EUnetHTA WP5 Joint Action 2 (2012-2015) Strand B, Rapid assessment of other health technologies such as medical devices, surgical interventions or diagnostics

Pilot rapid assessment of other health technologies using the HTA Core Model® for Rapid Relative Effectiveness Assessment

Biodegradable stents for the treatment of refractory or recurrent benign oesophageal stenosis

Pilot ID: SB-14

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Final Version

DOCUMENT HISTORY AND CONTRIBUTORS

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V 2.0	13/02/2015	Second draft including the first randomised controlled trial
V 3.0	13/03/2015	Third draft after revision from dedicated reviewers
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V 4.0	13/05/2015	Fourth draft after comments from external clinical experts, WP5 strand B members and the manufacturer

This assessment was produced by experts from the institutions listed below, and was reviewed by members of Work Package 5 (WP5) Joint Action 2 of the EUnetHTA network; the whole process was coordinated by the Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA).

Disclaimer

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Conflict of interest

All authors and reviewers involved in the production of this pilot assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA conflicts of interest statement form.

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Table of contents

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LIST OF TABLES

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SUMMARY OF RELATIVE EFFECTIVENESS OF BIODEGRADABLE OESOPHAGEAL STENTS

Scope

Description	Project scope
Population	Indication: • Refractory or recurrent benign oesophageal stenosis (RRBOS) Contraindications: • Inability to pass the 9.4 mm (28 F) delivery system through the stenosis • Benign stenosis in the upper part of the oesophagus too close to the cricopharyngeal muscle • Benign stenosis due to previously performed laryngectomy
Intervention	Oesophageal biodegradable stent (OBS) SX-ELLA Stent Esophageal Degradable BD is currently the only identified oesophageal biodegradable stent having CE (Conformité Européenne) mark (CE-1014), which was provided by ELEKTROTECHNICKY ZU in 2007. The stent has been designed for oesophageal stenosis, made of polydioxanone, and is available in several sizes.
Comparison	Comparators: • Self-expanding metal stents (SEMS) • Self-expanding plastic stents (SEPS) • Oesophageal dilation (balloon dilation, bougie dilation)
Outcomes	Primary effectiveness outcomes: • Reduction in dysphagia after intervention • Number of dilations per patient after intervention • Dysphagia-free patients after intervention Secondary effectiveness outcomes: • Time to recurrent dysphagia after intervention • Oesophageal lumen patency after intervention • Reduction of pain after intervention • Mortality (overall and disease-related mortality) • Health-related quality of life • Time to re-intervention • Patient satisfaction Safety outcomes: • Technical failure • Adverse events • Serious adverse events • Intervention-associated adverse events • Unexpected re-interventions • Procedure-related mortality
Study design	Effectiveness domain: comparative studies Safety domain: non-comparative studies were included with the following exclusions: • Studies with less than 10 patients • Retrospective case series with non-consecutive enrolment • Studies with less than 6 weeks of follow-up • Congress Abstracts
Languages	Articles written in the following languages were included: English, French, German, Italian, Portuguese, Spanish and Turkish.

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Introduction

Health problem

Benign oesophageal stenosis (BOS) is a condition in which the normal oesophageal lumen is constricted and the normal passage of swallowed food from the upper oesophagus to the stomach is impeded (**A0002**). BOS can be caused by a wide range of disorders such as peptic stenoses as a consequence to gastroesophageal reflux disease, eosinophilic oesophagitis, caustic injuries, medication-induced stenoses, radiation-induced stenoses, postendoscopy-induced stenoses, congenital anomalies, Schatzki ring, oesophageal web, or motility disorders such as achalasia (**A0003**).

The definition of RRBOS is not standardised. However, the most frequently used definition is that proposed by Kochman and adopted by the American Society for Gastrointestinal Endoscopy (ASGE) [1,2]. According to this definition, RRBOS is an anatomical restriction of the oesophageal lumen that results in the clinical symptoms of dysphagia in the absence of endoscopic evidence of inflammation, after the inability to either:

- Successfully dilate the stenosis to a diameter of 14 mm over 5 sessions at 2-weekly intervals (refractory) or
- Maintain a satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm has been achieved (recurrent) (**A0002**).

Oesophageal dysphagia is usually graded using the Mellow score [3]. The score is self-reported by the patient and ranges from 0 to 4:

- 0 – indicates no dysphagia
- 1 – dysphagia to normal solids
- 2 – dysphagia to soft solids
- 3 – dysphagia to solids and liquids
- 4 – complete dysphagia (inability to swallow saliva).

The available information about epidemiology and burden of BOS is fragmented and scarce (**A0005**). Dysphagia is the main symptom of BOS; in severe cases BOS can lead to progressive dysphagia, malnutrition and respiratory problems such as aspiration pneumonia. BOS-related mortality is uncommon (**A0004**).

Description of technology

Oesophageal dilation is the primary therapy for management of dysphagia related to BOS. Some patients achieve satisfactory results without further intervention but others may need repeated courses of dilation over many years (**A0025**). The use of stents is an alternative for patients with refractory or recurrent dysphagia despite repeated dilations.

The stents available for the treatment of RRBOS are SEMS, SEPS and more recently oesophageal biodegradable stents (OBS) (**B0001**).

SEMS were the first type of stents used to treat RRBOS. They are usually made of nitinol or stainless steel. SEMS were initially developed without a covering, but a variety of coverings and modifications of stent designs have been introduced in the last years in order to prevent embedding of stent mesh in the mucosa. There are several covered SEMS on the market. They can be partially or fully covered self-expanding metal stents (FCSEMS). Polyurethane, polyethylene, and silicone are used as coatings for SEMS (**B0001**).

Besides, SEPS have a woven polyester skeleton and are completely covered with a silicone membrane. The only available SEPS is Polyflex™, Boston Scientific, which is made of polyester netting embedded in a silicone membrane.

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In Europe, SEPS and fully covered SEMS are indicated both for the treatment of benign and malignant refractory oesophageal stenoses; however, uncovered and partially covered SEMS are not approved for benign stenosis, only for malignant stenosis [4] (**B0002**).

OBS are medical devices made of biodegradable materials that are indicated to treat RRBOS. SX-ELLA Stent Esophageal Degradable BD is the only CE marked OBS and received European market authorisation in 2007 (**A0020**). The stent is manufactured from woven polydioxanone monofilament, which degrades by random hydrolysis accelerated by a low ambient pH. Stent integrity and radial force are maintained for 6-8 weeks following deployment and its disintegration usually occurs by 11-12 weeks postdeployment. The degradation products are harmless; the stent material is partly absorbed and partly excreted through the bowel (**B0001**).

Methods

A systematic literature search in the following databases was used for compiling the 'Safety' and 'Clinical Effectiveness' domains (without restriction on publication date): PubMed®, Embase™, Cochrane Library and the Centre for Reviews and Dissemination (CRD) databases. The selection of assessment elements was primarily based on the *HTA Core Model for Rapid REA of Pharmaceuticals* (2.0). Furthermore, the rest of *EUnetHTA HTA Core Model Applications* were screened and finally 2 additional assessment elements of the EUnetHTA Core Model Applications for medical and surgical interventions were included (**D0010**, **D0023**).

Selection of relevant documents was done by 2 independent researchers in the following languages: English, French, German, Italian, Portuguese, Spanish and Turkish. In terms of study design, only comparative studies were included for analysing 'Clinical Effectiveness'. For the 'Safety' domain, non-comparative studies were also included but the following were excluded: studies with less than 10 patients, retrospective case series with non-consecutive enrolment, studies with less than 6 weeks of follow-up, and congress abstracts.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the quality of the evidence for effectiveness and safety: The quality of the evidence was classified and defined as high (i.e. "Further research is very unlikely to change our confidence in the estimate of effect"); moderate (i.e. "Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate"); low (i.e. "Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate"); very low (i.e. "Any estimate of effect is very uncertain").

The methodological quality of the studies was assessed using the Cochrane risk of bias tool for randomised controlled trials (RCT), the Newcastle-Ottawa scale for cohort studies and the Institute for Health Economics checklist for case series.

A hand search and a basic search in PubMed® and Google were performed for the domains 'Health problem and Current Use' and 'Description and Technical Characteristics'. A survey to seek for reimbursement status information in Europe was sent to EUnetHTA partners.

Results

Available evidence

Three comparative studies were included for the clinical effectiveness assessment:

- An RCT that compared 9 patients treated with OBS with 6 patients treated with endoscopic balloon dilation [5]
- A multicentre prospective cohort study that compared 3 cohorts of 10 patients treated with OBS, SEPS and FCSEMS [6]
- A unicentre prospective cohort study comparing 18 patients treated with OBS and 20 treated with SEPS [7].

Their inclusion criteria differed in terms of the definition used for RRBOS. A cohort study adopted

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the RRBOS definition established by the ASGE, requiring at least 5 dilations to consider a stenosis as refractory [6]. The other cohort study required repeated dilations every 2–4 weeks [7]. The inclusion criteria of the RCT were the least strict ones. The RCT included patients with only 1 previous dilation and others whose last dilation was performed more than a year before the intervention.

The quality of the evidence was rated as very low for all studies and all assessed outcomes. The 3 studies were affected by imprecision because of the small sample size but also by serious risk of bias. The RCT did not offer enough guarantees of comparability between groups, was not blinded to the participants and study personnel and did not properly describe the inclusion and exclusion criteria.

The cohort studies were affected by limitations related to the comparability between groups: use of historical controls, lack of control of confounding factors, and different follow-up between groups.

For assessing safety, 2 case series were additionally included [58,59].

Clinical effectiveness

- *OBS vs oesophageal dilation:*

The available evidence came from 1 very small RCT, was of very low quality and not clearly focused on the intended indication for OBS [5].

No deaths were reported in the study (**D0001**, **D0002**, **D0003**).

The RCT did not analyse dysphagia score changes before vs after the intervention, so the outcome 'reduction in dysphagia' could not be determined. The RCT analysed dysphagia scores at specific points in time. At baseline, no difference was observed between the groups. After the intervention, the dysphagia score was significantly higher for the OBS group than for the dilation group. After 3-12 months of follow-up, the mean score was of 1.21 (1.08 SD) in the OBS group and of 0 ± 0 in the dilation group ($p = 0.016$). However, reasons other than the intervention could explain these results because the study did not demonstrate that the groups were really similar in aetiology, clinical severity or comorbidities (**D0005**, **D0011**).

The RCT did not analyse health-related quality of life changes before vs after the intervention. The health-related quality of life was measured using EuroQol 5 dimensions (EQ5D) but at specifics points in time (baseline, 6 months and 12 months after the intervention). No statistically significant differences were found in quality of life comparing OBS vs dilation after 6 or 12 months of follow-up (**D0012** , **D0013**).

The following were not reported: number of dysphagia-free patients, time to recurrent dysphagia, time to re-intervention, oesophageal lumen patency, reduction of pain and patient satisfaction (**D0005**, **D0011**).

Additional balloon dilations after intervention were measured but no statistically significant differences were found between groups (**D0023**).

- *OBS vs SEPS:*

The available evidence derived from 2 cohort studies was of very low quality [6,7].

No deaths were reported in both studies (**D0001**, **D0002**, **D0003**).

The dysphagia recurrence risk was analysed in one study [6] and was 34% higher for the SEPS group than for the OBS group, but with a high amount of variance (Confidence interval (CI) 95%: 0.50-3.58) (**D0005**, **D0011**).

The studies did not analyse dysphagia score changes before vs after the intervention, so the outcome 'reduction in dysphagia' could not be determined. At baseline, no difference in dysphagia was observed between the groups. Four weeks after the intervention, the statistical difference in dysphagia score between groups was analysed only in one study, which found no statistically significant differences.

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Number of dysphagia-free patients was measured but no statistically significant differences were found between the groups (**D0005**, **D0011**).

The following were not reported: number of dilations after intervention, time to re-intervention, oesophageal lumen patency after intervention, health-related quality of life, reduction of pain and patient satisfaction (**D0023**, **D0012** , **D0013**, **D0017**).

- *OBS vs FCSEMS:*

The available evidence derived from 1 cohort study was of very low quality [6].

There was no information regarding deaths in the study (**D0001**, **D0002**, **D0003**).

The dysphagia recurrence risk was 15% higher for the OBS group than for the FCSEMS group, but with a high amount of variance (CI 95%: 0.39-3.41) (**D0005**, **D0011**).

The study did not analyse dysphagia score changes before vs after the intervention, so the outcome 'reduction in dysphagia' could not be determined. At baseline, no difference was observed between the groups. After follow-up the dysphagia score was not significantly different between OBS and FCSEMS.

Number of dysphagia-free patients were measured but no statistically significant differences were found between the groups (**D0005**, **D0011**).

The following were not reported: number of dilations after intervention, time to re-intervention, oesophageal lumen patency after intervention, health-related quality of life, reduction of pain and patient satisfaction (**D0023**, **D0012** , **D0013**, **D0017**).

Safety

Five studies with a total of 86 patients treated with OBS were analysed: 1 RCT [5], 2 cohort studies [6,7] and 2 case series [58,59]. In 2 of the 5 studies, the total number of patients with adverse events was stated. The proportion of patients with adverse events in these studies ranged from 33.3% [59] to 50.0% [6]. The most frequent adverse events in patients treated with OBS were the following: severe pain; severe dysphagia, tissue hyperplasia, stent migration, moderate pain and moderate dysphagia.

- *OBS vs oesophageal dilation:*

The available evidence came from 1 very small RCT, was of very low quality and not clearly focused on the intended indication for OBS [5].

No cases of technical failure were reported either in the OBS or the dilation group.

The mean number of adverse events per patient was 4.9 in the OBS group and 1.0 in the dilation group. The difference was statistically significant.

The mean number of serious adverse events per patient was 1.8 in the OBS group and 0 in the dilation group. The difference was statistically significant.

The number of unexpected re-interventions was measured but no statistically significant difference was found between the groups.

No cases of procedure-related mortality were reported either in the OBS or the dilation group (**C0008**).

- *OBS vs SEPS:*

The available evidence derived from 2 cohort studies was of very low quality [6,7].

Technical failure, adverse events, serious adverse events and the number of unexpected reinterventions were measured but no statistically significant differences were found between the groups.

No cases of procedure-related mortality were reported either in the OBS or in the dilation group (**C0008**).

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- *OBS vs FCSEMS:*

The available evidence derived from a cohort study was of very low quality [6].

No cases of technical failure were reported either in the OBS or the FCSEMS group.

Total adverse events and serious adverse events were measured but no statistically significant differences were found between the groups.

The mean number of unexpected re-interventions was the same in the OBS and the FCSEMS group: 1.3 per patient.

No cases of procedure-related mortality were reported either in the OBS or the dilation group (**C0008**).

Upcoming evidence

One ongoing RCT was identified (see *Table 8*). The trial compares OBS with oesophageal dilations. The final data collection was scheduled for January 2015.

Reimbursement

SX-ELLA Stent Esophageal Degradable BD™ (BD STENT) is currently the only OBS authorised for marketing in Europe. Some European countries currently reimburse OBS for the treatment of RRBOS, but others not. Other countries apply conditional coverage or cost limitations. In Spain, the technology is under evaluation for inclusion in the list of reimbursed services of the 'Common Health Care Services Portfolio of the Spanish Healthcare System' (see *Table 2*).

Discussion

Despite the fact that OBS has been authorised in Europe since 2007 for the treatment of RRBOS, there is insufficient evidence on its safety and clinical effectiveness. The currently available evidence on clinical effectiveness comes from 3 very low quality studies with very small sample sizes that compare OBS with dilation, SEPS and FCSEMS.

Different inclusion criteria for RRBOS were used in the studies. The RCT is affected by serious imprecision because of the small sample size, lack of comparability between groups, off-label patient inclusion, and ambiguities in the text. The cohort studies are affected by serious imprecision, but also by other limitations related to comparability between groups: use of historical controls, lack of control of confounding factors, and different follow-up between groups.

Although the available information is insufficient to accurately estimate the frequency of adverse events, non-negligible adverse events were reported related to the use of OBS.

The publication of the results of a second RCT comparing OBS vs dilation in recurrent BOS could provide higher quality evidence. The data collection was scheduled to finish in January 2015.

Conclusion

There is insufficient evidence to determine the safety and clinical effectiveness of SX-ELLA Stent Esophageal Degradable BD to treat RRBOS in comparison with other similar technologies. Despite the lack of evidence to date, the device is available and in clinical use in some European countries.

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Table 1: Summary table of relative effectiveness of oesophageal biodegradable stents for refractory or recurrent benign oesophageal stenosis

Refractory or Recurrent Benign Oesophageal Stenosis						
	Health benefit				Harms	
Outcomes	**Dysphagia score after intervention (score 0-4)**	**Risk of dysphagia recurrence (HR; CI 95%)**	**Dysphagia-free patients, n (%)**	**Number of dilations after intervention**	**Total AEs (mean per patient)**	**Serious AEs in n (%)**
Assessment elements	**D0005; D0011**	**D0005; D0011**	**D0005; D0011**	**D0010; D0023**	**C0001**	**C0001**
OBS vs dilation **Dhar 2014** [5]	At 3-6 m: 1.17 vs 0.0 (p = 0.004) At 3-12 m: 1.21 vs 0.0 (p = 0.016)	N/A	N/A	At 12 m (mean per patient): 1.38 vs 0.40 (p = 0.385)	4.9 vs 1.0 (p = 0.001)	1.8 vs 0 (p = 0.026)
Quality of evidence	*Very low*	-	-	*Very low*	*Very low*	*Very low*
OBS vs SEPS **Canena 2012** [6]	Means at 4 w: 0.4 vs 0.7 (p = N/A)	1.34 (0.50-3.58) higher for SEPS	3 (30) vs 1 (10) (p = 0.58)	N/A	0.7 vs 0.9 (p = N/A)	0.2 vs 0 (p = N/A)
Van Boeckel 2011 [7]	Medians at 4 w: 0.0 vs 0.0 (p = 0.91)	N/A	6 (33) vs 6 (30) (p = 0.83)	N/A	0.8 vs 0.4 (p = N/A)	0.2 vs 0.1 (p = 0.3)
Quality of evidence	*Very low*	*Very low*	*Very low*	-	*Very low*	*Very low*
OBS vs FCSEMS **Canena 2012** [6]	At 4 w: 0.4 vs 0.5 (p = N/A) At 10-18.5 m: 2.0 vs 1.6 (p = N/A)	1.15 (0.39-3.41) higher for OBS	3 (30) vs 4 (40) (p = 0.64)	N/A	0.7 vs 0.6 (p = N/A)	0.2 vs 0 (p = N/A)
Quality of evidence	*Very low*	*Very low*	*Very low*	-	*Very low*	*Very low*

Abbreviations: AE = adverse event; CI = Confidence interval; FCSEMS = Fully-covered self-expanding metal stent; HR = Hazard ratio; m = months; N/A = Not available; OBS = Oesophageal biodegradable stent; SEPS = Self-expanding plastic stent; w = weeks.

