.8% (4/41)
Canena <i>et al</i> ^[10] 2012	Prospect	Patients with RBES according to Kochman criteria: <i>n</i> = 30 1 Anastomotic stricture: 43% (13/30) 2 Peptic stricture: 23% (7/30) 3 Caustic stricture: 10% (3/10) 4 Radiation stricture: 7% (2/30) 5 Idiopathic stricture: 17% (5/30)	BD stent: 100% (10/10) SEPS: 100% (10/10) - 12 wk FC SEMS: 100% (10/10) - 12 wk	23.4 (8-66) mo	Patients with complications (<i>P</i> = 0.38): BD stent 50%, SEPS 70%, FC SEMS 60% Stent migration (<i>P</i> = 0.16): BD stent 20%, SEPS 60%, FC SEMS 30% Tissue hyperplasia (<i>P</i> = 0.09): BD stent 30%, SEPS 0%, FC SEMS 0% Associated with one major bleeding and recurrent dysphagia in two patients Minor complications in 17% (5/30) of patients: 1 Globus sensation: BD stent 0%, SEPS 0%, FC SEMS 10% 2 Moderate chest pain: BD stent 0%, SEPS 20%, FC SEMS 10% 3 Reflux: BD stent 0%, SEPS 10%, FC SEMS 10% Major complications in 7% (2/30) of patients: 1 Major bleeding: BD stent 10%, SEPS 0%, FC SEMS 0% 2 Severe chest pain: BD stent 10%, SEPS 0%, FC SEMS 0%	SEPS: 100% (10/10)	Overall: 27% (8/30) Stent type (<i>P</i> = 0.27): 1 BD stent: 30% (3/10) 2 SEPS: 10% (1/10) 3 FC SEMS: 40% (4/10)
Hirdes <i>et al</i> ^[11] 2012	Prospect	Patients with RBES according to Kochman criteria: <i>n</i> = 28 1 Peptic stricture: 32% (9/28) 2 Anastomotic stricture: 25% (7/28) 3 Radiation stricture: 11% (3/28) 4 Caustic stricture: 7% (2/28) 5 Others: 11% (3/28) 6 Unknown origin: 14% (4/28)	Single BD stent: <i>n</i> = 15 Sequential BD stent: <i>n</i> = 13 Technical success: 100% (28/28) In total 59 BD stent placed	630 (21-1121) d	Stent migration: 10.7% (3/28) Food impaction: 10.7% (3/28) Major complications of 59 stent placements in 28 patients: 29% (8/28) of patients 1 Retrosternal pain and vomiting: 7.1% (2/28) 2 Retrosternal pain: 7.1% (2/28) 3 Bleeding: 7.1% (2/28) 4 Fever and vomiting: 3.6% (1/28) 5 Aspiration pneumonia: 3.6% (1/28) Minor complications of 59 stent placements in 28 patients: 14% (4/28) of patients 1 Retrosternal pain: 7.1% (2/28) 2 Reflux: 3.6% (1/28) 3 Vomiting: 3.6% (1/28) One patient (3.6%) died of aspiration pneumonia, relation to stent unclear	Not applicable	At 6 mo after: First stent: 25% (7/28) Second stent: 15% (2/13) Third stent: 0% (0/7)

Author(s) [ref]	Study Design	Patients with RBES according to Kochman criteria: n =	FC SEMS: 100% (15/15)	After stent removal: 86 (14-330) d	Stent migration: 33% (5/15) Tissue overgrowth: 20% (3/15) Major complications in 20% (3/15) of patients: 1 Severe pain requiring stent removal: 7% (1/15) 2 Severe persistent odynophagia: 7% (1/15) 3 Nausea/vomiting: 13% (2/15) 4 Aspiration pneumonia: 7% (1/15) Minor complications: 1 Pain: 20% (3/15) Stent migration: 36.8% (7/19) Minor complications in patients with RBES: 1 Stent infolding/invasion: 16% (3/19) 2 Chest pain: 5% (1/19) 3 Abdominal pain: 11% (2/19) 4 Globus sensation: 5% (1/19) 5 Fever: 5% (1/19) Major complications in patients with RBES: 1 Arrhythmia: 5% (1/19)	93% (14/15) Stent-in-stent: 7%	0% (0/15)	
Hirdes <i>et al</i> ^[12] 2012	Prospect	1 Peptic stricture: 40% (6/15) 2 Caustic stricture: 20% (3/15) 3 Radiation stricture: 13% (2/15) 4 Other: 7% (1/15) 5 Unknown cause: 20% (3/15)	109 d (87-222)					
Eloubeidi <i>et al</i> ^[13] 2011	Pro- and retrospect	Patients with benign esophageal lesions treated with Alimaxx-E stent: n = 35 Leaks/fistulae: n = 12 Perforations: n = 4 RBES: n = 19 1 Anastomotic stricture: 37% (7/19) 2 Peptic stricture: 21% (4/19) 3 Caustic stricture: 11% (2/19) 4 Radiation stricture: 11% (2/19) 5 Others: 21% (4/19)	FC SEMS: 100% (19/19) In situ for: 64 ± 74 d (range 6-300)	161 ± 111 (range 24-360) d		97% (34/35) Stent fracture: 3%	21% (4/19)	
Van Boeckel <i>et al</i> ^[14] 2011	Prospect	Patients with RBES according to Kochman criteria: n = 38 1 Anastomotic stricture: 34% (13/38) 2 Peptic stricture: 18% (7/38) 3 Radiation stricture: 18% (7/38) 4 Caustic stricture: 16% (6/38) 5 Others: 11% (4/38) 6 Unknown etiology: 3% (1/38)	BD stent: 100% (18/18) SEPS: 95% (19/20) - 6 wk	BD stent: 166 (21-559) d SEPS: 385 (77-924) d		SEPS: 100% (16/16) 1 SEPS: 30% (6/20) 2 BD stent: 35% (6/18)	Stent type (P = 0.83): 1 SEPS: 30% (6/20) 2 BD stent: 35% (6/18)	
Repici <i>et al</i> ^[15] 2010	Prospect	Patients with RBES according to Kochman criteria: n = 21 1 Peptic stricture: 33% (7/21) 2 Anastomotic stricture: 24% (5/21) 3 Radiation stricture: 24% (5/21) 4 Caustic stricture: 10% (2/21) 5 Other: 5% (1/21) 6 Idiopathic stricture: 5% (1/21)	BD stent: 100% (21/21)	53 (25-88) wk		Not applicable	45% (9/20)	
Dua <i>et al</i> ^[16] 2008	Prospect	Patients with RBES according to Kochman criteria: n = 40 1 Anastomotic stricture: 30% (12/40) 2 Caustic stricture: 20% (8/40) 3 Radiation stricture: 18% (7/40) 4 Peptic stricture: 5% (2/40) 5 Others: 28% (11/40)	SEPS: 95% (38/40) 4 wk	53 (11-156) wk		94% (31/33) Inability to remove stent: 6% (2/33)	30% (12/40)	
Remaining prospective cohort studies								

Author	Study Design	Patients with an esophago-gastric anastomotic stricture who did not have had any endoscopic treatment: n = 10	SEMS-induced stricture: n = 5	Esophagocolonic anastomotic stricture: n = 4	Refractory benign strictures after a median of 6 (range 1-12) dilation sessions per year: n = 8	Anastomotic leak: n = 4	Patients with persisting benign esophageal strictures after at least 6 dilation sessions: n = 15	Caustic stricture: 33%	Anastomotic stricture: 27%	Radiation stricture: 27%	BD stent: 100% (10/10)	6 mo	Food impaction: 10% (1/10)	Hyperplasia-induced obstruction: 20% (2/10)	Not applicable	60% (6/10)
Van Hooff <i>et al.</i> ^[17] 2011	Prospect															
Evvard <i>et al.</i> ^[18] 2004	Prospect											After stent removal: 21 (8-39) mo	Stent migration: 57.1% (12/21)	Stridor due to tracheal compression: 4.8% (1/21)	100% (21/21)	76% (13/17)
Repici <i>et al.</i> ^[19] 2004	Prospect											Mean: 22.7 (19-27) mo	Severe chest pain requiring analgesics: 33% (5/15)	Mild/moderate mucosal hyperproliferation: 27% (4/15)	100% (15/15)	80% (12/15)

RBES: Refractory benign esophageal strictures; SEPS: Self-expandable plastic stent; BD stent: Biodegradable stent; FC SEMS: Fully covered self-expandable metal stent.

ported by one study after a mean of 4 (range 2-9) wk^[10]. After BD stent placement dysphagia recurred after mean periods ranging from 4 wk to 19 wk^[10,15].