Quality of body of evidence according to GRADE-methodology was classified as follows: high (i.e. "Further research is very unlikely to change our confidence in the estimate of effect"); moderate (i.e. "Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate"); low (i.e. "Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate"); very low (i.e. "Any estimate of effect is very uncertain").

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LIST OF ABBREVIATIONS

AE	Adverse Event
ASGE	The American Society for Gastrointestinal Endoscopy
BOS	Benign Oesophageal Stenosis
CE	Conformité Européenne
CI	Confidence Interval
CPT	Current Procedural Terminology
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
EQ5D	EuroQol 5 Dimensions
EQVAS	EuroQol Visual Analogue Scale
EUnetHTA	European Network for Health Technology Assessment
FCSEMS	Fully-Covered Self-Expanding Metal Stent
FDA	Food and Drug Administration
GIQLI	Gastrointestinal Quality of Life Index
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	Haute Autorité de Santé
HR	Hazard Ratio
HTA	Health Technology Assessment
ICD	International Classification of Diseases
IQWIG	Institute for Quality and Efficiency in Health Care
ISCIII	Instituto de Salud Carlos III – “Carlos III” Institute for Health, Spain
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment
MeSH	Medical Subject Headings
NHS-EED	National Health Service Economic Evaluation Database
OBS	Oesophageal Biodegradable Stent
PICOS	Population Intervention Control Outcome Study
RCT	Randomised Controlled Trial
REA	Relative Effectiveness Assessment
RRBOS	Refractory or Recurrent Benign Oesophageal Stenosis
SAGEM	General Directorate of Health Research – Ministry of Health, Turkey
SEMS	Self-Expanding Metal Stent
SEPS	Self-Expanding Plastic Stent
VASPVT	State Health Care Accreditation Agency, Lithuania
WP5	Work Package 5

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1. SCOPE

Description	Project scope
Population	Indication: • Refractory or recurrent benign oesophageal stenosis (RRBOS) Contraindications: • Inability to pass the 9.4 mm (28 F) delivery system through the stenosis • Benign stenosis in the upper part of the oesophagus too close to the cricopharyngeal muscle • Benign stenosis due to previously performed laryngectomy. Rationale: Benign oesophageal stenosis (BOS) can be caused by a wide range of factors/disorders such as the following: acid peptic, autoimmune, infectious, caustic, congenital, iatrogenic, medication-induced, radiation-induced and achalasia. Refractory and recurrent oesophageal stenosis can be defined as an anatomical restriction of the oesophageal lumen that results in the clinical symptom of dysphagia in the absence of endoscopic evidence of inflammation, after either inability to successfully dilate the stenosis to a diameter of 14 mm over 5 sessions at 2-weekly intervals (refractory) or after the inability to maintain satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm has been achieved (recurrent) [1,2]. Oesophageal stenoses due to malignant processes are not included among the indications of the CE mark for SX-ELLA Esophageal Stent, which is the only identified biodegradable stent having a CE mark. International Classification of Diseases (ICD)-10 codes: oesophagus obstruction (K22.2), achalasia of cardia (K22.0), dyskinesia of oesophagus (K22.4) Medical Subject Headings (MeSH) terms: Oesophageal Stenosis; Oesophageal Achalasia; Constriction, Pathologic; Oesophageal Spasm, Diffuse Intended use of the technology: Treatment
Intervention	Oesophageal biodegradable stent (OBS). SX-ELLA Stent Esophageal Degradable BD is currently the only identified oesophageal biodegradable stent having a CE mark (CE-1014), which was provided by ELEKTROTECHNICKY ZU in 2007. The stent has been designed for oesophageal stenosis and is available in several sizes. OBS are placed in the oesophageal tract to maintain lumen patency. OBS integrity and radial force should be maintained for 6–8 weeks following implantation. The stent has a dual ‘flared ends’ design in order to reduce migration rates. The stent is made of polydioxanone, which is a degradable polymer. Insertion is by means of endoscopic and/or fluoroscopic guidance. First, a guidewire is passed through the stricture and dilation is performed to allow passage of the stent delivery apparatus. The stent is then deployed. The stent has radiopaque markers at both ends in order to warrant an accurate stent positioning. Sometimes, proton-pump inhibitors are prescribed to avoid rapid stent degradation. MeSH-terms: Stents; Bioprosthesis; Absorbable Implants; Dilatation; Prosthesis Implantation; Prosthesis Failure; Device Removal
Comparison	Comparators: • Self-expanding metal stents (SEMS) • Self-expanding plastic stents (SEPS) • Oesophageal dilation (balloon dilation, bougie dilation). Rationale: BOS is initially treated by endoscopic dilation using push or balloons dilators. Temporary SEMS and SEPS placement was suggested as a treatment for RRBOS to prolong the dilatory effect [8]. OBS could have advantages over the above-mentioned treatments because of a potential reduction in adverse events, complications and number of interventions.
Outcomes	Primary effectiveness outcomes: • Reduction in dysphagia after intervention • Number of dilations per patient after intervention • Dysphagia-free patients after intervention.

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Description	Project scope
	Secondary effectiveness outcomes: • Time to recurrent dysphagia after intervention • Oesophageal lumen patency after intervention • Reduction of pain after intervention • Mortality (overall and disease-related mortality) • Health-related quality of life • Time to re-intervention • Patient satisfaction. Safety outcomes: • Technical failure • Adverse events • Serious adverse events • Intervention-associated adverse events • Unexpected re-interventions • Procedure-related mortality.
Study design	Effectiveness domain: comparative studies Safety domain: non-comparative studies were included with the following exclusions: • Studies with less than 10 patients • Retrospective case series with non-consecutive enrolment • Studies with less than 6 weeks of follow-up • Congress Abstracts.
Languages	Articles written in the following languages were included: English, French, German, Italian, Portuguese, Spanish and Turkish.

Deviations from project plan

In the 4th version of the project plan (13 June 2014), the assessment phase was planned between 16 June 2014 and 27 November 2014. However, on 03 September 2014, the pilot team decided to suspend the pilot because of the ongoing publication of the first Randomised Controlled Trial (RCT) on OBS. This RCT was published on 28 December 2014, and then the pilot was restarted on 06 January 2015.

The outcomes of the scope have been reworded and reorganised as shown in the table above. In the 4th version of the project plan (13 June 2014), the endpoints chosen were:

Primary effectiveness outcomes:

- *Incidence of dilations per patient before and after intervention*
- *Number of patients stricture-free or remaining dysphagia after stent degradation.*

Secondary effectiveness outcomes:

- *Time to recurrent significant dysphagia*
- *Time to dilation of recurrent stricture*
- *Oesophageal lumen patency before stent placement and after stent degradation*
- *Reduction in symptoms related with disease: dysphagia score, reduction of pain*
- *Mortality*
- *Health-related quality of life*
- *Time to re-intervention (dilation, because of stent migration, because of disease worsening, other surgical or endoscopic interventions).*

Safety outcomes:

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- *Adverse events and serious adverse events during follow-up*
- *Adverse events related with the stent placement (during and after implantation)*
- *Unexpected interventions because of the stent (removals, re-interventions).*

Since the available evidence did not clearly distinguish between adverse events that were associated with the intervention and those that were not associated, the outcome 'intervention-associated adverse events' has not been specifically analysed in the assessment.

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2. HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

2.1 Methods

Domain framing

No deviation from the general scope of the project was required.

Research questions

Element ID	Research question	Topic	Importance 3 = critical 2 = important 1 = optional
A0001	For which health conditions and populations, and for what purposes, are biodegradable oesophageal stents used?	Utilisation	2
A0002	What is refractory or recurrent benign oesophageal stenosis?	Target condition	3
A0003	What are the known risk factors for refractory or recurrent benign oesophageal stenosis?	Target condition	2
A0004	What is the natural course of refractory or recurrent benign oesophageal stenosis?	Target condition	3
A0005	What is the burden of refractory or recurrent benign oesophageal stenosis for the patient in terms of mortality, morbidity and quality of life measures?	Target condition	3
A0007	What is the target population for biodegradable oesophageal stents?	Target population	3
A0011	How much are biodegradable oesophageal stents utilised?	Utilisation	1
A0024	How is refractory or recurrent benign oesophageal stenosis currently diagnosed according to published guidelines and in practice?	Current management	2
A0025	How is refractory or recurrent benign oesophageal stenosis currently managed according to published guidelines and in practice?	Current management	2

Sources

A basic search was performed in PubMed® and Google. A hand search was carried out in text-books. Reference lists were also searched. An assessment element specific search was performed for answering questions about risk factors, natural course and burden of disease.

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2.2 Results

Overview of the disease or health condition

A0002 – *What is refractory or recurrent benign oesophageal stenosis?*

Both stricture and stenosis are defined as conditions where an anatomical structure is constricted beyond normal dimensions. BOS constricts the normal oesophageal lumen and impedes the passage of swallowed food from the upper oesophagus to the stomach. The main pathophysiological process is a severe or long-standing oesophageal mucosal or submucosal inflammation leading to cicatricial (fibrotic) tissue formation. Stricture of the oesophagus has been defined as “an anatomic restriction because of cicatricial luminal compromise or fibrosis that results in the clinical symptom of dysphagia in the absence of endoscopic evidence of inflammation” [1].

Oesophageal dysphagia is usually graded using the Mellow score [3].

The score is self-reported by the patient and ranges from 0 to 4:

- 0 – indicates no dysphagia
- 1 – dysphagia to normal solids
- 2 – dysphagia to soft solids
- 3 – dysphagia to solids and liquids
- 4 – complete dysphagia (inability to swallow saliva).

The score is self-reported by the patient and ranges from 0 to 4. A score of 0 indicates no dysphagia; 1 dysphagia to normal solids; 2 dysphagia to soft solids; 3 dysphagia to solids and liquids; and 4 complete dysphagia (inability to swallow saliva).

BOS can be caused by a wide range of disorders [9]. The most important are the following: peptic stenoses as a consquence to gastroesophageal reflux disease, eosinophilic oesophagitis, caustic injuries, medication-induced stenoses, radiation-induced stenoses, postendoscopy-induced stenoses, congenital anomalies, Schatzki ring, oesophageal web, or motility disorders such as achalasia.

Achalasia, which is a well-known condition leading to oesophageal stenosis, is a motility disorder of the oesophagus in which the lower oesophageal sphincter (i.e. a tonically contracted smooth muscle at the distal end of the tubular oesophagus near the cardia) fails to relax resulting in functional obstruction of the oesophagus [10].

The definition of RRBOS is not standardised. The American Society for Gastrointestinal Endoscopy (ASGE) adopted the Kochman proposal. According to this definition, RRBOS is an anatomical restriction of the oesophageal lumen that results in the clinical symptoms of dysphagia in the absence of endoscopic evidence of inflammation, after the inability to either:

- Successfully dilate the stenosis to a diameter of 14 mm over 5 sessions at 2-weekly intervals (refractory) or
- Maintain a satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm has been achieved (recurrent).

A0003 – *What are the known risk factors for refractory or recurrent benign oesophageal stenosis?*

Risk factors for RRBOS have not been clearly defined in medical literature since it is a group of different pathophysiological entities with low prevalence.

The most relevant risk factor is gastroesophageal reflux disease. BOS occurs in 7–23% of patients with untreated reflux oesophagitis, especially in older men. The increase in the use of proton pump inhibitors for treatment of gastroesophageal reflux disease led to a decrease in BOS incidence by approximately 33% [11].

Previous oesophageal surgery, irradiation and sclerotherapy are other common risk factors. Benign stenoses frequently occur with a prevalence rate of 30% (range 9–48%) when an oesoph-

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agogastric anastomosis is performed after oesophagectomy [12]. Long-term survivors after successful repair of isolated oesophageal atresia have a 42% increased risk of developing stenoses in adulthood [13]. Stenoses occur in approximately 15% of patients undergoing sclerotherapy for oesophageal varices. Nasogastric tubes have long been recognised as a potential source of oesophageal injury and stricture formation, and the putative mechanism is also gastroesophageal reflux. Potassium chloride pills have been associated with oesophageal injury and in severe cases with stricture formation. Bisphosphonates have the potential for oesophageal injury, and stricture formation can occur in severe cases [14].

A0004 – *What is the natural course of refractory or recurrent benign oesophageal stenosis?*

Dysphagia is the main symptom of BOS. In severe or untreated cases, BOS can lead to progressive dysphagia (dysphagia to normal solids, dysphagia to soft solids, dysphagia to solids and liquids, and finally complete dysphagia with inability to swallow saliva), malnutrition and respiratory problems such as aspiration pneumonia; but mortality related to BOS is unlikely. The stenosis is easy to detect by barium oesophagogram and endoscopy.

Schatzki ring can be found in 6–14% of people having a routine upper gastrointestinal series without dysphagia symptoms [11].

Dilation using bougie or balloon dilators is the treatment of choice for BOS and most patients respond well to oesophageal dilation. However, outcomes are influenced by the underlying pathology. Nearly half of the patients achieve satisfactory results without any further intervention after dilation but others may need repeated courses of dilation over many years. Dilation appears less effective in those with radiation- or corrosive-induced stenoses. Only a small number of patients require major surgical intervention – oesophagectomy being the ultimate option – to remove the constriction.

Effects of the disease or health condition on the individual and society

A0005 – *What is the burden of refractory or recurrent benign oesophageal stenosis for the patient in terms of mortality, morbidity and quality of life measures?*

Incidence and prevalence of BOS have not been reported in the medical literature, except for achalasia. The incidence of achalasia is approximately 1.6 cases per 100,000 individuals annually and the prevalence is 10 cases per 100,000 individuals [15].

Specific mortality, morbidity and quality of life measures are generally lacking for BOS. Some available data are related to mortality and morbidity of treatments rather than to the disease itself. In a study in which BOS, caused by a range of disorders, was treated by fluoroscopically guided balloon dilation, the incidence of oesophageal rupture was 14.7%. Most ruptures (98.6%) were types 1 and 2 and were successfully managed conservatively while few type 3 ruptures (0.96% of ruptures) were successfully treated only surgically. Type 1 rupture is an intramural rupture, type 2 is a transmural rupture with leakage restricted to the immediately adjacent area; and type 3 is transmural rupture with spillage of contrast medium into the mediastinum, pleura, or peritoneum [16].

There was no procedure-related mortality during any of the 1,421 balloon dilations. In a recent retrospective review of 500 patients who underwent laparoscopic myotomy for achalasia, there was no procedure-related mortality and median length of hospital stay was 2 days [9]. The procedure-related mortality was 2.9 in the largest retrospective analysis based on the US Nationwide Inpatient Sample over an 11-year period (2000–2010); this analysis examined outcomes after oesophagectomy in patients with achalasia [17].

Regarding quality of life, a variety of disease-specific and generic quality of life measures have been used for achalasia such as the Gastrointestinal Quality of Life Index (GIQLI), the Eckardt clinical symptom score and the Medical Outcomes Study 36-item Short-Form Health Survey [18–25]. The GIQLI includes 36 items covering 4 domains:

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- Gastrointestinal symptoms (19 questions)
- Physical function (7 questions)
- Social function (4 questions)
- Emotional function (5 questions)
- Subjective treatment assessment (1 question).

Every item is scored from 0 (least desirable option) to 4 (most desirable option). Summing the points, the GIQLI score theoretically ranges from 0 to 144, with an established normal score of 125.8 points (95% CI: 121.5–127.5) for healthy individuals. In studies for achalasia, preoperative median scores were 84-98 points [18, 25].

Target population

A0007 – *What is the target population for biodegradable oesophageal stents?*

According to the information included in the CE mark authorisation, SX-ELLA Stent Oesophageal Degradable, which is the only biodegradable stent authorised for use in the EU market, is indicated for BOS and achalasia refractory to standard therapy [26]. The CE mark does not specify criteria to define the term refractory.

There is no standard definition for RRBOS in the literature but the most commonly used definition is that proposed by Kochman et al. which has also been adopted by the ASGE [1] (see **A0002**).

The CE mark establishes the following contraindications for the use of SX-ELLA [26]:

- Inability to pass the 9.4 mm (28 F) delivery system through the stricture
- Benign strictures in the upper part of the oesophagus too close to the cricopharyngeal muscle
- Patientes with benign strictures due to previously performed laryngectomy.

Utilisation of Biodegradable Stents

A0001 – *For which health conditions and populations, and for what purposes, are biodegradable oesophageal stents used?*

The OBS has been designed to be used when a series of oesophageal dilations do not resolve the oesophageal stenosis. The CE mark establishes the following indication: “benign esophageal lesions namely: stenosis refractory to standard therapy” and “achalasia refractory to standard therapy” [26]. However, the CE mark does not define what should be understood by refractory.

The most accepted definition for refractory and recurrent BOS is that proposed by Kochman et al. and adopted by the ASGE [1] (see **A0002**). However, a wide range of characteristics determining refractory or recurrent BOS are found in the literature.

On the other hand, other requirements to use OBS are the benign nature of the lesion, and minor or no inflammation at the stenosis site. However, there are a couple of experimental applications for malign stenoses. The expectation is also to ensure a patent lumen to prevent dysphagia [27–29]. Peptic, anastomotic, radiotherapy-induced, caustic, postischaemic, idiopathic stenoses are frequent aetiologies for RRBOS.

A0011 – *How much are biodegradable oesophageal stents utilised?*

No evidence was found to answer this research question.

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Current clinical management of the disease or health condition

A0024 – *How is refractory or recurrent benign oesophageal stenosis currently diagnosed according to published guidelines and in practice?*

For diagnosis of RRBOS, clinical history should be considered first. Patient history is critically important in evaluating dysphagia while the main concern is to exclude malignancy. Algorithms have been defined in some guidelines to determine the likely aetiology of dysphagia and the further work-up of patients [30,31].

With regard to diagnostic tests, there is some debate as to whether endoscopy or barium swallow should be employed initially. The barium oesophagogram, conducted in a supine or upright position, outlines irregularities in the oesophageal lumen and identifies most cases of obstructions, webs, and rings; it can also be useful for the detection of achalasia and diffuse oesophageal spasm, although these conditions are more accurately diagnosed by manometry. It may also be useful to include a barium tablet to identify subtle stenoses. A barium swallow may also be helpful in dysphagic patients with a negative endoscopy if the tablet is added.

Endoscopy uses a fiberoptic endoscope, which is passed through the mouth into the stomach, allowing a detailed visualisation of the upper gastrointestinal tract. The introduction of the scope into the gastric cavity is crucial to exclude pseudoachalasia due to a tumour of the oesophagogastric junction.

Neither endoscopy nor radiography are completely accurate in all situations and they are not interchangeable. Both are operator dependent and often complementary. Endoscopy and barium swallow may delineate the lesion but both have specific advantages and disadvantages. Endoscopy allows biopsy of the lesion but perforation of the oesophagus, especially if the lesion is malignant, can occur. A barium swallow is usually required to clarify the nature and length of stenosis before attempting to pass the scope through the stricture. It may be appropriate to arrange an urgent barium swallow before endoscopy, when dysphagia and weight loss are prominent.

One study reported a diagnostic yield of 54% with endoscopy in the initial evaluation of patients aged over 40 years, who presented with dysphagia and concomitant heartburn, odynophagia, and weight loss. A cost analysis also showed that endoscopy with therapeutic intent in patients with histories suggestive of BOS is more cost effective than the initial diagnostic approach with barium swallow [9].

Oesophageal manometry is less commonly available than barium swallow and endoscopy, but it is being considered as very useful in selected cases [11]. It records the oesophageal lumen pressure using either solid-state or perfusion techniques. Manometry is indicated when an oesophageal cause of dysphagia is suspected following an inconclusive barium swallow and endoscopy and following adequate antireflux therapy (with healing of oesophagitis shown endoscopically).

A0025 – *How is refractory or recurrent benign oesophageal stenosis currently managed according to published guidelines and in practice?*

Oesophageal dilation is the primary therapeutic procedure for the management of dysphagia related to BOS. The primary objective for dilation is to provide immediate and durable symptomatic relief of dysphagia. Most of the data on oesophageal dilation is compiled from the adult population, but its safety and efficacy have also been confirmed in the paediatric population. In contrast to mechanical stenosis, motility disorders may not respond to dilation, with achalasia being the notable exception [9].

Patients with peptic stenoses may be treated with Maloney, push-type dilators and balloon dilators with similar efficacy [32,33]. Patients undergoing dilation of peptic stenoses should be treated with acid suppressive therapy to prevent stricture recurrence [34–36]. Adjunctive methods that have been used in addition to dilation are electrocautery incision with a needle-knife papillotome and 4-quadrant biopsies of rings. Although short stenoses (less than 1 cm) respond to a single electrocautery treatment, longer stenoses may require multiple sessions.

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Steroid injection into refractory benign stenoses immediately before or after dilation has been shown to increase the postdilation diameter, decrease the need for repeat dilations and increase the interval between dilations [37–39]. The mechanism of action is considered to be inhibition of matrix protein genes by the steroids, leading to a decrease in deposition of collagen and fibrous tissue in the oesophagus.

Temporary oesophageal stent placement is an adjunct to dilation in the management of patients with RRBOS. Because of the high rate of tissue ingrowth, uncovered metal stents have been replaced by plastic or fully-covered metal stents for this indication [2,40,41]. Self-bougienage is another option for patients who require multiple and frequent dilations. The initial dilation sessions should be performed under the supervision of a clinician to ensure that the patient learns the correct technique. A single Maloney dilator with a diameter of 14 mm, 15 mm, or 16 mm is used for this purpose.

Oesophageal dilation for achalasia involves forceful disruption of the lower oesophageal sphincter. This is usually accomplished with 30–40 mm diameter pneumatic balloon dilators. Dilation is generally performed over a wire under fluoroscopic guidance [10,42]. Although short-term relief of dysphagia can be achieved frequently, recurrence has been reported in approximately one-third of patients [43]. The management of achalasia depends largely on the surgical risk. A low-risk endoscopic procedure such as botulinum toxin injection, often effective but with only temporary effects (usually 6 months or less), is reserved for inoperable patients [31].

A large randomised trial of 201 patients compared pneumatic dilation with laparoscopic Heller myotomy and showed no statistically significant difference in therapeutic success between the 2 groups [44]. Also, cost analysis models indicate that initial pneumatic dilation is a more cost-effective approach compared with botulinum toxin injection or laparoscopic Heller myotomy for healthy patients with achalasia [45,46]. Before endoscopic treatment, patients with achalasia should be informed of all therapeutic options available. Graded pneumatic dilation or myotomy are options for symptomatic patients with achalasia who are eligible for surgery. The subset of patients in whom the myotomy has failed may require oesophagectomy.

The ASGE has recently published the following recommendations for the use of endoscopy in the evaluation and management of dysphagia [9]:

1. Endoscopic dilation is recommended for patients with dysphagia secondary to benign intrinsic strictures of the oesophagus
2. Wire-guided dilation, preferably under fluoroscopic guidance, or through-the-scope balloon dilation is recommended for complex oesophageal strictures
3. Antisecretory treatment is recommended in conjunction with dilation to reduce the recurrence rate of peptic strictures
4. Dilation for adult patients with eosinophilic oesophagitis is recommended to be reserved for those who have a dominant oesophageal stricture or ring and those who remain symptomatic despite medical therapy
5. Adjunctive treatment is recommended with corticosteroid injection into the strictures
6. Oesophageal stent placement is suggested to be reserved for RRBOS that does not respond to sequential dilation and/or steroid injection
7. Both endoscopic and surgical treatment options for achalasia are recommended to be discussed with the patient. In patients who opt for endoscopic management and are good surgical candidates, pneumatic dilation is recommended with large-calibre balloon dilators for the endoscopic treatment of achalasia
8. Botulinum toxin injection is recommended for endoscopic treatment of achalasia in patients who are poor candidates for surgery or pneumatic dilation.

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2.3 Discussion

BOS is caused by a wide range of disorders, but all constrict the normal oesophageal lumen without a cancerous cause. The constricting structure can either be a simple excessive mucosal formation or a distorted anatomical structure involving all layers of the oesophageal wall with excessive fibrotic tissue. The same applies to achalasia, which presents with hypertrophic muscle layer, higher than normal intraluminal pressure and decreased luminal calibre. Therefore, achalasia is discussed under the definition of BOS.

According to a definition suggested by Kochman et al., the following are not summarised under BOS: patients with an inflammatory stricture (which will not resolve successfully until the inflammation subsides) or those with a satisfactory diameter who have dysphagia on the basis of neuromuscular dysfunction (i.e. those with postoperative and postradiation therapy dysphagia) [1]. Whether their definition does include achalasia is unclear. The most common causal factors for BOS have been defined adequately in the medical literature, but for achalasia the origin is unknown.

Incidence and prevalence of BOS have not been directly defined in the medical literature, again except for achalasia. An explanation may be that this is a group of diseases with different natural histories, variable severity and a low burden of disease for society. General consensus exists on the management of BOS including both diagnosis and treatment. Barium oesophagogram and endoscopy are widely available, accessible and affordable at least in Europe. Diagnosis is therefore not a challenge. The main treatment option is dilation and many patients benefit from this approach. Those who do not benefit adequately in terms of relapsing dysphagia, which is then clearly defined as RRBOS, constitute the target population of this assessment. Prior to radical interventions, such as oesophagectomy, oesophageal stents are the preferred second-line treatment option for RRBOS with both limited results and evidence in terms of safety and efficacy.

Different types of stents are commercially available, with biodegradable ones being developed most recently. When compared with more conventional stents such as metal and plastic stents, biodegradable stents have the advantage of not needing removal and offer the possibility of repeated applications. So, biodegradable stents deserve attention in the treatment of RRBOS in terms of safety and efficacy, which is the main topic of this assessment.

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3. DESCRIPTION AND TECHNICAL CHARACTERISTICS OF THE TECHNOLOGY

3.1 Methods

Domain framing

No deviation from the general scope of the project was required.

Research questions

Element ID	Research question	Topic	Importance 3 = critical 2 = important 1 = optional
B0001	What are biodegradable oesophageal stents and the comparators?	Features of the technology	3
B0002	What is the approved indication and claimed benefit of biodegradable oesophageal stents and the comparators?	Features of the technology	3
B0004	Who implants biodegradable oesophageal stents and the comparators?	Features of the technology	3
B0005	In what context and level of care are biodegradable oesophageal stents and the comparators used?	Features of the technology	2
B0008	What kind of special premises are needed to use biodegradable oesophageal stents and the comparators?	Investments and tools required to use the technology	2
B0009	What supplies are needed to use biodegradable oesophageal stents and the comparators?	Investments and tools required to use the technology	1
B0010	What kind of data and records are needed to monitor the use of biodegradable oesophageal stents and the comparators?	Investments and tools required to use the technology	2
B0011	What kind of registry is needed to monitor the use of biodegradable oesophageal stents and comparators?	Investments and tools required to use the technology	2
A0020	What is the marketing authorisation status of biodegradable oesophageal stents?	Regulatory status	2
A0021	What is the reimbursement status of biodegradable oesophageal stents?	Regulatory status	2

Sources

A basic search was performed in PubMed® and Google. A hand search was carried out in text-books. An assessment element specific search was performed for the question **B0011**. EU legislation and guidelines were searched by looking through European Commission websites to check the marketing authorisation status. A survey of reimbursement status was sent to EUnetHTA partners, courtesy of LBI-HTA.

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3.2 Results

Features of the technology and comparators

B0001 – *What are biodegradable oesophageal stents and the comparators?*

Oesophageal dilation is the primary therapeutic procedure for the management of dysphagia caused by BOS. Some patients achieve satisfactory results without further intervention after dilation but others may need repeated courses of dilation over many years. Stents are an alternative for patients where sequential dilation does not achieve sufficiently positive results [9].

Stents are devices used to maintain or restore the lumen of hollow organs, vessels, and ducts. SEMS were the first type of stents used to treat RRBOS. SEMS consist of woven, knitted, or laser-cut metal mesh cylinders that exert self-expansive forces until they reach their maximum fixed diameter. They are generally packaged in a compressed form and are constrained on a delivery device. SEMSs are composed of stainless steel, alloys such as elgiloy and nitinol, or a combination of nitinol and silicone.

SEMS were initially developed without a covering, but a variety of coverings and modifications of stent designs have been introduced in the last few years in order to prevent embedding of stent mesh in the mucosa. There are several covered SEMS on the market. They can be partially or fully covered SEMS. Polyurethane, polyethylene, and silicone are used as coatings for SEMS.

SEMS placed for benign stenosis have been associated with high rates of tissue hyperplasia, migration, recurrent stenoses, bleeding, fistula and death [2,4,40,41]. Unsuccessful results with SEMS led to the development of fully covered SEMS and SEPS. However, neither the uncovered nor fully covered SEMS have been approved by the FDA for the treatment of BOS [4,47].

SEPS have been designed and approved for use in RRBOS. SEPS have a woven polyester skeleton and are completely covered with a silicone membrane. The only available SEPS is Polyflex™, Boston Scientific, which is made of polyester netting embedded in a silicone membrane. The silicone prevents tissue ingrowth through the mesh, and the polyester braids on the external surface anchor the stent to the mucosa to limit migration. Radiopaque markers positioned in the middle and at the ends of the stent facilitate visualisation of this non-metallic device during fluoroscopy [48].

Biodegradable stents have recently been developed as an alternative to SEMS and SEPS. An OBS is a medical device made of biodegradable materials that is used in the oesophageal lumen. Biodegradable materials are natural substances or synthetic compounds that disintegrate over time in the human body at the location of their implantation. Biodegradable stents can be made of different synthetic polymers (e.g. polylactide or polyglycolide) or their co-polymers (polydioxanone or caprolactone), polyethylene glycol, hybrid polyurethanes, chitosan glycerophosphate, hydroxyapatite non-polymer substance, manganese or magnesium alloys, special corrodible iron and others [49].

SX-ELLA Stent Esophageal Degradable, the only CE marked OBS, received European market authorisation in 2007. The stent is manufactured from woven polydioxanone monofilament, which degrades by random hydrolysis accelerated by a low ambient pH. Stent integrity and radial force are maintained for 6-8 weeks following deployment and its disintegration usually occurs by 11-12 weeks postdeployment. The degradation products are not harmful; the stent material is partly absorbed and partly excreted through the bowel.

Another biodegradable stent has been developed in Japan but it has not been commercialised in Europe. It is called Tanaka-Marui biodegradable stent (Marui Textile Machinery Co., Ltd., Japan) and it is made of poly-l-lactic acid monofilaments [50,51].

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B0002 – *What is the approved indication and claimed benefit of biodegradable oesophageal stents and the comparators?*

The approved indications for SX-ELLA Stent Esophageal Degradable BD (BD Stent) in Europe are stated in the CE mark (CE-1014), which was provided by ELEKTROTECHNICKY ZU in 2007 [26]. According to this, the SX-ELLA is designed for dilation of benign oesophageal lesions, namely:

- Stenosis (peptic, anastomotic or caustic) refractory to standard therapy
- Achalasia refractory to standard therapy.

The CE mark states the following contraindications:

- Inability to pass the 9.4 mm (28 F) delivery system through the stricutre
- Benign strictures in the upper part of the oesophagus too close to the cricopharyngeal muscle
- Patients with benign strictures due to previously performed laryngectomy.

In Europe, SEPS and FCSEMS are indicated for the treatment of both benign and malignant refractory oesophageal stenosis [4]; however, the uncovered or partially covered SEMS are only approved for malignant stenosis but not benign stenosis. In the USA, neither covered nor uncovered SEMS are approved for benign stenosis; they are approved only for malignant stenosis [4,47].

The aim of stent placement is to hold the stenosis open for prolonged periods of time, causing the stenosis, or the tissue around it, to remodel so that the stenosis does not recur when the stent is removed [40]. The main advantage of biodegradable stents over SEMS and SEPS is that endoscopic removal is not needed and potential repeated placement at the previously-used site is possible. Therefore, they may be an alternative to avoid the burden of serial dilations and repeated endoscopic interventions.

Administration, investments, personnel and tools required to use the technology and the comparator(s)

B0004 – *Who implants the biodegradable oesophageal stents and the comparators?*

Endoscopists formally trained in a gastroenterology fellowship or surgical residency perform oesophageal stent placement. However, oesophageal stent insertion is not the sole domain of the endoscopists; they are also placed non-endoscopically by interventional radiologists with effective results [52].

B0005 – *In what context and level of care are biodegradable oesophageal stents and the comparators used?*

Endoluminal stent deployment is an advanced procedure requiring complex diagnostic and therapeutic expertise and skills to manage potential complications. Surgeons should be proficient in upper and lower endoscopy and should have an understanding of the use and interpretation of fluoroscopy. Interpretation of cross-sectional imaging and contrast studies is also essential for the appropriate selection of patients [53]. Oesophageal stent deployment can be performed in an ambulatory setting but an emergency plan must be available so that a patient can be quickly referred to a high-level healthcare facility in the case of serious complications.

B0008 – *What kind of special premises are needed to use biodegradable oesophageal stents and the comparators?*

The hospital or clinical site should have a procedure room where both endoscopy and fluoroscopy can be performed simultaneously because both are commonly used in patients undergoing enteral stent placement. In many instances, however, oesophageal stents may be placed with only endoscopic or fluoroscopic guidance. Fluoroscopy, on the other hand, may require special conditions related to radiation protection issues [53].

Because of material shape memory the BOS has to be loaded into the delivery system just before its implantation. This requires specific training.

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B0009 – *What supplies are needed to use biodegradable oesophageal stents and the comparators?*

The following supplies are recommended by the ASGE [53]:

- Upper endoscope
- Guidewires
- Straight biliary catheters
- Fluoroscopy equipment
- Oesophageal stents.

B0010 – *What kind of data and records are needed to monitor the use of biodegradable oesophageal stents and the comparators?*

This assessment element is addressed in **B0011*.***

B0011 – *What kind of registry is needed to monitor the use of biodegradable oesophageal stents and comparators?*

It would be advisable to have national registries to gather large-scale OBS implantation data in countries where OBS are authorised for use. If not effectiveness data, at least safety information should be registered.

The British Society of Interventional Radiology has set up a number of vascular registries over several years and started the first Gastrointestinal Stent Registry in 2002. All patients undergoing oesophageal stent placement in the UK are potentially registered. The purpose of this registry is to assess the (changing) practice of oesophageal stenting and the performance of the newer oesophageal stents. The first and only report of the Registry of Oesophageal Stenting was published in 2004 but it is currently closed for data entries [52]. Our search has not revealed other registries for oesophageal stents.

In the US, there are specific Current Procedural Terminology (CPT) codes that must be used when performing stent placement in the alimentary tract, and facilities must include a separate code for the stent itself [48]. The code set describes medical, surgical, and diagnostic services and is designed to communicate uniform information about medical services and procedures among physicians, coders, patients, accreditation organisations, and payers for administrative, financial, and analytical purposes. The CPT coding is similar to ICD-9 and ICD-10 coding, except that it identifies the services rendered rather than the diagnosis on the claim. ICD code sets also contain procedure codes but these are only used in the inpatient setting.

Regulatory and reimbursement status

A0020 – *What is the marketing authorisation status of biodegradable oesophageal stents?*

An OBS is a long-term invasive medical device (normally intended for continuous use for more than 30 days) and, according to Rule 5 of Council Directive 93/42/EEC, it is considered as class IIb. Technical documentation relating to class IIb must be reviewed by a Notified Body in the context of Directive 93/42/EEC. SX-ELLA Stent Esophageal Degradable BD™ (BD STENT) was certified by the Notified Body ELEKTROTECHNICKÝ ZKUŠEBNÍ ÚSTAV, s.p., in 2007 and can be put on the EU market without further restrictions.

A0021 – *What is the reimbursement status of biodegradable oesophageal stents?*

Table 2 summarizes the results of a survey that was sent during the assessment phase (June–July 2014) to the EUnetHTA partners to elicit the reimbursement status of OBS in European countries. Some European countries (the Czech Republic, Germany and Italy) currently reimburse for the use of OBS in RRBOS. France has authorised them only for investigational use. Turkey reimburses with a cost limit by procedure. In Malta and Hungary the procedure is not reimbursed and

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in Scotland the technology is not purchased as parts of national contracts. In Spain, the technology is under evaluation for inclusion in the list of reimbursed services of the 'Common Health Care Services Portfolio of the Spanish Healthcare System'. Even though they are authorised for oesophageal and gastric stent implantation, in Spain this device is not specifically mentioned in the list of reimbursed services.

Table 2: Reimbursement status of biodegradable stents.