Stent migration, reactive tissue formation and food impaction: The overall pooled stent migration rate was 24.6% (57/232). By stent type migration rates were 31.8% (27/85) for FC SEMS, 14.3% (11/77) for BD stents and 27.1% (19/70) for SEPS.

Tissue hyperplasia was reported in 4.3% (10/232) of patients, causing recurrent dysphagia in 5 patients (2.2%) who all had received a BD stent. Hyperplastic tissue growth according to stent type was 3.5% (3/85) for FC SEMS, 7.8% (6/77) for BD stents and 1.4% (1/70) for SEPS. Food impaction was reported in 2.2% (5/232) of patients and occurred only in patients with a BD stent (6.5%, 5/77).

Adverse events: Excluding stent migration, reactive tissue formation and food impaction which were analyzed separately, 72 (31.0%) patients suffered a total of 77 complications due to stent placement. Major complications were reported in 17.7% of patients and minor complications in 13.4%. Major and minor complication rates per stent design are presented in Table 3. There was one (0.4%) stent-related death from a massive bleeding probably due to SEPS erosion into a major vessel^[16]. Another patient with a BD stent died of aspiration pneumonia, which may have been caused by stricture recurrence^[11].

Stent removal: Removal of SEPS or FC SEMS was scheduled after 4 to 12 wk and BD stents were left in place to dissolve. Stent removal was attempted in 92.9% (144/155) of patients with a SEPS or FC SEMS. Successful stent removal was achieved in 97.2% (140/144) of patients; FC SEMS (97.6%, 83/85) and SEPS (96.6%, 57/59). Two SEPS were removed during surgery, because one migrated SEPS could not be pulled through the ileocecal valve in a patient with a colon – ileocecal valve – terminal ileum interposition, and one was partially embedded by granulation tissue above the stent^[16]. One FC SEMS had to be removed by a stent-in-stent procedure due to severe reactive tissue growth through the disrupted cover of the stent^[12]. Another FC SEMS fractured during removal and was retrieved in two pieces^[13].

Benign esophageal leaks, perforations and fistulae

The literature search revealed a recently published systematic review that analyzed the clinical outcomes of self-expandable stent placement for benign esophageal leaks and perforations in the literature published from 1990 to 2012^[1]. Therefore, the studies published after the systematic review of Dasari *et al.*^[1] were considered for analysis. No RCTs that focused on the outcomes of stent placement for benign esophageal leaks, perforations or fistulae were identified. A total of 28 studies were selected from the literature, but after more careful reading of the articles eight more studies were excluded because they analyzed patients with active malignancy.

Table 2 Pooled analysis of 232 patients with refractory benign esophageal strictures according to Kochman's criteria treated with self-expandable stent placement *n* (%)

Stricture etiology	
Anastomotic strictures	69 (29.7)
Peptic strictures	58 (25.0)
Radiation strictures	36 (15.5)
Caustic strictures	29 (12.5)
Others	26 (11.2)
Unknown	14 (6.0)
Stent type	
FC SEMS	85 (36.6)
BD stent	77 (33.2)
SEPS	70 (30.2)
PC SEMS	0 (0)
Technical success	
Overall	229 (98.7)
FC SEMS	85 (100)
BD stent	77 (100)
SEPS	67 (95.7)
Clinical success	
Overall (<i>n</i> = 231)	56 (24.2)
FC SEMS (<i>n</i> = 85)	12 (14.1)
BD stent (<i>n</i> = 76)	25 (32.9)
SEPS (<i>n</i> = 70)	19 (27.1)

FC SEMS: Fully covered self-expandable metal stent; BD stent: Biodegradable stent; SEPS: Self-expandable plastic stent; PC SEMS: Partially covered self-expandable metal stent.

nancy^[21], performed a double stent strategy including airway stenting^[22-24], included only postsurgical foregut leaks^[25], did not perform subgroup analyses for patients with benign esophageal leaks, perforations or fistulae^[26,27], or because of duplicate publication^[28]. Ultimately, 20 studies were included for analysis, all with a retrospective study design (Table 4)^[13,29-47]. A total of 643 patients with benign esophageal leaks, perforations and fistulae were considered for analysis. A total of 852 stents were inserted in 573 patients. In the remaining 70 patients the number of stents used was not reported. The main indications for self-expandable stent placement were postsurgical leaks (64.5%), iatrogenic perforations (19.6%), Boerhaave's syndrome (7.8%) and fistulae (3.7%). The majority of inserted stents were FC SEMS (41.0%) and PC SEMS (37.7%). Stent placement was technically successful in 99.9% of cases. Further details are summarized in Table 5. Data on concurrent drainage of fluid collections were available for 425 patients, of whom 57.4% (244/425) underwent drainage procedures.

Clinical success: The overall clinical success rate of esophageal stent placement for benign leaks, perforations and fistulae was 76.8% (480/625). Subgroup analysis according to etiology was possible for 358 patients. The highest clinical success rate was achieved in patients with perforations (86.0%), followed by postsurgical leaks (81.4%) and fistulae (64.7%) (Table 5). When solely FC SEMS were used, clinical success was achieved in 73.0% (135/185) of

Table 3 Pooled analysis of adverse events in patients with refractory benign esophageal strictures *n* (%)

Overall complications	72 (31.0)
Overall major complications	41 (17.7)
FC SEMS (<i>n</i> = 85)	9 (10.6) ¹
Severe retrosternal pain	5 (5.9)
Severe nausea and vomiting	2 (2.4)
Aspiration pneumonia	2 (2.4)
Arrhythmia	1 (1.2)
Percutaneous endoscopic gastrostomy because of impaired intake caused by severe, persistent odynophagia	1 (1.2)
BD stents (<i>n</i> = 77)	22 (28.6) ¹
Severe retrosternal pain	10 (13.0)
Hyperplasia-induced stenosis	5 (6.5)
Bleeding, hematemesis	5 (6.5)
Severe nausea and vomiting	3 (3.9)
Aspiration pneumonia	1 (1.3)
SEPS (<i>n</i> = 70)	10 (14.3)
Severe retrosternal pain	4 (5.7)
Perforation	3 (4.3)
Bleeding, hematemesis ²	2 (2.9)
Stent-induced fistula	1 (1.4)
Overall minor complications	31 (13.4)
FC SEMS (<i>n</i> = 85)	15 (17.6) ¹
Retrosternal pain	6 (7.1)
Stent infolding/invagination	3 (3.5)
Abdominal pain	2 (2.4)
Globus sensation	2 (2.4)
Reflux symptoms	1 (1.2)
Vomiting	1 (1.2)
Fever	1 (1.2)
BD stents (<i>n</i> = 77)	8 (10.4)
Nausea and vomiting	3 (3.9)
Retrosternal pain	2 (2.6)
Reflux symptoms	2 (2.6)
Minor bleeding	1 (1.3)
SEPS (<i>n</i> = 70)	8 (11.4)
Reflux symptoms	3 (4.3)
Retrosternal pain	2 (2.9)
Minor bleeding	2 (2.9)
Nausea and vomiting	1 (1.4)

¹Patients can have more than one complication; ²Including one stent-related death from massive bleeding. FC SEMS: Fully covered self-expandable metal stent; BD stent: Biodegradable stent; SEPS: Self-expandable plastic stent; PC SEMS: Partially covered self-expandable metal stent.

patients. Solely PC SEMS were used in two studies with a pooled clinical success rate of 78.2% (68/87). Only one study focused on the outcomes of SEPS placement and reported clinical success in 90% (27/30) of patients with anastomotic leaks.