Country	Agency	Reimbursement status	Other relevant information
Czech Republic	Ministry of Health	Yes	Reimbursement is device-specific
France	HAS (Haute Autorité de Santé)	No	Only for investigational setting
Germany	IQWiG (Institute for Quality and Efficiency in Health Care)	Yes	Reimbursement is procedure-related (Diagnosis Related Group-based reimbursement)
Hungary	National Institute of Pharmacy and Nutrition	No	The company has not applied for reimbursement so far
Italy	Regione Veneto	Yes	Reimbursement is procedure-related
Malta	Ministry for Energy and Health	No	
Turkey	Ministry of Health	Yes	The maximum payable limit is up to 1500 Turkish liras per patient (equivalent to 500 Euro)
Scotland	HIS (Health Care Improvement Scotland)	No	Not purchased as part of national contracts
Spain	ISCIII (Instituto de Salud Carlos III)	Under consideration	

3.3 Discussion

The medical devices sector is an ever-growing area with new technologies produced by small- and medium-sized enterprises with ever-advancing generations of products, especially when compared with the pharmaceutical sector.

The research area of biodegradable digestive stents is in a quite early stage of development and more advancement is to be expected. SX-ELLA is the first product and first generation in the group of biodegradable stents for BOS. Biomaterials are generally the topic of engineering sciences. Therefore, close cooperation with health sciences is necessary for applicability and safety issues. The CE mark is granted on the basis of small technical feasibility and technical performance studies but long-term safety assessments based on registry data must be made available.

It has not yet been decided which group of medical specialists is responsible for the procedure of gastrointestinal interventions such as stenting: gastroenterologists, surgeons, endoscopists or interventional radiologists. The decision is strongly dependent on the organisation of healthcare systems. In addition, data collection of utilisation, performance and safety issues can be improved. Reliable and easily accessible data on stenting (SEPS, SEMS or BDS) for oesophageal stenosis are missing and no effective solutions such as voluntary or obligatory registries have been implemented. Additionally, information on reimbursement in EU-member states is difficult to obtain. When compared to pharmaceuticals, reimbursement decisions and practices are less standardised for medical devices globally, leading to challenges for all stakeholders including manufacturers, healthcare providers, researchers and policy makers.

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4. CLINICAL EFFECTIVENESS

4.1 Methods

Domain framing

The initial wording of some outcomes from the project plan has been modified in this draft assessment (see *Scope*).

Research questions

Element ID	Research question	Outcomes	Importance 3 = critical 2 = important 1 = optional
D0001	What is the expected beneficial effect of biodegradable oesophageal stents on overall mortality?	Overall mortality	3
D0002	What is the expected beneficial effect of biodegradable oesophageal stents on the disease-specific mortality?	Disease-related mortality	3
D0003	What is the expected beneficial effect of biodegradable oesophageal stents on the mortality due to causes other than the target disease?	Mortality due to other causes	2
D0005	How do biodegradable oesophageal stents affect symptoms and findings in relation to the comparators?	Morbidity and function	3
D0010	How do biodegradable oesophageal stents modify the need for hospitalisation?	Change in management	2
D0011	What is the effect of biodegradable oesophageal stents on digestive functions?	Morbidity and function	3
D0012	What is the effect of biodegradable stents on generic health-related quality of life in relation to the comparators?	Health-related quality of life	2
D0013	What is the effect of biodegradable oesophageal stents on disease-specific quality of life in relation to the comparators?	Health-related quality of life	2
D0017	Were patients satisfied overall with biodegradable oesophageal stents?	Patient satisfaction	2
D0023	How do biodegradable oesophageal stents modify the need for other technologies and use of resources?	Change in management	2

In terms of ‘morbidity and function’, we considered the following outcomes:

- Reduction in dysphagia after intervention
- Dysphagia-free patients after intervention
- Time to recurrent dysphagia after intervention
- Oesophageal lumen patency after intervention
- Reduction of pain after intervention.

For ‘change in management’, we considered the following outcomes:

- Number of dilations per patient after intervention

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- Time to re-intervention.

For 'mortality', we considered the following outcomes:

- Overall mortality
- Disease-related mortality.

Other outcomes assessed were:

- Health-related quality of life
- Patient satisfaction.

Sources

The following sources were used to obtain information:

- PubMed®
- Embase™
- The Cochrane Library
- DARE (Database of Abstracts of Reviews of Effects)
- HTA (Health Technology Assessment) database
- NHS-EED (National Health Service Economic Evaluation Database)
- Clinical trials registries for registered ongoing clinical trials or observational studies: ISRCTN (International Standard Randomised Controlled Trial Number), NIH (National Institutes of Health) ClinicalTrials, WHO (World Health Organization) International Clinical Trials Registry Platform
- Request to the manufacturer.

We selected relevant articles or documents according to the Population-Intervention-Control-Outcome-Study (PICOS) design-scheme described in the project plan. For the effectiveness domain only, comparative studies were included. A detailed description of the search strategy and selection process is available in Appendix 1 (see *Documentation of the search strategies, Flow chart of study selection*).

Analysis

Dysphagia was measured using the Mellow dysphagia score [3]. The score ranges from 0 to 4:

- 0 – indicates no dysphagia
- 1 – dysphagia to normal solids
- 2 – dysphagia to soft solids
- 3 – dysphagia to solids and liquids
- 4 – complete dysphagia (inability to swallow saliva).

The GRADE-methodology was used to assess the quality of the evidence [54]. The risk of bias was analysed using the Cochrane risk of bias tool for RCTs [55] and the Newcastle-Ottawa scale for cohort studies [56].

Synthesis

The questions were answered in plain text format with reference to evidence tables included in Appendix 1 (see *Table 6, Table 7*).

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4.2 Results

Included studies

Study characteristics

Three comparative studies [5–7] with a total of 83 patients were included for effectiveness assessment: 37 OBS, 6 dilation, 30 SEPS, 10 FCSEMS. One was a multicentre RCT that compared 9 patients treated with OBS (SX-ELLA Stent Oesophageal Degradable) with 6 patients treated with endoscopic balloon dilation (CRE® balloon, Boston Scientific) [5]. The second one was a multicentre prospective cohort study that compared 3 cohorts of 10 patients each [6]. One cohort was treated with OBS (SX-ELLA Stent Oesophageal Degradable), another with SEPS (Polyflex™, Boston Scientific), and the last one with FCSEMS (Wallflex stent™, Boston Scientific). The third study was a unicentre prospective cohort study comparing 18 RRBOS patients treated with OBS (SX-ELLA Stent Oesophageal Degradable) with 20 patients treated with SEPS (Polyflex™, Boston Scientific) [7].

The RCT was designed for a minimum sample size of 25 patients in each group, but after 12 months of follow-up the study was closed because only 17 patients had been recruited with no prospect of reaching the target within a reasonable time-scale. Of the 17 recruited patients, 15 of them were randomised and 12 of them followed until 12 months.

The cohorts of the observational studies differed in their average follow-up. In the study by Canena et al. the OBS and the FCSEMS groups were followed for a similar period: 18.5 months (OBS) and 10 months (FCSEMS) [6]. However, the SEPS group was followed for much longer: 42.7 months on average. In the study by van Boeckel et al., the OBS group was followed for a median of 5.5 months and the SEPS group for a median of 12.8 months [7].

Patient characteristics

Different inclusion criteria for RRBOS were used in the 3 studies. One cohort study [6] adopted the Kochman's definition of RRBOS (see **A0002**), but the other 2 studies used less restrictive inclusion criteria to define refractory and recurrent stenosis. The study by van Boeckel et al. applied the following criteria: "inability to achieve or maintain a diameter of 14mm despite dilation every 2 to 4 weeks" [7]. The RCT included patients with at least 1 previous oesophageal dilation [5].

On the other hand, the RCT groups differed in their severity. The mean number of dilations required by the OBS group before intervention was 6.2 (5.1 SD) (range 1-16). However, the dilation group required a mean number of 3.2 (2.3 SD) (range 1-6). Although the difference was not statistically significant, the OBS patients required more previous dilations suggesting a higher severity than the dilation patients group.

The RCT neither reported the aetiology nor the location of the stenosis. The aetiologies reported in the cohort studies were multiple, but peptic, postsurgical, and radiotherapy-induced strictures were the most common. Strictures had predominantly anastomotic and lower locations.

The study by Canena et al. [6] excluded stenoses located within 3 cm of the upper oesophageal sphincter, but these criteria were not applied in the other cohort study. The study by van Boeckel et al. [7] excluded Barrett's oesophagus, dismotility disorders and patients unfit for endoscopy, but these criteria were not applied in the other cohort study.

The 3 studies reported the mean stenosis length, which ranged from 1.8 to 4.0 cm. Two studies [5,6] reported the mean baseline dysphagia score, which ranged between 1.83 and 2.80. The study by van Boeckel et al. reported the median baseline dysphagia score as 3.00 in both groups [7].

The age range was between 24 and 80. The RCT reported mean ages of 62.7 for the OBS group and 63.8 for the dilation group. Canena et al. reported mean ages of 57.2 for the OBS group, 52.7 for the SEPS group and 50.7 for the FCSEMS group. Van Boeckel et al. reported median ages of 61 for the OBS group and 63 for the SEPS group. The proportion of men ranged between 40% and 89% across groups.

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Quality assessment

The quality of the evidence was rated as very low for all assessed outcomes. The RCT is affected by serious imprecision due to small sample size, lack of comparability between groups, performance bias, and ambiguities in the text. In addition, the inclusion and exclusion criteria for the RCT were not properly described.

The cohort studies are compromised by very serious imprecision due to small sample size and serious risk of bias. Both studies used historical controls, so for each cohort the intervention was done at different times, which can imply risk of bias. Other factors that threatened comparability between groups in the cohort studies were the following: one of the cohort studies [7] did not control for relevant confounding factors, and the other cohort study [6] used a longer follow-up time for the SEPS group than for the other 2 groups (OBS and FCSEMS groups). More detailed information on the quality assessment can be found in *Table 12* and *Table 13*.

Mortality

D0001 – *What is the expected beneficial effect of biodegradable oesophageal stents on overall mortality?*

D0002 – *What is the expected beneficial effect of biodegradable oesophageal stents on the disease-specific mortality?*

D0003 – *What is the expected beneficial effect of biodegradable oesophageal stents on the mortality due to causes other than the target disease?*

No deaths were reported in any of the 3 studies.

Morbidity and function

D0005 – *How do biodegradable oesophageal stents affect symptoms and findings in relation to the comparators?*

D0011 – *What is the effect of the biodegradable oesophageal stents on digestive functions?*

The studies reported data on the following outcomes related to morbidity and function:

- Reduction in dysphagia after intervention
- Dysphagia-free patients after intervention
- Time to recurrent dysphagia after intervention.

However, no information was reported on the following outcomes:

- Oesophageal lumen patency after intervention
- Reduction of pain after intervention.

Reduction in dysphagia after intervention

- *OBS vs dilation:*

The RCT (n = 15 patients: 9 OBS; 6 dilation) did not provide an analysis of dysphagia score changes before vs after the intervention, so the outcome ‘reduction in dysphagia’ could not be determined [5]. However the RCT provided dysphagia scores at specific points in time, at baseline and after the intervention. The quality of the evidence was very low.

The baseline mean dysphagia score was statistically similar between groups: 2.0 (1.2 SD) OBS group; 1.83 (0.98 SD) dilation group (p = 0.776). However, after the intervention, the dysphagia score was significantly higher for the OBS group than for the dilation group. After 3-12 months of

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follow-up, the mean score was 1.21 (1.08 SD) in the OBS group and 0 (0 SD) in the dilation group (p = 0.016). The authors of the RCT performed several sensitivity analyses that confirmed the differences in dysphagia score after intervention.

On the other hand, mismatches between tables and figures were noted in the information about dysphagia provided in the RCT; more information can be found in *Table 12.*

- OBS vs SEPS:

None of the studies provided information to assess 'reduction in dysphagia'. The 2 cohort studies provided dysphagia scores at specifics points in time, before and after intervention. One study provided means and the other one medians.

In the study by Canena et al., the mean dysphagia score before stent placement was the same in both groups (2.8 (0.42 SD)). The follow-up periods were very different between groups: a median follow-up of 18.5 months for the OBS group and 42.7 months for the SEPS group. After 4 weeks of follow-up, the OBS group had a mean dysphagia score of 0.4 (0.52 SD) and the SEPS group 0.7 (0.48 SD). Statistical significance was not analysed. The quality of the evidence was very low.

In the study by van Boeckel [7] the median dysphagia score before treatment was the same in both groups: 3.0 (p = 0.12). The OBS group was followed for a median of 5.5 months and the SEPS group for a median of 12.8 months. After 4 weeks of follow-up, both grous, OBS and SEPS, had a median dysphagia score of 0.0 (p = 0.91). The quality of the evidence was very low.

- *OBS vs FCSEMS:*

None of the studies provided information to assess 'reduction in dysphagia'. The study by Canena et al. provided dysphagia scores at specifics point in time, before and after the intervention [6]. The quality of the evidence was very low.

The mean dysphagia score before stent placement was similar for the OBS group (2.8 (0.42 SD)) and the FCSEMS group (2.7 (0.48 SD)). After 4 weeks of follow-up, the OBS group had a mean dysphagia score of 0.4 (0.52 SD) and the SEPS group 0.5 (0.53 SD). Statistical significance was not analysed.

After a median follow-up of 18.5 months, in the OBS group the mean score was 2.0 (0.82 SD). The FCSEMS group had a mean score of 1.6 (1.26 SD) after a median follow-up of 10 months. Statistical significance was not analysed.

***Dysphagia-free patients after intervention*:**

- *OBS vs dilation:*

This outcome was not reported in the included studies.

- *OBS vs SEPS:*

Neither of the 2 studies found statistically significant differences between OBS and SEPS in the percentage of patients free of dysphagia after follow-up. The quality of the evidence was very low. In the study by Canena et al., 3 of 10 patients in the OBS group and 1 of 10 patients in the SEPS group remained dysphagia-free after follow-up (p = 0.58) [6]. In this study, the duration of follow-up was considerably shorter for the OBS patients (median of 18.5 months) than for the SEPS patients (median of 42.7 months). In the study by van Boeckel et al. 6 of 18 OBS patients (median follow-up of 5.5 months) and 6 of 20 SEPS patients (median 12.8 months) remained dysphagia-free after follow-up (p = 0.83) [7].

- *OBS vs FCSEMS:*

In the study by Canena et al., 3 of the 10 patients treated with OBS were dysphagia-free after 18.5 of follow-up, and 4 of the 10 patients treated with FCSEMS were dysphagia-free after 10.0 months [6]. The difference was not statistically significant (p = 0.64). The quality of the evidence was very low.

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***Time to recurrent dysphagia after intervention*:**

- *OBS vs dilation:*

This outcome was not reported.

- *OBS vs SEPS:*

In the study by Canena et al., the mean time to recurrent dysphagia since stent placement was 19.5 months for the OBS group and 11.1 months for the SEPS group [6]. A Kaplan-Meier analysis found that the dysphagia recurrence risk was 34% higher for the SEPS group than for the OBS group, but with a high amount of variance (CI 95%: 0.50-3.58). The quality of the evidence was very low.

- *OBS vs FCSEMS:*

In the study by Canena et al., the mean time to recurrent dysphagia since stent placement was 19.5 months for the OBS group and 23.1 months for the FCSEMS group. A Kaplan-Meier analysis found that the dysphagia recurrence risk was 15% higher for the OBS group than for the FCSEMS group, but with a high amount of variance (CI 95%: 0.39-3.41). The quality of the evidence was very low.

Change in management

D0010 – *How do biodegradable oesophageal stents modify the need for hospitalisation?*

No evidence was found to answer the research question.

D0023 – *How do biodegradable oesophageal stents modify the need for other technologies and use of resources?*

The studies reported data on the number of dilations performed after intervention; however, no information was reported on time to re-intervention.

Number of dilations per patient after intervention:

- *OBS vs dilation:*

The RCT provided the mean number of additional balloon dilations after 6 and 12 months of follow-up [5] but the differences between groups were not statistically significant. The quality of the evidence was very low. The mean difference was 0.98 higher for the OBS group than for the dilation group after 12 months of follow-up: not statistically significant (p = 0.385).

- *OBS vs SEPS:*

The number of dilations per patient after intervention was not measured. One cohort study measured the number of patients who required dilations after intervention [6]. In this study, 3 of the 10 patients in the OBS group and 1 of the 10 patients in the SEPS group required dilations after intervention. Statistical significance was not analysed. The quality of the evidence was very low.

- *OBS vs FCSEMS:*

The number of dilations per patient after intervention was not measured. One cohort study measured the number of patients who required dilations after intervention [6]. In this study, 3 of the 10 patients in the OBS group and 2 of the 10 patients in the FCSEMS group required dilations after intervention. Statistical significance was not analysed. The quality of the evidence was very low.

Time to re-intervention:

No information was reported on time to re-intervention in the included studies.

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Health-related quality of life

D0012 – *What is the effect of biodegradable stents on generic health-related quality of life in relation to the comparators?*

- *OBS vs dilation:*

Health-related quality of life differences before vs after the intervention were not analysed in the included studies. The RCT measured the EuroQol 5 dimensions (EQ5D) and the EuroQol visual analogue scale (EQVAS) at specific points in time: baseline, 6 months and 12 months after the intervention; no statistically significant differences were found between groups at the 3 points in time. The quality of the evidence was very low.

- *OBS vs SEPS:*

This outcome was not measured.

- *OBS vs FCSEMS:*

This outcome was not measured.

D0013 – *What is the effect of the biodegradable oesophageal stents on disease-specific quality of life in relation to the comparators?*

No evidence was found to answer the research question.

Patient satisfaction

D0017 – *Were patients satisfied overall with biodegradable oesophageal stents?*

No evidence was found to answer the research question.

4.3 Discussion

The assessment of the clinical effectiveness of OBS for the treatment of RRBOS is based on 3 comparative studies with 83 patients, of whom 37 were treated with OBS. In addition to the small sample sizes, the available evidence is affected by its very low quality.

The 3 studies are affected by serious imprecision and lack of comparability between groups among other weaknesses. In terms of the study populations, considerable differences in terms of inclusion criteria were noted between studies.

Against the background of these limitations, comments can be made on the results. For the comparison of OBS vs dilation, the RCT reported statistically significant differences in dysphagia score after intervention.

The RCT found a statistically significant lower dysphagia score for the dilation group than for the OBS group after 6 and 12 months of follow-up. The mean dysphagia score decreased in the dilation group from 1.83 (inability to eat soft solids) to 0 (no dysphagia); on the other hand, the score decreased in the OBS group from 2.00 to 1.21. Although the minimally important clinical difference was not calculated in the studies, those dysphagia reductions appear to be clinically relevant. In any case, reasons other than the intervention itself could explain these results because the studies do not warrant comparability between groups.

The other assessed outcomes comparing OBS vs dilation were either not statistically significant or they had not been measured.

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For the comparison of OBS vs SEPS and FCSEMS, the studies found statistically significant differences for the risk of dysphagia recurrence, although the result is based on very low quality evidence. The probability of remaining without dysphagia after the intervention was higher for OBS than for SEPS, and was higher for FCSEMS than for OBS. The other assessed outcomes comparing OBS vs SEPS and FCSEMS were either not statistically significant or they had not been measured.

In summary, the available evidence is insufficient to determine the clinical effectiveness of OBS for the treatment of RRBOS in comparison with other similar technologies. There is only 1 RCT available comparing OBS vs dilation but it is of very low quality and has many limitations. For the other 2 comparators (SEPS and FCSEMS), the evidence comes from 2 very low quality cohort studies.

There is an ongoing RCT (NCT01337206) (see *Table 8*) that compares OBS to dilation with a scheduled final data collection in January 2015. Publication of the results from this second RCT could provide higher quality evidence.

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5. SAFETY

5.1 Methods

Domain framing

The initial wording of some outcomes from the project plan has been modified in this draft assessment (see *Scope*)

Research questions

Element ID	Research question	Outcomes	Importance 3 = critical 2 = important 1 = optional
C0001	What are the adverse events in patients with a biodegradable stent?	Patient safety	3
C0004	How does the frequency or severity of harms change over time or in different settings?	Patient safety	2
C0005	Are there any susceptible patient groups more likely to be harmed?	Patient safety	2
C0007	Can adverse events be caused by the behaviour of patients, professionals or manufacturers?	Patient safety	2
C0008	How safe is the biodegradable oesophageal stent in relation to the comparators?	Patient safety	3

The following outcomes were considered for assessing the safety of BOS:

- Technical failure
- Adverse events
- Serious adverse events
- Intervention-associated adverse events
- Unexpected re-interventions
- Procedure-related mortality.

The reported adverse events could not be separated into those associated and those not associated with the intervention. Therefore, the outcome 'Intervention-associated adverse events' was not specifically evaluated.

Sources

The following sources were used to obtain information:

- PubMed®
- Embase™
- The Cochrane Library
- DARE
- HTA database
- NHS-EED database
- Clinical trials registries for registered ongoing clinical trials or observational studies: ISRCTN, NIH ClinicalTrials, WHO International Clinical Trials Registry Platform
- Request to the manufacturer.

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We selected relevant articles or documents according to the PICOS design-scheme described in the project plan. In addition to comparative studies, we also included non-comparative studies excluding the following:

- Studies with less than 10 patients
- Retrospective case series with non-consecutive enrolment
- Studies with less than 6 weeks of follow-up
- Congress Abstracts.

A detailed description of the search strategy and selection process is available in *Documentation of the search strategies*.

Analysis

The GRADE-methodology was used to assess the quality of the evidence [54]. The risk of bias was analysed using the Cochrane risk of bias tool for RCTs [55] and the Newcastle-Ottawa scale for cohort studies [56]. The methodological quality of the case series was analysed using the case series checklist of the Institute for Health Economics [57].

Synthesis

The questions were answered in plain text format with reference to evidence tables that are included in Appendix 1 (*Table 6, Table 7*).

5.2 Results

Included studies

Five studies [5–7,58,59] with a total of 86 patients treated with OBS were included for the safety assessment. Besides the 3 comparative studies included for clinical effectiveness assessment, 2 additional case series met our inclusion criteria [58,59]. The characteristics of the 3 comparative studies have been described previously (see *Clinical effectiveness* domain).

The SX-ELLA Stent Oesophageal Degradable was inserted in consecutive patients in the 2 case series. The 2 case series were prospectively followed, ranging from 0.7 months to 37.4 months. One of them was multicentric [59] and the other one unicentric [58].

Patient characteristics

Different inclusion criteria for RRBOS were used by the studies. One of the cohort studies [6] adopted Kochman's definition (see **A0002**). The case series by Hirdes et al. included refractory stenosis according to Kochman's definition but did not include recurrent stenosis [59]. Two studies [7,58] considered the following criteria: "inability to achieve or maintain a diameter of 14 mm despite dilation every 2 to 4 weeks." Finally, the RCT included patients with at least 1 previous oesophageal dilation [5].

The RCT groups differed in their severity. The mean number of dilations required by the OBS group before intervention was 6.2 (5.1 SD) (range 1-16). However, the dilation group required a mean number of 3.2 (2.3 SD) (range 1-6). Although the difference was not statistically significant, the OBS patients required more previous dilations suggesting a higher severity than the dilation patients group.

On the other hand, the RCT neither reported the aetiology nor the location of the stenosis. The reported aetiologies in the rest of the studies were multiple, but peptic, postsurgical, and radiotherapy-induced strictures were most common. Strictures had predominantly anastomotic and lower locations.

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Four studies [5,6,58,59] reported the mean baseline dysphagia score, which ranged from 1.83 to 3.30. The study by van Boeckel et al. reported a median baseline dysphagia score of 3.0, both in the OBS and in the SEPS group [7].

All studies reported the mean stenoses length, which ranged from 1.8 to 4 cm. The age range was from 22 to 88 years. The proportion of men ranged from 40% to 89% across groups.

Quality assessment

The quality of the evidence was rated as very low for all assessed outcomes. The RCT was affected by serious imprecision due to small sample size, lack of comparability between groups, performance bias, and ambiguities in the text. In addition, the inclusion and exclusion criteria of the RCT were not properly described.

The cohort studies were compromised by very serious imprecision due to small sample size and serious risk of bias. Both studies used historical controls, so for each cohort the intervention was done at different times, which can imply risk of bias. Other factors that threatened comparability between groups in the cohort studies were the following: one of the cohort studies [7] did not control for relevant confounding factors, and the other cohort study [6] used a longer follow-up time for the SEPS group than for the other 2 groups (OBS and FCSEMS groups).

For the quality of the case series, the study by Repici et al. [58] obtained 17 out of 18 points in the score; while the study by Hirdes et al. obtained 13 points [59]. Repici et al. failed to provide the random variability of the results. Hirdes et al. was unicentric and did not measure outcomes before and after the intervention, among other weaknesses. More detailed information on the quality assessment can be found in Appendix 1 (*Table 12*, *Table 13*, *Table 14*).

Patient safety

C0001 – *What are the adverse events in patients with a biodegradable stent?*

Five studies comprising overall 86 patients treated with OBS were included for the safety assessment [5–7,58,59]. The number of patients treated with OBS and experiencing major and minor adverse events is reported in *Table 3*. Two of the 5 studies reported the total number of patients with adverse events ranging from 33.3% [58] to 50.0% [6].

The most frequent adverse events were: moderate pain (55.5% [5]), moderate dysphagia (55.5% [5]), tissue hyperplasia (30% [6]), severe dysphagia (22.2% [5]), severe pain (22.2% [5]), and stent migration (22.2% [7] and 20% [6]).

No deaths were reported in any of the included studies.

Table 3: Patients treated with OBS with adverse events

Author, date		Dhar 2014 [5]	Canena 2012 [6]	Van Boeckel 2011 [7]	Repici 2010 [58]	Hirdes 2012 [59]
Study design		RCT	Cohort study	Cohort study	Case series	Case series
Patients		9	10	18	21	28
Patients with major adverse events, n (%)	Acute pancreatitis	1 (11.1)	-	-	-	-
	Aspiration pneumonia	-	-	-	-	1 (3.6)
	Fever, nausea, vomiting	-	-	-	-	1 (3.6)
	Haemorrhage	-	1 (10)	2 (11.1)	-	2 (7.1)
	Severe dysphagia	2 (22.2)	-	-	-	-
	Severe pain	2 (22.2)	1 (10)	2 (11.1)	1 (4.8)	4 (14.3)
	Vomiting	-	-	-	-	2 (7.1)
	Total	N/A	2 (20)	4 (22.2)	1 (4.8)	N/A

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Author, date		Dhar 2014 [5]	Canena 2012 [6]	Van Boeckel 2011 [7]	Repici 2010 [58]	Hirdes 2012 [59]
Patients with minor adverse events, n (%)	Bleeding	3 (33.3)	-	-	1 (4.8)	-
	Constipation	1 (11.1)	-	-	-	-
	Cough	1 (11.1)	-	-	-	-
	Diverticulosis	1 (11.1)	-	-	-	-
	Dry mouth	1 (11.1)	-	-	-	-
	Oesophageal candidiasis	1 (11.1)	-	-	-	-
	Food bolus obstruction	-	-	2 (11.1)	-	-
	Foul taste	1 (11.1)	-	-	-	-
	Hiccups	1 (11.1)	-	-	-	-
	Hyperglycaemia	1 (11.1)	-	-	-	-
	Insomnia	1 (11.1)	-	-	-	-
	Moderate dysphagia	5 (55.5)	-	-	-	-
	Moderate pain	5 (55.5)	-	-	2 (9.5)	2 (7.1)
	Nausea, vomiting	1 (11.1)	-	2 (11.1)	-	1 (3.6)
	Reflux symptoms	1 (11.1)	-	1 (5.6)	-	1 (3.6)
	Stent migration	-	2 (20)	4 (22.2)	2 (9.5)	3 (10.7)
	Tissue hyperplasia	-	3 (30)	2 (11.1)	1 (4.8)	-
	Total	N/A	5 (50)	N/A	6 (28.6)	N/A
TOTAL		N/A	5 (50)	N/A	7 (33.3)	N/A

N/A= Not Available

C0004 – *How does the frequency or severity of harms change over time or in different settings?*

The technology is in an early phase of use. No information is available about the performance of different generations of the technology, the performance in different settings or on change over time. The scarcity of available information does not allow estimating differences for the use of the technology.

C0005 – *Are there any susceptible patient groups more likely to be harmed?*

No evidence was found to answer the research question.

C0007 – *Can adverse events be caused by the behaviour of patients, professionals or manufacturers?*

No evidence was found to answer the research question.

C0008 – *How safe is the biodegradable oesophageal stent in relation to the comparators?*

Technical failure:

- *OBS vs dilation:*

No technical failure was reported in the RCT that compared OBS vs dilation [5]. The quality of the evidence was very low.

- *OBS vs SEPS:*

One of the cohort studies [7] reported 2 cases of technical failure among the OBS patients (11% of the patients) and 1 case among the SEPS patients (5%). The difference was not statistically significant (p = 0.49). The quality of the evidence was very low.

The study by Canena et al. reported no technical failure cases [6]. The quality of the evidence was very low.

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- *OBS vs FCSEMS:*

No technical failure was reported in the cohort study that compared OBS vs FCSEMS [6]. The quality of the evidence was very low.

***Total adverse events*:**

- *OBS vs dilation:*

The mean number of adverse events per patient reported in the RCT was higher (statistically significant) for the OBS than for the dilation group [5], being 4.9 in the OBS group and 1.0 in the dilation group (p = 0.001). The quality of the evidence was very low.

- *OBS vs SEPS:*

In the study by Canena et al., the mean number of adverse events per patient was 0.7 for the OBS group and 0.9 for the SEPS group [6]. In the study by van Boeckel et al., the mean number of adverse events per patient was 0.8 in the OBS group and 0.4 in the SEPS group [7]. The quality of the evidence was very low in both studies. Statistical significance was not analysed in either study.

- *OBS vs FCSEMS:*

In the study by Canena et al., the mean number of adverse events per patient was 0.7 in the OBS group and 0.6 in the FCSEMS group [6]. The quality of the evidence was very low. Statistical significance was not analysed.

Serious adverse events:

- *OBS vs dilation:*

The mean number of serious adverse events per patient was higher (statistically significant) in the OBS than in the dilation group [5]. The mean number of serious adverse events per patient was 1.8 in the OBS group and 0 in the dilation group (p = 0.026). The quality of the evidence was very low.

- *OBS vs SEPS:*

In the study by Canena et al., the mean number of serious adverse events per patient was 0.2 in the OBS group and 0 in the SEPS group [6]. Statistical significance was not analysed. In the study by van Boeckel et al., the mean number of serious adverse events per patient was 0.2 in the OBS group and 0.1 in the SEPS group [7]. The difference was not statistically significant (p = 0.3). The quality of the evidence was very low in both studies.

- *OBS vs FCSEMS:*

The study by Canena et al. reported that the mean number of serious adverse per patient was 0.27 in the OBS group and 0 in the FCSEMS group [6]. The quality of the evidence was very low. Statistical significance was not analysed.

Unexpected re-interventions:

- *OBS vs dilation:*

The RCT reported the number of additional procedures performed after intervention including both diagnostic and therapeutic ones [5]. No statistically significant difference was observed between the OBS and the dilation group in the mean number of additional procedures either after 6 or 12 months of follow-up. The quality of the evidence was very low.

- *OBS vs SEPS:*

The study by van Boeckel et al. found a higher mean number of unexpected re-interventions in the SEPS group than in the OBS group, and the difference was statistically significant [7]: 0.8 (0.6 SD) in the OBS group and 1.3 (0.4 SD) in the SEPS group (p = 0.03). The study by Canena et al. did not analyse the statistical differences among OBS and SEPS in terms of unexpected re-interventions [6]. The quality of the evidence was very low.

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- *OBS vs FCSEMS:*

The study by Canena et al. reported a mean of 1.3 re-interventions per patient both in the OBS and FCSEMS groups [6]. The quality of the evidence was very low.

Procedure-related mortality:

No deaths were reported in any of the included studies.

5.3 Discussion

The assessment of safety is based on 5 studies with 86 patients treated with OBS. In addition to the 3 studies included in the effectiveness assessment, 2 further prospective and consecutive case series were included in the body of evidence for safety analysis. The available clinical evidence is limited because of the small study samples and the evidence was of very low quality. In terms of the study populations, considerable differences in terms of inclusion criteria were noted between studies.

For some outcomes, statistically significant differences were found between groups. However, the very low quality of the evidence did not allow us to draw conclusions on safety assessment.

Comparing OBS vs dilation, in the RCT the number of total and serious adverse events were statistically significantly higher for the OBS. For the comparison of OBS vs SEPS, there was a statistically significant higher number of unexpected interventions in the SEPS group. For the comparison of OBS vs FCSEMS, no statistically significant differences were found.

For frequency of adverse events, the available information did not allow the frequency of adverse events to be estimated in relation to use of OBS. Most of the included studies used different methods of reporting adverse events, so it was difficult to make a global assessment. It was also difficult, with the information provided within the articles, to distinguish between adverse events associated with the intervention and those not associated.

The information on adverse events shows that individually some studies reported high percentages of adverse events. The highest frequencies were for moderate pain, severe pain, moderate dysphagia, severe dysphagia, tissue hyperplasia and stent migration.

In summary, reported data indicate non-negligible adverse events occurred, in terms of both frequency and severity. Nevertheless, the available evidence does not allow a reliable safety assessment to be made comparing OBS with other similar technologies for the treatment of RRBOS. With the available evidence, it is not currently possible to assess the safety profile of OBS to treat RRBOS. In the near future, however, the results of an ongoing RCT comparing OBS with oesophageal dilations could provide higher quality evidence.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

METHODS

Overall description of methods

For this pilot rapid assessment, SAGEM (Turkey) was responsible for assessing the "Health problem and current use" and the "Description and technical characteristics" domains. ISCIII (Spain) was responsible for compiling the "Clinical effectiveness" and "Safety" domains, for producing the final assessment containing all domains and for writing the final summary of the assessment.

The general methodology consisted of a systematic review of the literature to obtain information for selected assessment elements. The selection of assessment elements was primarily based on the *HTA Core Model for Rapid REA of Pharmaceuticals (2.0).* Furthermore, the rest of EUnetHTA Core Model Applications were screened and finally 2 additional assessment elements of the EUnetHTA Core Model Applications for *medical and surgical interventions* were included. The following 2 issues were added to the list of clinical effectiveness assessment elements:

- **D0010** – How does the technology modify the need for hospitalisation?
- **D0023** – How does the technology modify the need for other technologies and use of resources?

The following sources were used to obtain information:

- PubMed®
- Embase™
- The Cochrane Library
- DARE (Database of Abstracts of Reviews of Effects)
- HTA (Health Technology Assessment) database
- NHS-EED (National Health Service Economic Evaluation Database)
- Clinical trials registries for registered ongoing clinical trials or observational studies: ISRCTN, NIH ClinicalTrials, WHO International Clinical Trials Registry Platform
- Request to the manufacturer.

We selected relevant articles or documents according to the PICOS design-scheme described in the project plan.

For the effectiveness domain only comparative studies were included.

For the safety domain we selected also non-comparative studies but excluded the following:

- Studies with less than 10 patients
- Retrospective case series with non-consecutive enrolment
- Studies with less than 6 weeks of follow-up
- Congress Abstracts.

For the domains "Health Problem and Current Use of the Technology" and "Description and Technical Characteristics of the Technology" a basic search was performed in PubMed® and Google and a hand search was carried out in textbooks. An assessment element specific search was performed for the research question concerning kind of registry. EU legislation and guidelines accessed by European Commission websites were searched for marketing authorisation status. A survey for gathering information on the reimbursement status was sent to EUnetHTA partners.

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A detailed description of the search and selection process for the domains “Safety” and “Clinical Effectivenes” is available below. The included and excluded articles with their exclusion reasons are listed in *Table 4* and *Table 5*.

Articles written in the following languages were included: English, Spanish, French, Turkish, German, Italian, and Portuguese. As a consequence of the selection process 1 article written in Czech was excluded [60]. It was a case series reporting data of patients treated with biodegradable stent (SX-ELLA Stent Oesophageal Degradable) between 2001 and 2007 (previous to the CE mark authorisation).

We used the GRADE-methodology to assess the quality of evidence for effectiveness and safety [54]. The quality of evidence was classified and defined as high (i.e. “Further research is very unlikely to change our confidence in the estimate of effect”); moderate (i.e. “Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate”); low (i.e. “Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate”); very low (i.e. “Any estimate of effect is very uncertain”).

The risk of bias was analysed by using the Cochrane risk of bias tool for RCTs [55] and the Newcastle-Ottawa scale for cohort studies [56]. The quality of case series was analysed by using the Case series checklist of the Institute for Health Economics [57]. We did not combine results in a meta-analysis because of the absence of large and homogeneous studies.

From the selected studies, study characteristics and results concerning effectiveness and safety were extracted into a data extraction table by 2 independent researchers, resolving disagreements by consensus.