Stent migration, reactive tissue formation and food impaction: Stent migration could be analyzed in 320 patients who received a total of 468 self-expandable stents. The overall pooled stent migration rate was 16.5% (77/468). By stent type migration rates were 21.8% (53/243) for FC SEMS and 10.6% (23/218) for PC SEMS. Data were insufficient to analyze the stent migration rate of SEPS.

Pooled analysis of tissue hyperplasia was possible for 384 patients in whom 530 stents were inserted.

Table 4 Literature on self-expandable stent placement for benign esophageal leaks, perforations and fistulae

Ref.	Study design	Patients	Stent type, technical success (%) and time to removal	Additional sepsis-related procedures, follow-up	Complications and mortality	Successful stent removal	Clinical success
Dua <i>et al</i> ^[29] 2014	Pro- and retrospect	Patients treated with a non-foreshortening FC SEMS for benign esophageal leaks: <i>n</i> = 6 1 Postsurgical leaks: <i>n</i> = 5 2 Esophagopericardial fistula: <i>n</i> = 1 Single stent: 83% (5/6) Multiple stents: 17% (1/6) Patients with attempted stent placement for esophageal leaks, fistulae and perforations: 1 1 Postsurgical leaks: <i>n</i> = 29	FC SEMS: 100% (7/7) Median time to removal: 50 (49-56) d	Unknown FU: unknown	Minor complications: Pneumoperitoneum during endoscopy secondary to air insufflation: 17% (1/6) Stent migration: 17% (1/7) Mortality rate: 33.3% (2/6) - cerebral embolism: 16.7% (1/6) - sepsis-related: 16.7% (1/6) No subgroup analysis for patients with esophageal leaks 1 Chest pain 2 GI Bleed 3 Pneumothorax 4 Increase size of leak during deployment 5 Breakage of stent 6 Dysphagia 7 Aspiration pneumonia Stent migration not analyzed for subgroup of patients with esophageal leaks Mortality rate: 0% (0/29)	FC SEMS: 100% (4/4)	Overall: 67% (4/6) - Postsurgical leaks: 80% (4/5) - Fistula: 0% (0/1)
El Hajji <i>et al</i> ^[30] 2014	Retrospect	Patients with attempted stent placement for esophageal leaks, fistulae and perforations: 4 to 6 wk 1 Postsurgical leaks: <i>n</i> = 29	PC SEMS: 100% (19/19) FC SEMS: 100% (30/30) SEPS: 100% (15/15) - 4 to 6 wk - 6 to 8 wk	Not analyzed for subgroup of patients with anastomotic leaks ≥ 3 mo FU: 100%	1 Chest pain 2 GI Bleed 3 Pneumothorax 4 Increase size of leak during deployment 5 Breakage of stent 6 Dysphagia 7 Aspiration pneumonia Stent migration not analyzed for subgroup of patients with esophageal leaks Mortality rate: 0% (0/29)	No subgroup analysis for patients with postsurgical leaks - Stent-in-stent procedure: 2 - Breakage of stent: 1	Overall: 82.8% (24/29) - Primary closure rate: 72% (21/29) - Secondary closure rate: 38% (3/8)
Freeman <i>et al</i> ^[31] 2014	Retrospect	Excluded from analysis because patients were included with active malignancy: 1 Perforations: <i>n</i> = 10 2 Fistulae: <i>n</i> = 15 Patients with intrathoracic leak after surgical repair of an acute iatrogenic esophageal perforation: <i>n</i> = 29 Single stent: 100% (29/29)	SEPS: 100% (15/15) FC SEMS: 100% (24/24) FC SEMS: 100% (5/5) Mean time to removal: 22 (13-41) d	PEG: 10.3% (3/29) Thoracoscopic decortication: 10.3% (3/29) Jejunostomy: 3.4% (1/29)	No stent-related complications. Stent migration: 17.2% (5/29) - not analyzed according to stent type Mortality rate: 0% (0/29)	100% (25/25)	86.2% (25/29)
Gubler <i>et al</i> ^[32] 2014	Retrospect	Patients with benign (gastro)esophageal leaks, fistulae or perforations: <i>n</i> = 85 1 Iatrogenic perforations: <i>n</i> = 32 2 Anastomotic leaks: <i>n</i> = 31 3 Fistulae: <i>n</i> = 7 4 Boerhaave: <i>n</i> = 7 5 Other perforations: <i>n</i> = 8 Single stent: 78% (66/85) Multiple stents: 22% (19/85)	Total SEMS: <i>n</i> = 113 PC SEMS: <i>n</i> = 72 FC SEMS: <i>n</i> = 28 Unknown: <i>n</i> = 13 Technical success: 100% Average time to removal: 15 (1-111) d	Median FU: 6 wk Percutaneous/thoracoscopic drainage: 55.3% (47/85) OTSC: 2.4% (2/85) Vacuum-therapy: 2.4% (2/85) FU: at least 4 wk after stent removal	Stent migration: 8.8% (10/113) - not analyzed according to stent type Food bolus obstruction: 0.9% (1/113) - not analyzed according to stent type Mortality rate: 9.4% (8/85) 1 Unrelated to in situ stent: 3.5% (3/85) 2 Multi-organ failure: 2.4% (2/85) 3 Acute respiratory distress syndrome: 1.2% (1/85) 4 Heart insufficiency: 1.2% (1/85) 5 Aortic dissection: 1.2% (1/85)	98.2% (107/109) - Irremovable: 2 - Spontaneous passage after migration: 1 Not analyzed according to stent type	Overall: 79% (67/85) - Postsurgical leaks: 74% (23/31) - Fistulae: 43% (3/7) - Iatrogenic: 94% (30/32) - Boerhaave: 71% (5/7) - Others: 75% (6/8) PC SEMS: 68% (49/72) FC SEMS: 54% (15/28)

Orive-Calzada <i>et al</i> ^[33] 2014	Pro- and retrospect	Patients treated with FC SEMs for benign upper gastrointestinal fistulae and perforations: <i>n</i> = 56 1 Postsurgical leaks: <i>n</i> = 44 2 Iatrogenic perforations: <i>n</i> = 6 3 Boerhaave syndrome: <i>n</i> = 4 4 Other perforations: <i>n</i> = 2 Single stent: 59% (33/56) Multiple stents: 41% (23/56)	FC SEMs: 100% (87/87) PC SEMs: 100% (1/1) Median time to removal: 42 (9-1460) d	Surgical drainage: 30% (17/56) Percutaneous drainage: 41% (23/56) FU: unknown	Minor complications: Atrial fibrillation: 1.8% (1/56) Major complications: Stent-related perforation: 5.4% (3/56) Stent migration: 20.5% (18/88) - FC SEMs: 20.7 (18/87) - PC SEMs: 0% (0/1) Mortality rate: 16% (9/56) - cerebrovascular accident: 1.8% (1/56) - nosocomial pneumonia: 1.8% (1/56) - neoplasia: 1.8% (1/56) - secondary to sepsis: 10.7% (6/56) No stent-related complications Stent migration not analyzed according to stent type Mortality rate: 7.5% (3/40) 1 Multi-organ failure: 5% (2/40) 2 Respiratory insufficiency without sepsis: 2.5% (1/40)	FC SEMs: 100% (87/87) PC SEMs: 0/1 -Stent-in-stent procedure: 1	Overall: 79% (44/56) -Postsurgical leaks: 78% (36/46) -Perforations: 80% (8/10)
Persson <i>et al</i> ^[34] 2014	Retrospect	Patients with benign spontaneous, iatrogenic or traumatic esophageal perforations: <i>n</i> = 40 1 Iatrogenic perforation: <i>n</i> = 16 2 Boerhaave syndrome: <i>n</i> = 23 3 Other perforations: <i>n</i> = 1 Single stent: missing Multiple stents: missing	Total No. of stents missing Stent type missing Time to removal: 4-6 wk	Unknown FU: unknown	No subgroup analysis for patients with benign leaks -Stent-in-stent procedure: 7 -Irremovable uncovered stent: 1	Overall: 47% (7/15) -Postsurgical leaks: (5/11) -Fistula: 67% (2/3) -Iatrogenic: 0% (0/1)	
Shariha <i>et al</i> ^[35] 2014	Retrospect	Patients treated with stent placement for benign upper GI leaks: <i>n</i> = 18 1 Postsurgical leaks: <i>n</i> = 12 2 Iatrogenic perforation: <i>n</i> = 1 3 Other fistulae: <i>n</i> = 5 Single stent: 28% (5/18) Multiple stents: 72% (13/18)	Total stents: <i>n</i> = 47 1 FC SEMS 2 PC SEMS 3 SEPS 4 Uncovered Technical success: 100% Mean time to removal: 54 (18-118) d	Clip/endolooop: 27.8% (5/18) Dilation: 33.3% (6/18) Surgery: 16.7% (3/18) FU: median 283 d (IQR 38-762)	Overall 9 complications in 5 patients 5 minor complications in 4 patients: - reflux/esophagitis: 16.7% (3/18) - abdominal pain: 5.6% (1/18) - collapsed stent: 5.6% (1/18) 4 Major complications in 3 patients: - aspiration pneumonia: 11.1% (2/18) - perforation: 5.6% (1/18) - stricture: 5.6% (1/18) Tissue hyperplasia: 5.6% (1/47) - stent type unknown Food impaction/bezoar: 11.1% (2/47) - stent type unknown Stent migration not analyzed for subgroup of patients with esophageal leaks Overall mortality rate: 5.6% (1/18) Not specified	No subgroup analysis for patients with benign leaks -Stent-in-stent procedure: 7 -Irremovable uncovered stent: 1	Overall: 67% (8/12) -Primary closure rate: 67% (8/12) -Secondary closure rate: 0% (0/4)
Shim <i>et al</i> ^[36] 2014	Retrospect	Patients who underwent endoscopic treatment for anastomotic leakage after total gastrectomy: <i>n</i> = 27 1 FC SEMs: <i>n</i> = 13 2 Non stent therapy: <i>n</i> = 14 Single stent: 85% (11/13) Multiple stents: 15% (2/13)	FC SEMs: 100% (15/15) PC SEMs: 100% (1/1) Median time to removal: 38 (0-69) d	Concurrent fluid drainage: 61.5% (8/13) FU: unknown	Minor complication: Stent malposition: 6.3% (1/13) Stent migration: 25% (4/16) - FC SEMs: 26.7% (4/15) - PC SEMs: 0% (0/1) Tissue in- or overgrowth: 6.3% (1/16) - FC SEMs: 6.7% (1/15) Mortality rate: 15.4% (2/13) - sepsis related: 7.7% (1/13) - non-stent related bleeding: 7.7% (1/13)	FC SEMs: 100% (11/11) PC SEMs: 100% (1/1)	Overall: 67% (8/12) -Primary closure rate: 67% (8/12) -Secondary closure rate: 0% (0/4)

Brangewitz <i>et al</i> ^[57] 2013	Retrospect	Patients with esophageal defects treated with stent placement: <i>n</i> = 39 1 Postsurgical leaks: <i>n</i> = 31 2 Iatrogenic perforations: <i>n</i> = 6 3 Boerhaave syndrome: <i>n</i> = 2 Single stent: 100% (39/39)	FC SEMS: 100% (39/39) Median time to removal: 33 (9-132) d	Unknown FU: unknown	Minor complications: - stent-related ulcers: 12.8% (5/39) Major complications: - severe bleed at upper end of stent: 2.6% (1/39) - death due to esophageal necrosis at proximal end of stent: 2.6% (1/39) Stent migration: 15.4% (6/39) Mortality rate: 25.6% (10/39) - esophageal necrosis at proximal stent end: 2.6% (1/39) - not specified: 23.1% (9/39) Minor complications: - stent disintegration all with FC SEMS: 11.5% (3/26) Major complications: - stent-related perforation with FC SEMS: 3.8% (1/26) Stent migration: 24.2% (8/33) - FC SEMS: 25.8% (8/31) Tissue ingrowth: 6.1% (2/33) - PC SEMS: 100% (2/2) Mortality rate: 19.2% (5/26) - sepsis-related: 19.2% (5/26) Major complications: - severe hemorrhage from aorta-esophageal fistula: 3.0% (1/33) No subgroup analysis for patients with esophageal leaks, fistulae and perforations: - stent migration - food impaction Mortality rate: 0% (0/33)	FC SEMS: 90.3% (28/31) 53.8% (21/39) -Self-limiting bleed: 2 -Migrated stent requiring surgical removal: 1 No subgroup analysis according to etiology
Leenders <i>et al</i> ^[58] 2013	Retrospect	Patients with anastomotic leakage after esophageal resection or bariatric surgery: <i>n</i> = 26 Single stent: 81% (21/26) Multiple stents: 19% (5/26)	FC SEMS: 100% (31/31) PC SEMS: 100% (2/2) Mean time to removal: 11 (1-63) wk	Unknown FU: range 2-144 wk	FC SEMS: 100% (26/26) 80.8% (21/26) PC SEMS: 0% (0/2) -Traumatic removal due to tissue ingrowth: 2	
Wilson <i>et al</i> ^[59] 2013	Retrospect	Patients treated with FC SEMS placement for benign esophago-gastric diseases: <i>n</i> = 33 1 Perforation: <i>n</i> = 7 2 Anastomotic leak: <i>n</i> = 14 3 Sleeve gastrectomy leak: <i>n</i> = 6 4 Fistula: <i>n</i> = 6 Single stent: missing Multiple stents: missing	FC SEMS: 100% (40/40) Average time to removal: 47 d (12/33)	Drainage procedure: 66.7% (22/33) VATS/open: 36.4% (12/33) Tube thoracostomy: 21.2% (7/33) Percutaneous: 9.1% (3/33)	No subgroup analysis for patients with esophageal leaks, fistulae and perforations: - Stent fracture: 2 (6/7) -Fistulae: 100% (6/6)	
Van Boeckel <i>et al</i> ^[60] 2012	Retrospect	Patients treated with a SEMS or SEPS for sealing a benign esophageal rupture or anastomotic leak: <i>n</i> = 52 1 Anastomotic leak: <i>n</i> = 32 2 Iatrogenic perforation: <i>n</i> = 13 3 Boerhaave syndrome: <i>n</i> = 4 4 Others: <i>n</i> = 3 Single stent: missing Multiple stents: missing	PC SEMS: 98% (60/61) FC SEMS: 100% (15/15) SEPS: 100% (7/7) Median time to removal: 25 (1-197) d	FU: unknown Concurrent fluid drainage: 46.2% (24/52) Median FU: 470 (25-1200) d	88.7% (63/71) Tissue in- and/or overgrowth at removal of 8 PC SEMS -Stent-in-stent procedure: 4 -Esophageal rupture: 2 -Second endoscopic procedure: 1 -Esophagectomy: 1 Not analyzed according to stent type	