Documentation of the search strategies

Search strategy for PubMed®

Database: PubMed® No restrictions Date of search: January 14, 2015	
(“Absorbable implants”[Mesh] OR “bioprosthesis”[Mesh] OR ((bioabsorbable OR biodegradable) AND “Stents”[Mesh])) AND ("Esophageal Stenosis”[Mesh] OR “Esophageal achalasia”[Mesh] OR “esophageal spasm, diffuse”[Mesh] OR ((“Constriction, Pathologic”[Mesh] OR obstruction OR dyskinesia OR dysphagia OR stricture OR stenosis) AND “Esophagus”[Mesh]))	63

Search strategy for Embase™

Database: Embase™ No restrictions Date of search: January 14, 2015	
((absorbable AND ('implants'/exp OR implants) OR 'bioprosthesis'/exp OR bioprosthesis OR (bioabsorbable OR biodegradable AND ('stents'/exp OR stents)) AND (oesophageal AND ('stenosis'/exp OR stenosis) OR oesophageal AND ('achalasia'/exp OR achalasia) OR oesophageal AND ('spasm'/exp OR spasm) AND diffuse OR ('constriction'/exp OR constriction AND pathologic OR 'obstruction'/exp OR obstruction OR 'dyskinesia'/exp OR dyskinesia OR 'dysphagia'/exp OR dysphagia OR stricture OR 'stenosis'/exp OR stenosis AND ('oesophagus'/exp OR oesophagus)))	136

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Search strategy for Centre for Reviews and Dissemination (CRD) databases

Databases: Cochrane, DARE, HTA, NHS-EED No restrictions Date of search: January 14, 2015	
(“Absorbable implants” OR “bioprosthesis” OR ((bioabsorbable OR biodegradable) AND “Stents”)) AND (“Esophageal Stenosis” OR Oesophageal Stenosis) OR (“Esophageal achalasia” OR “Oesophageal achalasia”) OR (“Esophageal spasm” OR “Oesophageal spasm”) OR ((“Constriction OR obstruction OR dyskinesia OR dysphagia OR stricture OR stenosis) AND (“Esophagus" OR “Oesophagus”))	18

Search strategy for Clinical Trials

Databases: ISRCTN, NIH ClinicalTrials, WHO International Clinical Trials Registry Platform No restrictions Date of search: January 15, 2015	
Biodegradable stent, absorbable stent, degradable stent	1

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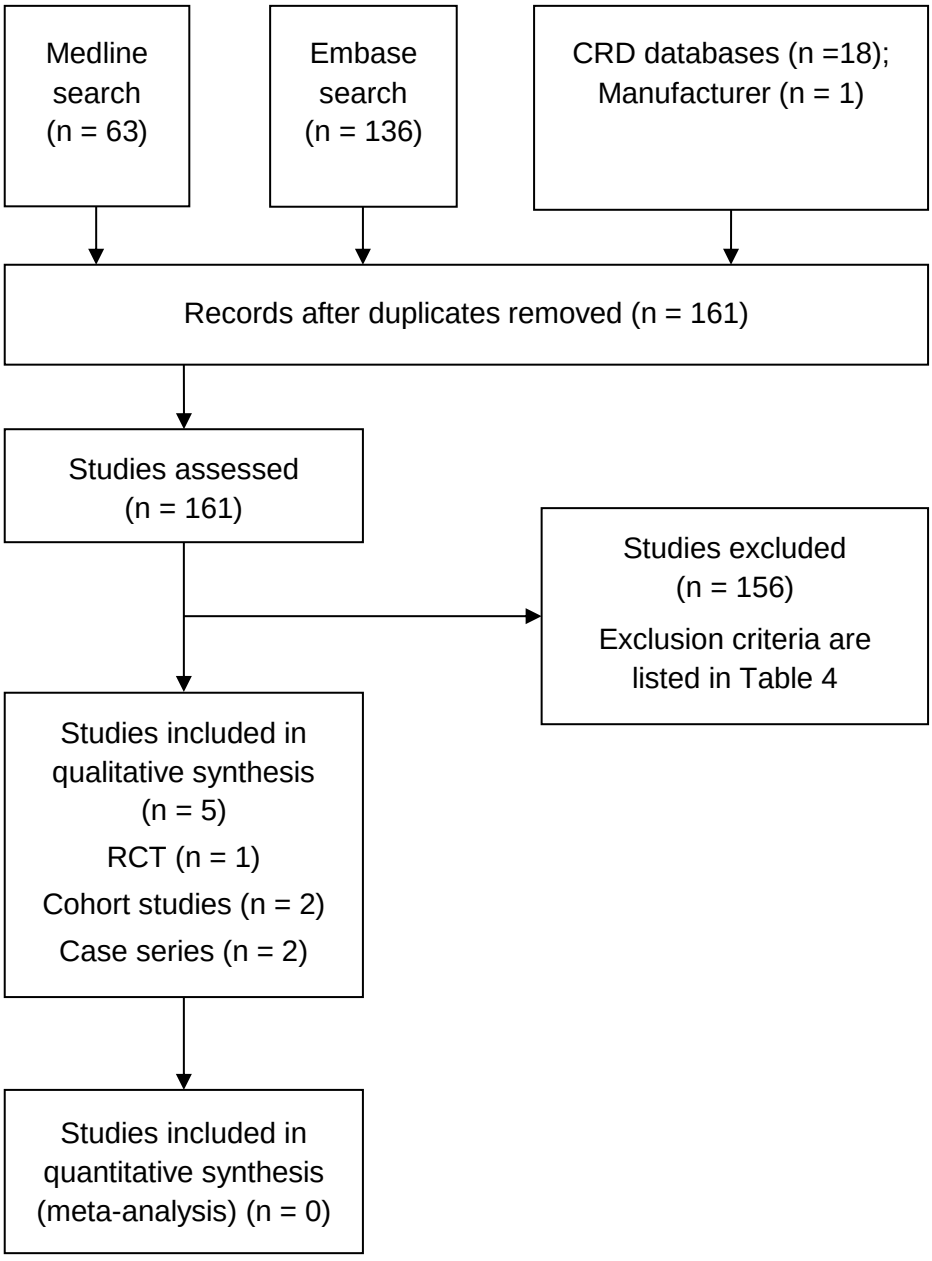
Flow chart of study selection



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DESCRIPTION OF THE EVIDENCE USED

List of included and excluded studies

Table 4: Included studies

Reference	
1	Canena JMT, Liberato MJA, Rio-Tinto RAN, Pinto-Marques PM, Romão CMM, Coutinho AVMP, Neves BAHC, Santos-Silva MFCN. A comparison of the temporary placement of 3 different self-expanding stents for the treatment of refractory benign esophageal strictures: a prospective multicentre study. BMC Gastroenterol. 2012; 12: 70.
2	Dhar A, Close H, Viswanath YK, Rees CJ, Hancock HC, Dwarakanath AD, et al. Biodegradable stent or balloon dilatation for benign oesophageal stricture: pilot randomised controlled trial. World J Gastroenterol 2014 ; 20 (48): 18199-206.
3	Hirdes MMC, Siersema PD, Van Boeckel PGA, Vleggaar FP. Single and sequential biodegradable stent placement for refractory benign esophageal strictures: A prospective follow-up study. Endoscopy 2012; 44 (7): 649-54.
4	Repici A, Vleggaar FP, Hassan C, van Boeckel PG, Romeo F, Pagano N, et al. Efficacy and safety of biodegradable stents for refractory benign esophageal strictures: the BEST (Biodegradable Esophageal Stent) study. Gastrointest Endosc 2010; 72 (5): 927-34.
5	Boeckel van PGA, Vleggaar FP, Siersema PD. A comparison of temporary self-expanding plastic and biodegradable stents for refractory benign esophageal strictures. Clin Gastroenterol Hepatol 2011; 9 (8): 653-9.

Table 5: Excluded studies

Reference		Exclusion criteria
1	Abu Dayyeh BK, Vandamme JJ, Miller RC, Baron TH. Esophageal self-expandable metal stents material and mesh grid density are the biggest determinants of radiation dose enhancement in the setting of esophageal radiotherapy. Gastrointest Endosc 2012; 75 (4): AB458.	Intervention: Metal stents
2	Abu Dayyeh BK, Vandamme JJ, Miller RC, Baron TH. Esophageal self-expandable stent material and mesh grid density are the major determining factors of external beam radiation dose perturbation: results from a phantom model. Endoscopy 2013; 45 (1): 42-7.	Intervention: No biodegradable stents
3	Ahmad M. Corrosive oesophageal stricture-efficacy of maintained over intermittent dilatation-a case report. J Gastroenterol Hepatol 2013; 28: 297-8.	Design: Single case
4	Aikawa M, Miyazawa M, Okamoto K, Okada K, Akimoto N, Sato H, et al. A bioabsorbable polymer patch for the treatment of esophageal defect in a porcine model. J Gastroenterol 2013 Jul;48(7):822-9.	Population: Animal model
5	Aikawa M, Miyazawa M, Ueno Y, Nonaka K, Okada K, Toshimitsu Y, et al. Treatment of perforated esophagus with a bio-degradable polymer stent. Gastroenterology 2011; 140 (5):S185-S186.	Population: Animal model
6	Alam M, Rosman HS, Polanco GA, Sheth M, Garcia R, Serwin JB. Transesophageal echocardiographic features of stenotic bioprosthetic valves in the mitral and tricuspid valve positions. AM J CARDIOL 1991; 68 (6): 689-90.	Intervention: Cardiac valve
7	Alberca F, Navalon-Rubio M, Egea-Valenuela J, Munoz-Tornero M, Alvarez-Higueras J, Carballo-Alvarez F. Management of refractory esophageal stenosis in pediatric age. Gastrointest Endosc 2014; 79 (5): AB289.	Congress abstract
8	Arend SM, Kuijper EJ, De Vaal BJ, De Fijter JW, Van't Wout JW. Successful treatment of fungus balls due to fluconazole-resistant Candida sake obstructing ureter stents in a renal transplant patient. Eur J Clin Microbiol Infect Dis 2006; 25 (1): 43-5.	Intervention: Ureter stents
9	Ashraf S, Willert R. Use of biodegradable stent in refractory benign oesophageal stricture. Am J Gastroenterol 2013; 108: S207.	Design: Single case

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Reference		Exclusion criteria
10	Atienza G. Endoluminal brachytherapy in the treatment of cancer of the oesophagus. Santiago de Compostela: Galician Agency for Health Technology Assessment (AVALIA-T). CT2010/04. 2010	Population: esophageal cancer
11	Basha J, Appasani S, Vaiphei K, Gupta V, Singh K, Kochhar R. Biodegradable stents: Truly biodegradable with good tissue harmony. Endoscopy 2013;45(SUPPL.2):E116-E117.	Design: Narrative review
12	Battaglia G, Bocus P, Diamantis G, Pomerri F, Realdon S. Which stent stenosis of the esophagus which. G Ital Endosc Dig 2010;33(3):207-12.	Design: Narrative review
13	Battersby I, Doyle R. Use of a biodegradable self-expanding stent in the management of a benign oesophageal stricture in a cat. J Small Anim Pract 2010; 51 (1): 49-52.	Population: Animal model
14	Birch JF, White SA, Berry DP, Veitch PS. A cost-benefit comparison of self-expanding metal stents and Atkinson tubes for the palliation of obstructing esophageal tumors. Dis Esophagus 1998 ;11 (3) :172-6.	Intervention: metal stents vs Atkinson tubes
15	Bozzo C, Meloni F, Trignano M, Profili S. Mediastinal abscess and esophageal stricture following voice prosthesis insertion. Auris Nasus Larynx 2014; 41 (2): 229-33.	Intervention: Tracheoesophageal voice prosthesis
16	Carachi R, Azmy A, Gorham S, Reid J, French DA. Use of a bioprosthesis to relieve tension in oesophageal anastomosis: An experimental study. BR J SURG 1989; 76 (5): 496-8.	Population: Animal model
17	Cerna M, Kocher M, Valek V, Aujesky R, Neoral C, Andrasina T, et al. Covered biodegradable stent: New therapeutic option for the management of esophageal perforation or anastomotic leak. Cardiovasc Intervent Radiol 2011; 34 (6): 1267-71.	Design: Case series. 5 patients
18	Cerna M, Kocher M, Valek V, Aujesky R, Neoral C, Andrasina T, et al. Treatment of benign esophageal fistulae by covered biodegradable stents – The first results. Ceska Radiol 2011; 65 (2):112-6.	Duplicated patients
19	Cerna M, Kocher M, Valek V, Panek J, Andrasina T. The effectiveness of treatment of benign oesophageal strictures resistant to the balloon dilation by biodegradable stents. Cardiovasc Intervent Radiol 2012; 35: S231.	Congress abstract
20	Conio M, Blanchi S, De CA. Removable and biodegradable stents for benign esophageal strictures. G Ital Endosc Dig 2012; 35 (3): 245-9.	Design: Narrative review
21	Contini S, Scarpignato C. Caustic injury of the upper gastrointestinal tract: A comprehensive review. World J Gastroenterol 2013; 19 (25): 3918-30.	Design: Narrative review
22	Dasari BV, Neely D, Kennedy A, Spence G, Rice P, Mackle E, Epanomeritakis E. The role of esophageal stents in the management of esophageal anastomotic leaks and benign esophageal perforations. Annals of Surgery 2014; 259 (5): 852-860.	Intervention: Metal and plastic stents
23	De Gregorio MA, Laborda A. GI stenting. Cardiovasc Intervent Radiol 2009;32:242-3.	Design: Narrative review
24	Delikaris PG, Hatzipantelis KP, Filintatzi C, Kotakidou RE, Kitis G, Raptopoulos D. The use of a dura mater patch to cover oesophageal defects of different sizes: an experimental study in chickens. Eur J Surg 1999 Feb; 165 (2): 151-7.	Population: Animal model
25	Desai KM, Diaz S, Dorward IG, Winslow ER, La Regina MC, Halpin V, et al. Histologic results 1 year after bioprosthetic repair of paraesophageal hernia in a canine model. Surg Endosc Interv Tech 2006; 20 (11): 1693-7.	Population: Animal model
26	Detweiler MB, Kobos JW, Fenton J. Gastrointestinal sutureless anastomosis in pigs using absorbable intraluminal stents, stent placement devices, and fibrin glue – A summary. Langenbeck's Arch Surg 1999; 384 (5): 445-52.	Population: Animal model
27	Deviere J, Pastorelli A, Louis H, de M, V, Lehman G, Cicala M, et al. Endoscopic implantation of a biopolymer in the lower esophageal sphincter for gastroesophageal reflux: a pilot study. Gastrointest Endosc 2002; 55 (3): 335-41.	Population: Grastroesophagial reflux disease
28	Dhar A, Topping JH, Johns E, O'Neill D. Biodegradable stents in refractory benign oesophageal strictures – First report of 4 patients from UK. Gastrointest Endosc 2009; 69 (5): AB254-AB255.	Congress abstract

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Reference		Exclusion criteria
29	Didden P, Spaander MCW, Bruno MJ, Kuipers EJ. Esophageal stents in malignant and benign disorders. Curr Gastroenterol Rep 2013; 15 (4).	Design: Narrative review
30	Digestive Diease Week 2012, DDW 2012. Gastrointest Endosc 2012; 75 (4).	Design: Narrative review
31	Doede T, Bondartschuk M, Joerck C, Schulze E, Goernig M. Unsuccessful alloplastic esophageal replacement with porcine small intestinal submucosa. Artif Organs 2009; 33 (4): 328-33.	Intervention: No biodegradable stents
32	Dua KS. Expandable stents for benign esophageal disease. Gastrointest Endosc Clin North Am 2011; 21 (3): 359-76.	Design: Narrative review
33	Dumoulin FL, Plassmann D. Tissue hyperplasia following placement of a biodegradable stent for a refractory esophageal stricture: treatment with argon plasma coagulation. Endoscopy 2012; 44 Suppl 2 UCTN: E356-E357.	Intervention: Argon plasma coagulation
34	Erickson L. Assessment of photodynamic therapy using porfimer sodium for esophageal, bladder and lung cancers. Montreal: Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS), 2004.	Population: esophageal cancer
35	Esophagus: Biodegradable stents deliver good dysphagia relief in patients with esophageal strictures. Nat Rev Gastroenterol Hepatol 2012.	Design: Narrative review. Comment on Griffiths 2012
36	Fischer A, Bausch D, Baier P, Braun A, Richter-Schrag H. Risk of biodegradable stent-induced hypergranulation causing re-stenosis of a gastric conduit after esophageal resection. Endoscopy 2012; 44 (SUPPL. 2): E125-E126.	Population: Gastric stenosis
37	Freud E, Efrati I, Kidron D, Finally R, Mares AJ. Comparative experimental study of esophageal wall regeneration after prosthetic replacement. J Biomed Mater Res 1999 May; 45 (2): 84-91.	Intervention: Oesophageal wall regeneration
38	Fry SW, Fleischer DE. Management of a refractory benign esophageal stricture with a new biodegradable stent. Gastrointest Endosc 1997; 45 (2): 179-82.	Design: Single case
39	Fukunaga N, Okada Y, Konishi Y, Murashita T, Yuzaki M, Shomura Y, et al. Aortic valve replacement after esophagectomy with substernal gastric tube and total laryngectomy with tracheostoma. Ann Thorac Surg 2012; 94 (1): 271-3.	Intervention: No biodegradable stents
40	Gajraj R, Moore D, Jones B, Song F. Expandable metal stents for inoperable oesophageal cancer. DPHE Report No. 40. Birmingham, UK: West Midlands Health Technology Assessment Collaboration, Department of Public Health and Epidemiology, University of Birmingham (WMHTAC); 2002	Intervention: No biodegradable stents
41	Ganz RA, Bonavina L, DeMeester TR, Dunn DH, Lipham JC, Saino G, et al. Magnetic sphincter augmentation is safe and effective for the long-term treatment of gastroesophageal reflux disease (GERD). Gastroenterology 2009; 136 (5): A739.	Intervention: No biodegradable stents
42	Ganz RA, DeMeester TR, Dunn DH, Lipham JC, Saino G, Bona D, et al. Long-term, safe and effective treatment of gastroesophageal reflux disease using a sphincter augmentation device. Gastroenterology 2010; 138(5):S645.	Intervention: No biodegradable stents
43	Ge X. Clinical application of covered stents in treating esophageal malignant stenosis. J Clin Rehab Tissue Eng Res 2010;14(4):702-5.	Population: Malignant stenosis
44	Giercksky KE, Gronbech JE, Hammelbo T, Hirschberg H, Lundar T, Mjaland O, et al. Use of palliative surgery in the treatment of cancer patients. Report 8. The Norwegian Centre for Health Technology Assessment: Oslo, 2003	Population: esophageal cancer
45	Girgis RE, Rosman H, del BR, Fitzmaurice M, Silverman NA. Porcine bioprosthetic aortic valve endocarditis with ring abscess and aortic stenosis. Henry Ford Hosp Med J 1991; 39(2):123-5.	Population: Animal model
46	Gossot D, Azoulay D, Piriou P, Sarfati E, Celerier M. [Use of the colon for esophageal substitution. Mortality and morbidity. Report of 105 cases]. Gastroenterol Clin Biol 1990; 14(12):977-81.	Intervention: Oesophageal substitution
47	Griffiths EA, Gregory CJ, Pursnani KG, Ward JB, Stockwell RC. The use of biodegradable (SX-ELLA) oesophageal stents to treat dysphagia due to benign and malignant oesophageal disease. Surg Endosc Interv Tech 2012; 26(8):2367-75.	Design: Case series. 7 patients