Buscaglia <i>et al</i> ^[41] 2011	Retrospect	<p>Patients treated for benign esophageal conditions by FC SEMS placement:</p> <ul style="list-style-type: none"> - fistula or leak: <i>n</i> = 15 Single stent: 67% (10/15) Multiple stents: 33% (5/15) 	<p>FC SEMS: 100% (24/24)</p> <p>Unknown</p> <p>Median time to removal: 42.5 FU: unknown (3-122) d</p>	<p>- SEPS: 14% (1/7)</p> <p>Food obstruction: 3.6% (3/83)</p> <p>- PC SEMS: 4.9% (3/61)</p> <p>Mortality rate: 13.5% (7/52)</p> <p>- severe stent-related hemorrhage: 1.9% (1/52)</p> <p>- sepsis related: 7.7% (4/52)</p> <p>- malignancy: 1.9% (1/52)</p> <p>- active euthanasia: 1.9% (1/52)</p> <p>Stent migration: 33.3% (8/24)</p> <p>Further complications not analyzed for subgroup of patients with fistulae and leaks</p> <ul style="list-style-type: none"> - chest pain - globus sensation <p>Mortality rate: 6.7% (1/15)</p> <ul style="list-style-type: none"> - paraspinal abscess related to persistent fistula 	<p>No subgroup analysis for patients with esophageal leaks and fistulae</p> <ul style="list-style-type: none"> - Removal during surgery: 1 - Stent-in-stent procedure: 1 <p>No subgroup analysis according to etiology</p>	<p>79% (11/14)</p> <p>No subgroup analysis according to etiology</p>
Dai <i>et al</i> ^[42] 2011	Retrospect	<p>Patients treated with SEPS for:</p> <ul style="list-style-type: none"> - Postoperative esophageal anastomotic leaks: <i>n</i> = 30 Single stent: missing Multiple stents: missing <p>Excluded from analysis because patients were included with active malignancy:</p> <ul style="list-style-type: none"> - esophageal perforations: <i>n</i> = 6 - fistulae: <i>n</i> = 5 	<p>Total no. of SEPS missing: 40% (12/30)</p> <p>Technical success: 100% (13/30)</p> <p>Mean time to stent removal: 30 (7-62) d</p> <p>Interventional drainage: 40% (12/30)</p> <p>Tracheotomy: 43% (13/30)</p> <p>Mean FU: 12.8 (1-61) mo</p>	<p>Major complications:</p> <ul style="list-style-type: none"> - stent dislocation and inability to place new stent requiring rethoracotomy: 3.3% (1/30) <p>Stent migration not analyzed for subgroup of patients with esophageal leaks</p> <p>Mortality rate: (2/30)</p> <ul style="list-style-type: none"> - persistent sepsis and multi-organ failure: 6.7% (2/30) 	<p>No. of removed stents missing</p> <p>One migrated stent</p> <p>Stent migration not analyzed for subgroup of patients with an esophago-colonic anastomotic leak could not be removed</p>	<p>90% (27/30)</p>
David <i>et al</i> ^[43] 2011	Pro- and retrospect	<p>Patients treated with SEMS for esophageal or gastric perforation and intrathoracic contamination: <i>n</i> = 30</p> <ul style="list-style-type: none"> - Postsurgical leak: <i>n</i> = 13 - boerhaave syndrome: <i>n</i> = 6 - iatrogenic perforation: <i>n</i> = 6 - fistulae: <i>n</i> = 4 - other perforation: <i>n</i> = 1 <p>Single stent: 50% (15/30)</p> <p>Multiple stents: 50% (15/30)</p>	<p>At least 62 stents</p> <ul style="list-style-type: none"> - FC SEMS - PC SEMS <p>Technical success: 100%</p> <p>Average duration of stenting: 29 d</p> <p>Chest tube thoracostomy:</p> <ul style="list-style-type: none"> - Alone: 23.3% (7/30) - Additional intervention: 76.7% (23/30) <p>Pleural decortication: 56.7% (17/30)</p> <p>Muscle-flap reinforcement: 36.7% (11/30)</p> <p>Average FU: 8.1 mo</p>	<p>Minor complications:</p> <ul style="list-style-type: none"> - pain: 6.7% (2/30) - hiccups: 3.3% (1/30) - nausea: 3.3% (1/30) <p>Major complications:</p> <ul style="list-style-type: none"> - bowel obstruction: 6.7% (2/30) - erosion: 3.3% (1/30) - left atrial compression: 3.3% (1/30) <p>Stent migration: 6.7% (2/30)</p> <ul style="list-style-type: none"> - not analyzed according to stent type <p>Mortality rate: 10% (3/30)</p> <ul style="list-style-type: none"> - multi-organ failure: 3.3% (1/30) - multiple emboli caused by esophago-atrial fistula: 3.3% (1/30) - aspiration during contrast study: 3.3% (1/30) 	<p>No. of removed stents missing</p> <p>Not analyzed according to stent type</p> <p>No subgroup analysis according to etiology</p>	<p>76.7% (23/30)</p> <p>No subgroup analysis according to etiology</p>

Eloubeidi <i>et al</i> ^[13] 2011	Pro- and retrospect	Patients with benign esophageal lesions treated with Alimaxx-E stent: <i>n</i> = 16 - postsurgical leaks: <i>n</i> = 11 - fistula: <i>n</i> = 1 - iatrogenic perforations: <i>n</i> = 3 - other: <i>n</i> = 1 Single stent: 81% (13/16) Multiple stents: 19% (3/16)	FC SEMS: 100% (16/16) In situ for: 51 ± 45 d (range 9-163)	Dilation: 6.3% (1/16) PEG placement: 6.3% (1/16) FU: unknown	Minor complications: 1 Stent infolding/invagination: 6.3% (1/16) 2 Chest pain: 6.3% (1/16) 3 Dysphagia: 6.3% (1/16) 4 Globus sensation: 6.3% (1/16) Major complications: 1 Respiratory compromise: 6.3% (1/16) 2 Aspiration pneumonia: 12.5% (2/16) Stent migration: 31.3% (5/16) Mortality rate: 0% (0/16) No complications associated with stent placement or removal Stent migration: 17.6% (3/17) - not analyzed according to stent type Mortality rate: 0% (0/17)	FC SEMS: 100% (16/16) One stent was retrieved in two pieces No subgroup analysis according to etiology
Freeman <i>et al</i> ^[14] 2011	Unknown	Hospitalized patients with an anastomotic leak after esophagectomy: <i>n</i> = 17 Single stent: 100% (17/17)	SEPS: 100% (14/14) FC SEMS: 100% (3/3) Mean time to removal: 17 (12-27) d	VATS pleural drainage: 29.4% (5/17) Pharyngostomy: 5.9% (1/17) Tube jejunostomy: 5.9% (1/17)	SEPS: 100% (14/14) FC SEMS: 100% (3/3)	94% (16/17)
Nguyen <i>et al</i> ^[15] 2011	Retrospect	Patients who developed postoperative leaks after minimally invasive esophagectomy: <i>n</i> = 18 - conventional treatment: <i>n</i> = 9 - FC SEMS placement: <i>n</i> = 9	FC SEMS: 100% (9/9) Removal after 6 wk	Percutaneous drainage: 22% (2/9) Tracheostomy: 11% (1/9) FU: unknown	No stent-related complications Mortality rate: 0% (0/9)	FC SEMS: 100% (9/9) 100% (9/9)
Schweigert <i>et al</i> ^[16] 2011	Retrospect	Single stent: 100% (9/9) Patients treated with stent placement for intrathoracic leak after esophagectomy: <i>n</i> = 12 Single stent: 100% (12/12)	PC SEMS: 100% (12/12) Median time to removal: 48 (16-99) d	Tube thoracostomy: 100% (12/12) FU: unknown	Major complications: 1 Death by hemorrhage from stent-related erosion into the aorta: 8.3% (1/12) 2 Stent-related fistula after removal: 8.3% (1/12) Stent migration: <i>n</i> = missing Mucosal hyperproliferation: <i>n</i> = missing Mortality rate: 16.7% (2/12) 1 Stent-related death by hemorrhage: 8.3% (1/12) 2 Pulmonary aspiration after stent removal and successful healing of the leak: 8.3% (1/12)	PC SEMS: 100% (10/10) 81.8% (9/11)
Swinnen <i>et al</i> ^[17] 2011	Retrospect	Patient treated with PC SEMS placement for benign upper GI leaks or perforations: <i>n</i> = 88 - postsurgical leaks: <i>n</i> = 65 - boerhaave syndrome: <i>n</i> = 4 - iatrogenic perforation: <i>n</i> = 14 - other perforations: <i>n</i> = 5	PC SEMS: 100% (153/153) Median time to removal for 33 PC SEMS: 23 d Median time to removal for 99 PC SEMS: 69 d	Drainage of collections: 47.7% (42/88) - Surgical: 26.1% (23/88) - Percutaneous: 15.9% (14/88) - Endoscopic: 5.7% (5/88)	Minor complications: - transient stent-related dysphagia: 11.4% (10/88) Major complications: - bleeding requiring intervention: 5.7% (5/88) - stent-related perforation: 1.1% (1/88)	PC SEMS: 24.4% (33/135) Stent-in-stent procedure: 73.3% (99/135) Removal during surgery: 2.2% (3/135) 77.6% (59/76) No subgroup analysis according to etiology

Single stent: 58% (51/88)
Multiple stents: 42% (37/88)

Follow-up after removal:
3 mo: 83%
7 mo: 81%
1 yr: 72%

- tracheal compression: 1.1% (1/88)
- dysphagia due to tissue hyperplasia: 18.2% (16/88); PC SEMS: 10.5% (16/153)
Stent migration: 11.1% (17/153) of PC SEMS mortality rate: 10.2% (9/88)
1 Sepsis related: 3.4% (3/88)
2 Pulmonary embolism: 1.1% (1/88)
3 Full-blown AIDS: 1.1% (1/88)
4 Cardiac disease: 1.1% (1/88)
Three additional deaths during first 3 mo after treatment:
1 Sepsis after surgery: 1.1% (1/88)
2 Tension pneumothorax: 1.1% (1/88)
3 Pneumonia: 1.1% (1/88)

FC SEMS: Fully covered self-expandable metal stent; FU: Follow-up; PC SEMS: Partially covered self-expandable metal stent; SEPS: Self-expandable plastic stent; VATS: Video-assisted thoracic surgery; PEG: Percutaneous endoscopic gastrostomy; OTSC: Over-the-scope-clips; IQR: Interquartile range.

Tissue hyperplasia was directly reported or deduced out of context (e.g., stent-in-stent procedure for removal) in 111 cases (28.9% of patients and 20.9% of stents). The rate of reactive tissue formation according to stent type was 0.4% (1/267) for FC SEMS, 50.5% (110/218) for PC SEMS and 0% (0/45) for SEPS.

Of the 812 stents that were inserted in 540 patients, food impaction was reported in 6 cases (1.1% of patients and 0.7% of stents). Data were insufficient to analyze food impaction according to type of stent.

Adverse events and mortality: Two studies including 44 patients and 88 stent placements could not be analyzed because of missing subgroup analyses for patients with benign esophageal leaks^[30,41]. So adverse events were evaluated for 599 patients. Excluding stent migration, reactive tissue formation and food impaction, which were analyzed separately, 80 (13.4%) patients suffered a total of 82 complications due to stent placement. The overall pooled major and minor complication rate were 7.8% and 5.5%, respectively. Complication rates according to stent type are presented in Table 6.

Mortality during the course of stent therapy was reported in 10.0% of all patients with benign leaks, perforations and fistulae. Stent-related mortality was reported in three cases (0.5%). One was caused by severe bleeding in a patient treated with a FC SEMS who refused further interventions^[40]. In another case esophageal necrosis at the proximal end of a FC SEMS resulted in a fatal outcome^[37]. The third stent-related death was due to massive hemorrhage caused by erosion of a PC SEMS into the aorta^[46]. Other non-stent-related causes for mortality are summarized in Table 7.

Stent removal: The outcome of stent removal could be analyzed in 13 studies in which 555 of the 615 inserted stents were subsequently removed. The overall pooled successful removal rate was 78.7% (437/555). Causes of failure were stent embedding by granulation tissue requiring stent-in-stent procedures for removal ($n = 104$, 18.7%), surgical removal ($n = 5$, 0.9%), esophageal ruptures ($n = 2$, 0.4%), irremovable stent ($n = 2$, 0.4%), self-limiting bleedings ($n = 2$, 0.4%), traumatic removal due to tissue ingrowth ($n = 2$, 0.4%) and additional endoscopic procedures ($n = 1$, 0.2%). When uneventful stent-in-stent procedures were considered as successful removals, the overall successful stent removal rate increased up to 97.5% (541/555). Stent removal outcome could be analyzed for 187 FC SEMS of which 84% (158/187) were removed after a median period of 5 to 7 wk. FC SEMS removal was successful in 98.4% (184/187) of procedures, including one fractured stent that was retrieved in two pieces. There were two cases of a self-limiting bleeding and one migrated FC SEMS required surgical removal. The majority of PC SEMS (73%, 109/149) were removed after a median period of 7 to 10 wk. One study accounted for 91% (135/149) of the PC SEMS removals^[47]. Successful endoscopic removal of PC SEMS was achieved in 29.5% (44/149) of cases and in 96.6% (144/149) after stent-in-stent procedures. Three PC SEMS were removed during surgery and two removals were traumatic due to tissue ingrowth. The two cases of esophageal rupture also occurred during the removal of PC SEMS, but could not be included

Table 5 Pooled analysis of 643 patients with benign esophageal leaks, perforations and fistulae treated with self-expandable stent placement