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Reference		Exclusion criteria
48	Grubnik VV, Malynovskyy AV. Laparoscopic repair of hiatal hernias: New classification supported by long-term results. Surg Endosc Interv Tech 2013; 27(11):4337-46.	Intervention: Laparoscopic repair of hiatal hernia
49	Guitron-Cantu A, Adalid-Martinez R, Gutierrez-Bermudez JA, Meza ME, Segura Lopez FK, Garcia VA. Foreign body reaction of a biodegradable esophageal stent. A case report. Rev Gastroenterol Mex 2010;75(2):203-7.	Design: Single case
50	Hair CS, Devonshire DA. Severe hyperplastic tissue stenosis of a novel biodegradable esophageal stent and subsequent successful management with high-pressure balloon dilation. Endoscopy 2010; 42(SUPPL. 2):E132-E133.	Design: Single case
51	Harewood GC, Wiersema MJ. A cost analysis of endoscopic ultrasound in the evaluation of esophageal cancer. American Journal of Gastroenterology 2002; 97(2): 452-458.	Population: esophageal cancer
52	Hazeldine S, Wu J, Law R, Przemioslo R. Biodegradable oesophageal stents for refractory benign disease: A case series. Gut 2011; 60:A174-A175.	Congress abstract
53	Herzog J, Eickhoff A. Self-expandable metal stents in the gastrointestinal tract – Indications and fields of application. Gastroenterologe 2012; 7(5):435-45.	Intervention: No biodegradable stents
54	Hinze J. A novel method of securing airway stents. Chest 2012; 142 (4).	Intervention: Securing airway stents
55	Hirdes,MMC.; Siersema,P. Endoprosthetics for malignant esophageal disease. Techniques in Gastrointestinal Endoscopy 2014.Vol 16, Issue 2, 64–70	Population: Malignant stenosis
56	Hirdes MMC, Van Hooft JE, Wijrdeman HK, Hulshof MCCM, Fockens P, Reerink O, et al. Combination of biodegradable stent placement and single-dose brachytherapy is associated with an unacceptably high complication rate in the treatment of dysphagia from esophageal cancer. Gastrointest Endosc 2012;76(2):267-74.	Population: Malignant stenosis
57	Hirdes MMC, Vleggaar FP, SierseM.A.P.D. Stent placement for esophageal strictures: An update. Expert Rev Med Devices 2011;8 (6):733-55.	Design: Narrative review
58	Hlavaty,T.; Koller,T.; Toth,J.; Huorka,M. Expandable stents in the treatment of benign and malignant tumors of the esophagus. Gastroent Hepatol 2014; 68 (5): 441-450.	Design: Narrative review
59	Holt BA, Hair CS, Barnes MB, Alexander S, Moore GT, Devonshire DA. Clinical outcome following placement of biodegradable stents for benign oesophageal stenoses: Preliminary Results from the Victorian BD stent study group. J Gastroenterol Hepatol 2010;25:A62.	Congress abstract. Design: Case series. 9 patients
60	Holt BA, Hair CS, Barnes MB, Alexander S, Moore GT, Devonshire DA. Severe hyperplastic tissue stenosis complicating biodegradable stents for benign oesophageal stenosis: Successful management with balloon dilation. J Gastroenterol Hepatol 2010;25: A62-A63.	Congress Abstract
61	Hourneaux,G.; de,Moura E.; Sakai,P.; Cecconello,I.; Ishioka,S. Palliative treatment of advanced esophageal cancer. Comparative study: auto-expandable metal stent and isoperistaltic esophagogastric bypass. Acta Gastroenterol.Latinoam. 2001; 31(1): 13-22.	Population: Malignant stenosis
62	Husein BB, Iqbal J, Al-Ani Z, Stockwell R. Bio-degradable oesophageal stents. Are they worth the pain? Gastroenterology 2012;142(5):S585.	Congress abstract. Population: Includes malignancy
63	Ibrahim M. et al. Belgian multicenter experience with biodegradable ELLA stent in benign strictures of digestive tract. Endoscopy 2010; 42 (Suppl I) A259	Congress abstract
64	Irani S, Kozarek R. Esophageal stents: Past, present, and future. Tech Gastrointest Endosc 2010;12(4):178-90.	Design: Narrative review
65	Jones,C.M.; Griffiths,E.A. Should oesophageal stents be used before neo-adjuvant therapy to treat dysphagia in patients awaiting oesophagectomy? Best evidence topic (BET). International Journal of Surgery 2014; 12(11): 1172-1180.	Population: Malignant stenosis

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Reference		Exclusion criteria
66	Jung GE, Sauer P, Schaible A. Tracheoesophageal fistula following implantation of a biodegradable stent for a refractory benign esophageal stricture. Endoscopy 2010;42(SUPPL. 2):E338-E339.	Design: Single case
67	Kang S-G. Gastrointestinal stent update. Gut Liver 2010;4(SUPPL. 1):S19-S24.	Design: Narrative review
68	Karakan T, Utku OG, Dorukoz O, Sen I, Colak B, Erdal H, et al. Biodegradable stents for caustic esophageal strictures: A new therapeutic approach. Dis Esophagus 2013;26(3):319-22.	Design: Case series. 7 patients
69	Karalis DG, Chandrasekaran K, Ross JJ, Jr., Micklin A, Brown BM, Ren JF, et al. Single-plane transesophageal echocardiography for assessing function of mechanical or bioprosthetic valves in the aortic valve position. Am J Cardiol 1992 May 15;69(16):1310-5.	Intervention: Transeophageal echocardiography
70	Ket S, Lee S, Devonshire D. Endoscopic management of stoma stenosis following vertical banded gastroplasty. J Gastroenterol Hepatol 2013;28:48.	Intervention: No biodegradable stents
71	Khan KM. Endoscopic management of strictures in pediatrics. Tech Gastrointest Endosc 2013;15(1):25-31.	Design: Narrative review
72	Kim CD, Kim ES. Now and the future of gastrointestinal and biliary stent. Dig Endosc 2010;22(4):A25.	Population: Gastrointestinal and biliar diseases
73	Kim S, Van Oijen MG, Agarwal N, Hamerski CM, Watson RR, Muthusamy VR. Biodegradable stents are superior to fully covered metal stents in the endoscopic management of refractory benign esophageal strictures: A meta-analysis. Gastrointest Endosc 2013; 77(5):AB213-AB214.	Congress abstract
74	Kim S, Van Oijen MG, Watson RR, Hamerski CM, Siersema PD, Muthusamy VR. Identifying the ideal strategy for the management of refractory benign esophageal strictures: A cost-minimization analysis. Gastrointest Endosc 2013; 77(5):AB213.	Design: Narrative review
75	Kochar R, Shah N. Enteral stents: From esophagus to colon. Gastrointest Endosc 2013; 78(6):913-8.	Design: Narrative review
76	Kocher M, Valek V, Cerna M, Kozak J, Neoral C, Aujesky R, et al. The treatment of benign oesophageal strictures resistant to the balloon dilation by biodegradable stents. Ceska Radiol 2011;65(2):131-6.	Duplicated patients
77	Kochhar R, Choudury G, Lakhtakia S, Verma A, Khaliq A, Appasani S, et al. Biodegradable stents for caustic esophageal strictures: Do they work? J Gastroenterol Hepatol 2012;27:327.	Congress abstract
78	Konigsrainer A, Riedmann B, De Vries A, Ofner D, Spechtenhauser B, Aigner F, et al. Expandable metal stents versus laser combined with radiotherapy for palliation of unresectable esophageal cancer: a prospective randomized trial. Hepato-Gastroenterology 2000; 47 (33): 724-727.	Intervention: No biodegradable stents
79	Kovacs T, Nemeth T, Orosz Z, Koves I. Endoscopy and autopsy follow-up of biodegradable oesophageal anastomoses in dogs. Acta Vet Hung 2001;49(4):451-63.	Population: Animal model
80	Krokidis M, Burke C, Spiliopoulos S, Gkoutzios P, Hynes O, Ahmed I, et al. The use of biodegradable stents in malignant oesophageal strictures for the treatment of dysphagia before neoadjuvant treatment or radical radiotherapy: A feasibility study. Cardiovasc Intervent Radiol 2013;36(4):1047-54.	Population: Malignant stenosis
81	Kunihisa T, Handa N, Okada Y. Mini-sternotomy approach for aortic valve replacement in the patient with retrosternal gastric tube. Thorac Cardiovasc Surg 2008 Aug;56(5):300-1.	Population: Malignant stenosis
82	Lambert R. Treatment of esophagogastric tumors. Endoscopy 2003;35(2):118-26.	Population: Malignant stenosis
83	Lampe P, Kabat J, Gorka Z, Mrowiec S, Bursig H. Biostatic endoprosthesis of the esophagus for prevention of leakage and stenosis at the site of anastomosis. Wiad Lek 1997;50 Suppl 1 Pt 1:372-6.	Intervention: Type of prosthesis
84	Lee E, Frisella MM, Matthews BD, Brunt LM. Evaluation of acellular human dermis reinforcement of the crural closure in patients with difficult hiatal hernias. Surg Endosc Interv Tech 2007;21(4):641-5.	Intervention: Laparoscopic repair of hiatal hernia

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Reference		Exclusion criteria
85	Li F, Cheng Y-S. Application progress of stent placement in esophageal malignant and benign stenosis. World Chin J Dig 2008;16(25):2841-7.	Design: Narrative review
86	Lopasso FP, Bernardes JL, de Macedo SJ. [Round ligament-gastroplasty associated with antireflux valve in the treatment of sliding hiatal hernia. Study of 33 cases]. Rev Paul Med 1982 Jul;100(1):4-7.	Population: Hiatal hernia
87	Lopez-Viedma B, Lorente-Poyatos R, Domper-Bardaji F, Santa-Belda E, Hernandez-Albujar A, Paton-Arenas R, et al. [Usefulness of self-expanding biodegradable prosthesis in the treatment of refractory benign stenosis: a case series study]. Rev Gastroenterol Mex 2011 Apr;76(2):81-8.	Design: Case series. 7 patients
88	Luc G, Durand M, Collet D, Guillemot F, Bordenave L. Esophageal tissue engineering. Expert Rev Med Devices 2014;11(2):225-41.	Design: Narrative review
89	Manova G, Totev M, Garvanska G, Ilieva E. Biodegradable esophageal stent placement: A novel or routine procedure? Cardiovasc Intervent Radiol 2013;36:S300-S301.	Congress abstract. Design: Case series. 6 patients
90	Mansour KA, Hansen HA, Hersh T, Miller JI, Jr., Hatcher CR, Jr. Colon interposition for advanced nonmalignant esophageal stricture: experience with 40 patients. Ann Thorac Surg 1981 Dec;32(6):584-91.	Intervention: Colon interposition
91	Martin CF, Rodriguez VJ, Velasco SB, Herrera M, I. [Use of self-expandable prosthesis in esophageal stenosis in children]. Cir Pediatr 2012;25(4):207-10.	Design: Case series. 3 patients
92	Mazzitelli D, Bedda W, Petrova D, Lange R. Right parasternal approach for aortic valve replacement after retrosternal gastropexy. Eur J Cardio-thorac Surg 2004;25(2):290-2.	Intervention: Aortic valve replacement
93	McLoughlin MT, Byrne MF. Endoscopic stenting – Where are we now and where can we go? World J Gastroenterol 2008;14(24):3798-803.	Design: Narrative review
94	Mochizuki Y, Saito Y, Tanaka T, Nitta N, Yamada H, Tsujikawa T, et al. Endoscopic submucosal dissection combined with the placement of biodegradable stents for recurrent esophageal cancer after chemoradiotherapy. J Gastrointest Cancer 2012;43(2):324-8.	Population: Malignant stenosis
95	Mondragon OVH, De Leon Salazar OED, Valencia JMB. Safety and efficacy of biodegradable stents (BS) in elderly patients (EP) with achalasia. Gastrointest Endosc 2013;77(5):AB352-AB353.	Congress abstract. Intervention: Unknown device
96	Morgan R, Adam A. Use of metallic stents and balloons in the esophagus and gastrointestinal tract. J Vasc Intervent Radiol 2001;12(3):283-97.	Intervention: No biodegradable stents
97	Nagashima A, Ando N, Sato M, Ozawa S, Kitajima M. Basic studies on the application of an artificial esophagus using cultured epidermal cells. Surg Today 1997;27(10):915-23.	Intervention: Cultured epidermal cells
98	Nandipati,K.; Bye,M.; Yamamoto,S.R.; Pallati,P.; Lee,T.; Mittal,S.K. Reoperative Intervention in Patients with Mesh at the Hiatus is Associated with High Incidence of Esophageal Resection-A Single-Center Experience. Journal of Gastrointestinal Surgery 2013; 17 (12): 2039-2044.	Intervention: Mesh hiatoplasty
99	Nicholson DA, Haycox A, Kay CL, Rate A, Attwood S, Bancewicz J. The cost effectiveness of metal oesophageal stenting in malignant disease compared with conventional therapy. Clinical Radiology 1999; 54(4): 212-215.	Intervention: No biodegradable stents
100	Nogales RO, Huerta MA, Merino RB, Gonzalez AC, Cos AE, Menchen Fernandez-Pacheco P. Esophageal obstruction due to a collapsed bio-degradable esophageal stent. Endoscopy 2011;43(SUPPL. 2):E189-E190.	Design: Single case
101	O'Donnell CA, Fullarton GM, Watt E, Lennon K, Murray GD, Moss JG. Randomized clinical trial comparing self-expanding metallic stents with plastic endoprostheses in the palliation of oesophageal cancer. British Journal of Surgery 2002; 89(8): 985-992.	Intervention: No biodegradable stents
102	Oelschlager B, Pellegrini C, Nelson J, Mitsumori L, Hunter J, Sheppard B, et al. Does a biologic prosthesis really reduce recurrence after laparo-scopic paraesophageal hernia repair? [3]. Ann Surg 2007;246(6):1117-8.	Design: Narrative review

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Reference		Exclusion criteria
103	Okata,Y.; Hisamatsu,C.; Bitoh,Y.; Yokoi,A.; Nishijima,E.; Maeda,K.; Yoshida, M.; Ishida,T.; Azuma,T.; Kutsumi,H. Efficacy and histopathological esophageal wall damage of biodegradable esophageal stents for treatment of severe refractory esophageal anastomotic stricture in a child with long gap esophageal atresia. Clinical Journal of Gastroenterology 2014; 7 (6): 496-501.	Design: Single case
104	Orifjonov,N.; Tilavov,U.H. Using of biodegradable stent extension cicatricial esophageal strictures in children. Pediatric Critical Care Medicine 2014;15(4):45.	Congress abstract
105	Orive-Calzada A, Alvarez-Rubio M, Romero-Izquierdo S, Cobo MM, Juanmartinena JF, Ogueta-Fernandez M, et al. Severe epithelial hyperplasia as a complication of a novel biodegradable stent. Endoscopy 2009;41 Suppl 2:E137-E138.	Design: Single case
106	Papachristou GI, Baron TH. Use of stents in benign and malignant esophageal disease. Rev Gastroenterol Disord 2007;7(2):74-88.	Design: Narrative review
107	Pauli EM, Schomisch SJ, Furlan JP, Marks AS, Chak A, Lash RH, et al. Biodegradable esophageal stent placement does not prevent high-grade stricture formation after circumferential mucosal resection in a porcine model. Surg Endosc Interv Tech 2012;26(12):3500-8.	Population: Animal model
108	Petruzziello L, Costamagna G. Stenting in esophageal strictures. Dig Dis 2002; 20 (2): 154-66.	Design: Narrative review
109	Pichon Riviere A, Augustovski F, Garcia Marti S, Glujovsky D, Alcaraz A, Lopez A, Bardach A. Photodynamic therapy for Barrett's esophagus and esophageal cancer. Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS), 2012.	
110	Placer Peralta LJ, Diarte de Miguel JA, Sanchez-Navarro F, Artal BA, Monzon Lomas FJ, San Pedro FA. Coronary ostial stenosis after an aortic valve replacement diagnosed by transesophageal echocardiography. Rev Esp Cardiol 1993; 46(4):255-6.	Intervention: Coronary ostial stenosis
111	Ragunath K. Refractory benign esophageal strictures: Extending the role of expandable stents. Am J Gastroenterol 2008;103(12):2995-6.	Design: Narrative review
112	Rameshshanker R, Patel P, Moorghen M, Pitcher M. Clinical and laboratory characteristics and the use of biodegradable stents in eosinophilic oesophagitis: A single centre UK experience. Gut 2012;61:A369-A370.	Congress abstract
113	Rao,C.; Haycock,A.; Zacharakis,E.; Krasopoulos,G.; Yakoub,D.; Protopapas,A.; Darzi,A.; Hanna,G.B.; Athanasiou,T. Economic analysis of esophageal stenting for management of malignant dysphagia. Dis.Esophagus 2009; 22(4): 337-347.	Population: Malignant stenosis
114	Repici,A.; Genco,C.; Bravata` I.; Anderloni,A. Endoprosthetics in the treatment of benign esophageal strictures. Techniques in Gastrointestinal Endoscopy 2014; Vol 16,(2): 71–78.	Design: Narrative review
115	Repici A, Hassan C, Sharma P, Conio M, Siersema P. Systematic review: the role of self-expanding plastic stents for benign oesophageal strictures. Alimentary Pharmacology and Therapeutics 2010; 31(12):1268-1275.	Intervention: No biodegradable stents
116	Repici,A.; Jovani,M.; Bianchetti,M.; Genco,C.; Ferrara,E.C.; Ciscato,C.; Strangio,G.; Ghezzo,L.; Omodei,P.D.; Carrara,S.; Rosati,R.; Malesci,A. Long-term outcome in patients with benign esophageal refractory strictures treated. Digestive and Liver Disease 2014; 46: S89.	Congress abstract
117	Repici A, Vleggaar FP, Carlino A, Van Boeckel PG, Romeo F, Siersema PD. Benign refractory esophageal strictures: Preliminary results from the best (biodegradable esophageal stent) study. Gastrointest Endosc 2009;69(5):AB123.	Duplicated patients
118	Rodriguez Sanchez MJ, Lopez VB, Fernandez G, Lorente PR, Domper BF, De La Santa BE, et al. Initial experience with biodegradable stents in the treatment of refractary benign gastrointestinal strictures. Clin Gastroenterol Hepatol 2011;9(2):187-8.	Design: Case series. 7 patients
119	Roebuck DJ, Hogan MJ, Connolly B, McLaren CA. Interventions in the Chest in Children. Tech Vasc Intervent Radiol 2011;14(1):8-15.	Design: Narrative review