Etiology	
Postsurgical leaks	415 (64.5)
Iatrogenic perforations	126 (19.6)
Boerhaave's syndrome	50 (7.8)
Fistulae	24 (3.7)
Others/not specified	28 (4.4)
Stent type of 852 stents used in 573 patients ¹	
FC SEMS	349 (41.0)
PC SEMS	321 (37.7)
SEPS	60 (7.0)
Stent type unknown	122 (14.3)
Technical success	
Overall	851 (99.9)
FC SEMS	349 (100)
PC SEMS	320 (99.7)
SEPS	60 (100)
Stent type unknown	122 (100)
No. of stents per patient	
Single stent placement	357 (55.5)
Multiple stents inserted	131 (20.4)
Unknown	155 (24.1)
Clinical success	
Overall (<i>n</i> = 625)	480 (76.8)
According to etiology (<i>n</i> = 358)	
Postsurgical leaks (<i>n</i> = 247)	201 (81.4)
Perforations ² (<i>n</i> = 86)	74 (86.0)
Fistulae (<i>n</i> = 17)	11 (64.7)
Others/not specified (<i>n</i> = 8)	6 (75.0)

¹In two studies including 70 patients the total number of stents used was not reported; ²Including iatrogenic and spontaneous perforations. FC SEMS: Fully covered self-expandable metal stent; PC SEMS: Partially covered self-expandable metal stent; SEPS: Self-expandable plastic stent.

in the pooled analysis because the overall number of removed PC SEMS was not reported^[40]. The ruptures were successfully treated with another stent. The outcome of SEPS removal could be extracted from one study and was successful in 100% (14/14) of cases after a mean stent time of 17 d^[44].

DISCUSSION

This pooled analysis of the literature showed that the overall clinical success rate of self-expandable stent placement was 24.2% for refractory benign esophageal strictures and 76.8% for benign esophageal leaks, perforations and fistulae. With regard to refractory benign strictures, the meta-analysis by Thomas *et al*^[7] found sustained improvement of dysphagia in 46.2% of patients treated with self-expandable stents, which is almost twice as high as the clinical success rate (24.2%) in this pooled analysis. Also the systematic review by Repici *et al*^[48] reported a much higher clinical success rate of 52% after SEPS placement for benign esophageal strictures. The difference in clinical success between our pooled analysis and the aforementioned systematic reviews may be explained by the etiology and the severity of the strictures. The study population of Thomas *et al*^[7] mainly

included corrosive (43%), postsurgical (25%) and radiation (11%) strictures. The etiologies of the patients in the systematic review on SEPS treatment mainly included postsurgical (38%), corrosive (25%) and radiation (15%) strictures^[48]. In our analysis, peptic strictures accounted for 25.0% of patients, while corrosive strictures represented only 12.5%. However, the literature data were insufficient to analyze the clinical outcomes of stent placement according to stricture etiology. With regard to the severity of the strictures, Thomas *et al*^[7] included three studies, that accounted for 50% of weight in the meta-analysis, in which patients had a history of two or less dilatations before stent placement. The review by Repici *et al*^[48] did not provide details on the number of previous dilatations, but included mainly retrospective studies with heterogeneous definitions of refractory or recurrent strictures. We think that the more homogeneous population included in this analysis of prospective studies, that fulfilled Kochman's criteria^[8], had more severe strictures and therefore a poorer outcome of stent therapy. Thomas *et al*^[7] reported a significantly higher clinical success rate for Polyflex stents (55.3%) compared with nitinol stents (36.7%). Our results also showed a lower clinical success rate with the use of FC SEMS (14.1%) compared with SEPS (27.1%) and BD stents (32.9%). We do not have a good explanation for this finding. Complication, stent migration and tissue response rates were not significantly higher with the use of FC SEMS.

Safety analyses in patients treated with self-expandable stents for refractory benign strictures showed an overall complication rate of 31.0%, including a major complication rate of 17.7%. That complications are frequent during the course of stent therapy has also been demonstrated by several retrospective studies that were not included in our analyses^[49-53]. The major complication rate of BD stents (28.6%) was twice as high as those of SEPS (14.3%) and FC SEMS (10.6%), because they caused more retrosternal pain, hyperplasia-induced stenoses and bleedings. Severe retrosternal pain occurred in 13.0% of patients who received a BD stent. Pain after stent placement has been postulated to be caused by the radial force of the stent against the tight stricture and is mainly reported within the first week after stent placement^[9,11,15,49,53]. However, *in vitro* analysis of the radial and axial forces of 23 esophageal stent models showed that BD stents had a relatively low radial force and high axial force^[54]. Therefore, it is more likely that because of the rigid stent design BD stents interact less well with the peristalsis of the esophagus causing more spasm and pain. In this analysis clinically relevant hyperplastic tissue growth was reported in 7.8% of BD stents. Two case series not included in this review also showed that reactive tissue formation is common after BD stent placement (Figure 3)^[17,55]. The occurrence of tissue growth may be explained as a reaction to the chemical processes of degradation,

Table 6 Pooled analysis of adverse events in patients with benign esophageal leaks, perforations and fistulae

Total number of patients analyzed: <i>n</i> = 599	No. of patients (<i>n</i> = 599)	No. of FC SEMS (<i>n</i> = 295)	No. of PC SEMS (<i>n</i> = 302)	No. of SEPS (<i>n</i> = 75) ¹	Stent type unknown (<i>n</i> = 162) ²
Overall complications	80 ³ (13.4)	26 (8.8)	38 (12.6)	1 (1.3)	17 (10.5)
Overall major complications	47 ³ (7.8)	11 (3.7)	28 (9.3)	1 (1.3)	8 (4.9)
Hyperplasia-induced stenosis	16 (2.7)	0	16	0	0
Hemorrhage ⁴	8 (1.3)	2 ⁴	6	0	0
Stent-related perforation	6 (1.0)	4	1	0	1
Aspiration pneumonia	4 (0.7)	2	0	0	2
Respiratory compromise/ tracheal compression	2 (0.3)	1	1	0	0
Severe retrosternal pain	2 (0.3)	0	2	0	0
Bowel obstruction	2 (0.3)	0	0	0	2
Erosion ⁴	2 (0.3)	0	1 ⁴	0	1
Hemorrhage from aorta-esophageal fistula	1 (0.2)	1	0	0	0
Stricture formation	1 (0.2)	0	0	0	1
Stent-related fistula	1 (0.2)	0	1	0	0
Stent dislocation and inability to place new stent requiring rethoracotomy	1 (0.2)	0	0	1	0
Left atrial compression	1 (0.2)	0	0	0	1
Death due to esophageal necrosis at proximal stent end	1 (0.2)	1	0	0	0
Overall minor complications	33 ³ (5.5)	15 (5.1)	10 (3.3)	0 (0)	9 (5.6)
Transient stent-related dysphagia	11 (1.8)	1	10	0	0
Stent-related ulcers	5 (0.8)	5	0	0	0
Reflux/esophagitis	3 (0.5)	0	0	0	3
Chest pain	3 (0.5)	1	0	0	2
Stent disintegration	3 (0.5)	3	0	0	0
Stent collapse/invagination	2 (0.3)	1	0	0	1
Pneumoperitoneum during endoscopy secondary to air insufflation	1 (0.2)	1	0	0	0
Atrial fibrillation related to sedation	1 (0.2)	1	0	0	0
Stent malposition	1 (0.2)	1	0	0	0
Abdominal pain	1 (0.2)	0	0	0	1
Nausea	1 (0.2)	0	0	0	1
Globus sensation	1 (0.2)	1	0	0	0
Hiccups	1 (0.2)	0	0	0	1

¹Including 30 patients in whom the number of SEPS used was not reported; ²Including 40 patients in whom the number of stents used was not reported; ³Patients can have more than one complication; ⁴Including one stent-related death. FC SEMS: Fully covered self-expandable metal stent; PC SEMS: Partially covered self-expandable metal stent; SEPS: Self-expandable plastic stent.

Table 7 Overall mortality in 643 patients treated with self-expandable stents for benign esophageal leaks, perforations and fistulae *n* (%)

Overall mortality	64 (10.0)
Stent-related	3 (0.5)
Sepsis-related	23 (3.6)
Multi-organ failure	5 (0.8)
Cerebral embolism/cerebrovascular accident	2 (0.3)
Heart insufficiency/cardiac disease	2 (0.3)
Pneumonia	2 (0.3)
Malignancy	2 (0.3)
Non stent-related bleeding	1 (0.2)
Respiratory insufficiency without sepsis	1 (0.2)
Pulmonary embolism	1 (0.2)
Acute respiratory distress syndrome	1 (0.2)
Pulmonary aspiration after healing of leak	1 (0.2)
Aortic dissection	1 (0.2)
Tension pneumothorax	1 (0.2)
Paraspinal abscess related to persistent fistula	1 (0.2)
Full-blown AIDS	1 (0.2)
Aspiration during contrast study	1 (0.2)
Multiple emboli caused by esophago-atrial fistula	1 (0.2)
Active euthanasia	1 (0.2)
Not specified	13 (2.0)

which may also trigger bleedings from the affected esophageal mucosa. So one should be aware that the higher efficacy of BD stent placement is attended by an increased risk of complications.

The clinical success rate (76.8%) of self-expandable stent placement for benign esophageal leaks, perforations and fistulae found in this pooled analysis is comparable with the 81% of the systematic review by Dasari *et al.*^[1] (Figure 4A and B). In contrast to our analysis, the latter review excluded patients with leaks from the gastric staple line after sleeve gastrectomy and did not analyze patients with fistulae. In our study clinical success according to etiology was 81.4% for postsurgical leaks, 86.0% for perforations and 64.7% for fistulae. Though derived from retrospective series, these results seem promising. Patients with esophageal leaks or ruptures are usually in poor condition with elevated septic parameters and require invasive management, like drainage procedures, surgery and ICU care. This is reflected by the increased mortality rate of 7.2%-25.8% after postsurgical esophageal leakage^[56-58]. Several treatment strategies have been described for the management



Figure 3 Endoscopic image of granulation tissue growth 4 mo after biodegradable stent placement for a refractory benign esophageal anastomotic stricture.

of esophageal leaks, such as endoscopic vacuum therapy, nose fistula tube drainage, surgical repair and conservative management^[59-61]. Retrospective comparison of 41 patients with an anastomotic leak after esophagectomy who were matched by clinical status, showed that endoscopic vacuum therapy resulted in a lower mortality rate (12%, 2/17) compared with surgical treatment (50%, 9/18) and stent placement (83%, 5/6) in systemically ill patients^[58]. Another retrospective study reported a significantly higher closure rate after endoscopic vacuum therapy (84%) compared with stent therapy (53.8%) in 71 patients with esophageal defects^[37]. However, one should keep in mind that success of stent placement depends on the size of the esophageal lesion, the delay between diagnosis and stent placement and if the patient has elevated septic parameters^[30,33,34,47]. Stent placement is most likely to fail in a large lesion (> 15 mm), that exists for several weeks in a septic patient. Therefore, patients with an esophageal leak should receive a multidisciplinary patient-tailored approach.

The removability of self-expandable stents was safe and feasible with an overall successful removal rate of 97.2% in patients with refractory strictures and 78.7% in patients with esophageal leaks. The fact that PC SEMS were used in 38% of patients with esophageal leaks resulted in a lower overall successful removal rate. PC SEMS removal was often complicated by stent embedding requiring stent-in-stent procedures to induce pressure-necrosis of the granulation tissue to facilitate the removal procedure. The vast majority of stent-in-stent procedures were reported in the study by Swinnen *et al.*^[47]. The removal of FC SEMS and SEPS removal was much safer with successful removal rates of 96.6% up to 98.4%. The relation between the use of PC SEMS and complicated stent removal has also been demonstrated by several large retrospective series^[62,63].

This pooled analysis of the literature has several limitations. The prospective data on the outcomes of stent placement for refractory benign esophageal strictures reflect a patient population with various

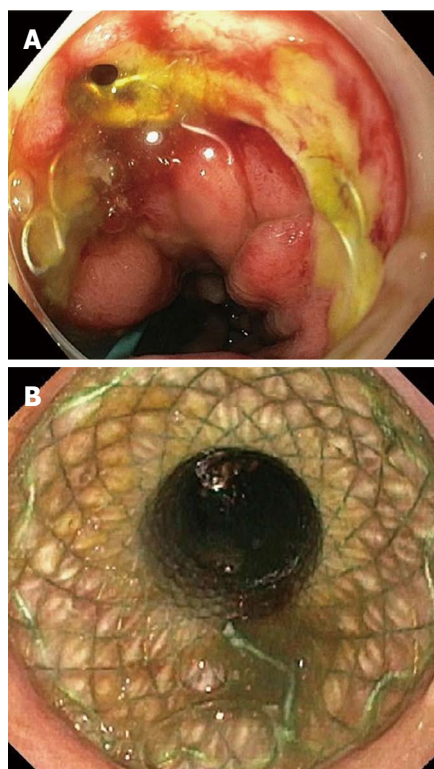


Figure 4 A small leak at the anastomosis of the esophagus and the gastric tube 5 d after esophagectomy (A) and esophageal fully covered self-expandable metal stent placement for a small anastomotic leak (B).

causes for stricture formation. Data were insufficient to provide analyses according to stricture etiology. The studies that were analyzed on the outcomes of esophageal stent placement for benign leaks, perforations and fistulae were all retrospective, causing heterogeneity and underreporting of adverse outcomes.

In conclusion, the outcomes of self-expandable stent placement for refractory benign esophageal strictures were poor with a clinical success rate of 24.4% and a major complication rate of 17.7%. However, randomized trials are needed to put these outcomes into perspective. Although derived from retrospective series, the evidence on stent placement for benign esophageal leaks, perforations and fistulae is promising with an overall clinical success rate of 76.8%.

COMMENTS

Background

Self-expandable stents in various types are increasingly being used for the treatment of refractory benign esophageal strictures and benign esophageal leaks, perforations and fistulae.

Research frontiers

It is hypothesized that esophageal stent placement for benign refractory strictures prolongs the dysphagia-free period compared with conventional dilatation therapy. Besides application for the treatment of strictures, esophageal stents are also used to seal leaks, perforations and fistulae.

Innovations and breakthroughs

The literature on esophageal stent placement for benign indications is heterogeneous and usually includes small samples. In this systematic review

we performed a pooled analysis on the treatment outcomes of 232 patients with refractory strictures and 643 patients with leaks, perforations and fistulae.

Applications

This pooled analysis may be helpful for the endoscopist in the decision-making on the indication for esophageal stent placement and also to inform the patient on the risks and benefits of stent therapy.

Terminology

Biodegradable stents are only used for strictures, because they have the property to dissolve. Nitinol metal stents (SEMS) have an outer membrane of silicone or polytetrafluoroethylene to prevent hyperplastic tissue ingrowth. Because they are covered, they are removable and can also be used to seal leaks. Partially covered SEMS usually become partially embedded by granulation tissue, which prevents stent migration, but makes them harder to remove. Self-expandable plastic stents consist of plastic instead of metal and are fully covered.

Peer-review

This review is well-written and comprehensive review about this subject.

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