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Reference		Exclusion criteria
120	Saito Y, Imamura H. Airway stenting. Surg Today 2005;35(4):265-70.	Intervention: Airway stenting
121	Saito Y, Tanaka T, Andoh A, Minematsu H, Hata K, Tsujikawa T, et al. Novel biodegradable stents for benign esophageal strictures following endoscopic submucosal dissection. Dig Dis Sci 2008;53(2):330-3.	Intervention: No SX-ELLA
122	Saito Y, Tanaka T, Andoh A, Minematsu H, Hata K, Tsujikawa T, et al. Usefulness of biodegradable stents constructed of poly-/-lactic acid monofilaments in patients with benign esophageal stenosis. World J Gastroenterol 2007;13(29):3977-80.	Intervention: No SX-ELLA
123	Sanchez MD, Ortiz-Moyano C, Gomez-Rodriguez B. Resolution of a refractory anastomotic stricture with a novel biodegradable esophageal stent. Clin Gastroenterol Hepatol 2013;11(9):e63.	Design: Single case
124	Sato M, Ando N, Ozawa S, Nagashima A, Kitajima M. A hybrid artificial esophagus using cultured human esophageal epithelial cells. ASAIO J 1993 Jul;39(3):M554-M557.	Intervention: No biodegradable stents
125	Schmidt E, Shaligram A, Reynoso JF, Kothari V, Oleynikov D. Hiatal hernia repair with biologic mesh reinforcement reduces recurrence rate in small hiatal hernias. Dis Esophagus 2014;27(1):13-7.	Intervention: Laparoscopic repair of hiatal hernia
126	Sepulveda M, Alamo M, Guzman H, Hermosilla J, Astorga C, Maira A. Transitory esophagostomy with pezzer's catheter: A novel therapeutic solution to upper gastrointestinal suture's leakage or rupture of the esophagus. Obes Surg 2013;23(8):1120.	Intervention: No biodegradable stents
127	Siddhi,S.S.; Plevris,J.; Bow,S. Biodegradable oesophageal stents in benign and malignant disease – A single centre experience. Gut 2014; **63**: A59.	Congress abstract
128	Siersema,P.D. Stenting for benign esophageal strictures. Endoscopy 2009; 41(4): 363-373	Design: Narrative review
129	Solbakken AM, Hovde O, Glomsaker T. The use of self-expanding stents in benign oesophageal conditions: An overview. Tidsskr Nor Laegeforen 2005;125(16):2175-8.	Design: Narrative review
130	Spicak J. Treatment of gastroesophageal reflux disease: Endoscopic aspects. Dig Dis 2007;25(3):183-7.	Design: Narrative review
131	Srinivasan,N.; Kozarek,R.A. The future of esophageal endoprosthetics including the use of biodegradable materials. Techniques in Gastrointestinal Endoscopy 2014; Vol 16,(2): 92–98.	Design: Narrative review
132	Stivaros SM, Williams LR, Senger C, Wilbraham L, Laasch H-U. Woven polydioxanone biodegradable stents: A new treatment option for benign and malignant oesophageal strictures. Eur Radiol 2010; 20(5):1069-72.	Design: Single case
133	Tanaka T, Takahashi M, Nitta N, Furukawa A, Andoh A, Saito Y, et al. Newly developed biodegradable stents for benign gastrointestinal tract stenoses: A preliminary clinical trial. Digestion 2006;74(3-4):199-205.	Intervention: No SX-ELLA
134	Tokar JL, Banerjee S, Barth BA, Desilets DJ, Kaul V, Kethi SR, et al. Drug-eluting/biodegradable stents. Gastrointest Endosc 2011;74(5):954-8.	Design: Narrative review
135	Tvrdon J, Harustiak T, Pazdro A, Tersip T, Pafko P. Stents--palliative and curative management of esophageal conditions. Seven-year surgical experience. Rozhl Chir 2008;87(7):355-9.	Language: Czech
136	Ueno Y, Miyazawa M, Aikawa M, Nonaka K, Okada K, Toshimitsu Y, et al. Repair of perforated esophagus with a bio-degradable polymer stent. J Gastroenterol Hepatol 2010;25:A120.	Population: Animal model
137	Vakil N. Expandable metal stents: Principles and tissue responses. Gastrointest Endosc Clin North Am 2011;21(3):351-7.	Design: Narrative review
138	Van Boeckel PG, Sijbring A, Vleggaar FP, Siersema PD. Systematic review: temporary stent placement for benign rupture or anastomotic leak of the oesophagus. Alimentary Pharmacology and Therapeutics 2011; 33(12): 1292-1301.	Intervention: No biodegradable stents
139	Van Boeckel PG, Vleggaar FP, Siersema PD. Temporary self-expanding plastic stent placement or biodegradable stent placement for refractory benign esophageal strictures: A comparison. Gastrointest Endosc 2011;73(4):AB204.	Duplicated patients

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Reference		Exclusion criteria
140	Van Boeckel PGA, Vleggaar FP, Siersema PD. Biodegradable stent placement in the esophagus. Expert Rev Med Devices 2013;10(1):37-43.	Design: Narrative review
141	Van Den Berg MW, De Vries EM, Walter D, Vleggaar FP, Van Berge Henegouwen MI, Van HR, et al. Safety and efficacy of a biodegradable stent during neoadjuvant therapy in patients with advanced esophageal cancer (ESNEBIO). Gastrointest Endosc 2013;77(5):AB355.	Population: Malignant stenosis
142	Van Halsema EE, Fleischer DE, Wong Kee SLM, Baron TH, Siersema PD, Vleggaar FP, et al. Technical aspects of endoscopic removal of stents placed for benign esophageal diseases. Gastrointest Endosc 2012;75(4):AB458.	Intervention: Stents removal
143	Van Hooft JE, Van Berge Henegouwen MI, Rauws EA, Bergman JJ, Busch OR, Fockens P. Endoscopic treatment of benign anastomotic esophagogastric strictures with a biodegradable stent. Gastrointest Endosc 2011;73(5):1043-7.	Population: No refractory or recurrent oesophageal stenosis
144	Vandenplas Y, Hauser B, Devreker T, Urbain D, Reynaert H. A bio-degradable esophageal stent in the treatment of a corrosive esophageal stenosis in a child. J Pediatr Gastroenterol Nutr 2009;49(2):254-7.	Design: Single case
145	Vlavianos P, Zabron A. Clinical outcomes, quality of life, advantages and disadvantages of metal stent placement in the upper gastrointestinal tract. Curr Opin Support Palliat Care 2012;6(1):27-32.	Intervention: No biodegradable stents
146	Vleggaar FP, Siersema PD. Stents for benign esophageal strictures. Tech Gastrointest Endosc 2010;12(4):231-6.	Design: Narrative review
147	Wadsworth CA, East JE, Hoare JM. Early covered-stent fracture after placement for a benign esophageal stricture. Gastrointest Endosc 2010;72(6):1260-1.	Design: Single case
148	Wenger U, Johnsson E, Bergquist H, Nyman J, Ejnell H, Lagergren J, et al. Health economic evaluation of stent or endoluminal brachytherapy as a palliative strategy in patients with incurable cancer of the oesophagus or gastro-oesophageal junction: results of a randomized clinical trial. European Journal of Gastroenterology and Hepatology 2005; 17(12): 369-1377.	Population: esophageal cancer
149	Xinopoulos D.; Dimitroulopoulos D.; Moschandrea I.; Skordilis P.; Bazinis A.; Kontis M.; Paraskevas I.; Kouroumalis E.; Paraskevas E. Natural course of inoperable esophageal cancer treated with metallic expandable stents: quality of life and cost-effectiveness analysis. J.Gastroenterol.Hepatol 2004; 19(12): 1397-1402.	Population: Malignant stenosis
150	Xinopoulos D, Dimitroulopoulos D, Tsamakidis K, Korkolis D, Fotopoulou A, Bazinis A, et al. Palliative treatment of advanced esophageal cancer with metal-covered expandable stents: a cost-effectiveness and quality of life study. JBUON 2005; 10(4): 523-528.	Intervention: No biodegradable stents
151	Yamamoto Y, Nakamura T, Shimizu Y, Takimoto Y, Matsumoto K, Kiyotani T, et al. Experimental replacement of the thoracic esophagus with a bioabsorbable collagen sponge scaffold supported by a silicone stent in dogs. ASAIO J 1999;45(4):311-6.	Population: Animal model
152	Yu X, Wang L, Huang M, Gong T, Li W, Cao Y, et al. A shape memory stent of poly(e-caprolactone-co-DL-lactide) copolymer for potential treatment of esophageal stenosis. J Mater Sci Mater Med 2012;23(2):581-9.	Intervention: No biodegradable stents
153	Zhu Y, Cheng Y. Biodegradable self-expanding stents for the treatment of benign cardia stricture in a dog model. J Vasc Intervent Radiol 2012;23(3):S45.	Population: Animal model
154	Zhu Y, Hu C, Li B, Yang H, Cheng Y, Cui W. A highly flexible paclitaxel-loaded poly((epsilon)-caprolactone) electrospun fibrous-membrane-covered stent for benign cardia stricture. Acta Biomater 2013;9(9):8328-36.	Population: Cardia stricture
155	Zhu YQ, Cui WG, Cheng YS, Chang J, Chen NW, Yan L, et al. Biodegradable rapamycin-eluting nano-fiber membrane-covered metal stent placement to reduce fibroblast proliferation in experimental stricture in a canine model. Endoscopy 2013;45(6):458-68.	Population: Animal model
156	Zilberman M, Eberhart RC. Drug-eluting bioresorbable stents for various applications. Annual Review of Biomedical Engineering 8, 153-180. 2006.	Design: Narrative review

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Evidence tables of individual studies included for clinical effectiveness and safety

Table 6: Characteristics of comparative studies

Study	**Dhar 2014** [5]	**Canena 2012** [6]	**Van Boeckel 2011** [7]
Country		Portugal	The Netherlands
Sponsor	Supported by NIHR under its Research for Patient Benefit Programme (PB-PG-1208-17025)	J Canena is consultant for Boston Scientific Corp. (USA) but not receive any financial arrangement	PD Siersema serves as advisor to Boston Scientific Corp. (USA) and receives research support from Cook Medical Ltd. (Ireland)
Intervention/Product	SX-ELLA Stent Oesophageal Degradable	SX-ELLA Stent Oesophageal Degradable	SX-ELLA Stent Oesophageal Degradable
Comparator	Endoscopic dilation using CRE® balloon (Boston Scientific)	SEPS: Polyflex™ (Boston Scientific) FCSEMS: Wallflex stent™ (Boston Scientific)	SEPS: Polyflex™ (Boston Scientific)
Study design	Multicentre randomised controlled trial	Multicentre prospective cohort study	Unicentre prospective cohort study
Number of pts	OBS: 9 Dilation: 6	OBS: 10 SEPS:10 FCSEMS: 10	OBS: 18 SEPS: 20
In-/Exclusion criteria	Inclusion criteria: confirmed diagnosis of BOS; aged 18-85 years; at least 1 previous oesophageal dilation. Exclusion criteria: upper oesophageal sphincter within 2 cm of the stenosis; pregnancy or not taking appropriate contraception; receiving anti-coagulants; oesophageal cancer (previous or current) or terminal disease; lack capacity or illness inhibiting participation in the view of the recruiting clinician.	Inclusion criteria: RRBOS defined as: no inflammation at the stenosis site, inability to achieve a diameter of 14 mm over 5 dilations at 2-week interval, or to maintain for 4 weeks once 14 mm diameter is achieved. Exclusion criteria: Oesophageal fistulas or leaks, malignancy suspicion and upper oesophageal sphincter within 3 cm of the stenosis.	Inclusion criteria: RRBOS defined as: biopsy-proven benign stenosis, minor or no inflammation at the stenosis site, inability to achieve or maintain a diameter of 14 mm despite dilation every 2 to 4 weeks. Exclusion criteria: malignancy suspicion, Barret oesophagus, dysmotility disorder, fistulae or leak, unfit for endoscopy.
Age of pts in years: mean (range)	OBS: 62.7 (40-78) Dilation: 63.8 (54-74)	OBS: 57.2 (42-79) SEPS: 52.7 (28-67) FCSEMS: 50.7 (27-78)	OBS: median 61 (24-80) SEPS: median 63 (27-79)
Sex of pts (M/F) in %	OBS: 89/11 Dilation: 83/17	OBS: 40/60 SEPS: 50/50 FCSEMS: 70/30	OBS: 56/44 SEPS: 65/35
Stenoses etiology in n (%)	N/A	OBS: Peptic 3 (30); caustic ingestion 1 (10), Post-surgical 6 (60) SEPS: Peptic 1 (10); radiotherapy 2 (20); caustic ingestion 1 (10), Post-surgical 4 (40); idiophatic 2 (20) FCSEMS: Peptic 3 (30); caustic ingestion 1 (10), Post-surgical 3 (30); idiophatic 3 (30)	OBS: Peptic 6 (33); anastomotic 5 (27); radiotherapy 2 (11); caustic ingestion 2 (11); following multiple stents 1 (6); following ischemic oesophagitis 1 (6); unknown 1 (6) SEPS: Peptic 1 (5); anastomotic 8 (40); radiotherapy 5 (25); caustic 4 (20); following ischemic oesophagitis 1 (5); pill-induced 1 (5)

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Study	**Dhar 2014** [5]	**Canena 2012** [6]	**Van Boeckel 2011** [7]
Oesophagus location of the stenoses in n (%)	N/A	OBS: lower 4 (40), anastomotic 6 (60) SEPS: mid 2 (20), lower 4 (40), anastomotic 4 (40) FCSEMS: Upper 2 (20), mid 2 (20), lower 3 (30), anastomotic 3 (30)	N/A
Stenoses length in cm: mean (range)	OBS: 3.5 (2-5) Dilation: 4 (2-6)	OBS: 2.9 (1-8) SEPS: 2.9 (1-5) FCSEMS: 2.8 (1-6)	OBS: 4 (1-9) SEPS: 3 (r 1-6)
Baseline dysphagia score (Mellow score 0-4): mean (SD)	OBS: 2.0 (1.2) Dilation: 1.83 (0.98) P = 0.776	OBS: 2.8 (0.42) SEPS: 2.8 (0.42) FCSEMS: 2.7 (0.48) P = 0.84	OBS: median 3 SEPS: median 3
Dilations per patient before intervention: mean (SD)	12 months before: OBS: 1.9 (1.8); Dilation: 1.2 (0.8) (p = 0.607) Before (ever): OBS: 6.2 (5.1); Dilation: 3.2 (2.3) (p = 0.224)	N/A	N/A
Baseline health related quality of life: mean (SD)	EQ5D: OBS: 0.69 (0.24); Dilation: 0.69 (0.31) (p = 0.955)	N/A	N/A
Time for stent degradation	N/A	At the 3-months endoscopy stents were almost dissolved. At the 6-months endoscopy there were no traces of biodegradable stents	N/A
Follow-up	OBS: 6 months (9 in 9 pts); 12 months (8 in 9 pts) Dilation: 6 months (5 in 6 pts); 12 months (4 in 6 pts)	From stent insertion until at least 8 months follow-up (follow-up started after stent removal, degradation or migration) OBS: Median months 18.5 (range: 11-21) SEPS: Median months 42.7 (range: 16-66) FCSEMS: Median months 10 (range: 8-12)	OBS: median 5.5 months (range: 0.7-18.6) SEPS: median 12.8 months (2.6-30.8)
Loss to follow-up in n (%) patients	OBS: 1 in 9 (11.1) Dilation: 2 in 6 (33.3)	OBS: 0 SEPS: 0 FCSEMS: 0	0
OUTCOMES			
Effectiveness			
Dilations per patient after intervention: mean (SD)	6 m after: OBS: 1.22 (1.39); Dilation: 0.4 (0.55) (p = 0.275) 12 m after: OBS: 1.38 (1.77); Dilation: 0.4 (0.55) (p = 0.385)	OBS: 3 pts (30%) SEPS: 1 pts (10%) FCSEMS: 2 pts (20%)	N/A
Number of patients free of dysphagia (score 0-1) after follow-up (%)	N/A	OBS: 3 (30); SEPS: 1 (10); FCSEMS: 4 (40) OBS vs SEPS: p = 0.58; OBS vs FCSEMS: p = 0.64; SEPS vs FCSEMS: p = 0.3	OBS: 6 (33) SEPS: 6 (30) P = 0.83

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Study	**Dhar 2014** [5]	**Canena 2012** [6]	**Van Boeckel 2011** [7]
Dysphagia score (0-4) after intervention: mean (SD)	After 3-6 months: OBS: 1.17 (0.9); Dilation: 0 (0) (p = 0.004) After 3-12 months: OBS: 1.21 (1.08); Dilation: 0 (0) (p = 0.016)	After 4 weeks: OBS: 0.4 (0.52); SEPS: 0.7 (0.48); FCSEMS: 0.5 (0.53) (p = 0.4) After median follow up of 18.5 months (OBS), 42.7 months (SEPS) and 10 months (FCSEMS): OBS: 2.0 (0.82); SEPS: 2.4 (1.26); FCSEMS: 1.6 (1.26) (p = 0.23)	After 4 weeks: OBS: median 0.0 SEPS: median 0.0 (p = 0.91)
Time to recurrent dysphagia: HR: Hazard Ratio (95% CI)	N/A	SEPS vs OBS: HR= 1.34 (0.50-3.58) SEPS vs FCSEMS: HR= 1.6 (0.58-4.41) OBS vs FCSEMS: HR= 1.15 (0.39-3.41)	N/A
Oesophageal lumen patency (before- after intervention)	N/A	N/A	N/A
Reduction of pain before/after stent	N/A	N/A	N/A
Overall mortality in n (%)	OBS: 0 (0) Dilation: 0 (0)	OBS: 0 (0) SEPS: 0 (0) FCSEMS: 0(0)	OBS: 0 SEPS: 0
Disease related mortality in n (%)	OBS: 0 (0) Dilation: 0 (0)	OBS: 0 (0) SEPS: 0 (0) FCSEMS: 0(0)	OBS: 0 SEPS: 0
Health-related quality of life: mean QALY (SD)	After 6 months: EQ5D: OBS: 0.35 (0.1); Dilation: 0.34 (0.16) (p = 1) After 12 months: EQ5D: OBS: 0.66 (0.23); Dilation: 0.64 (0.42) (p = 0.927) After 6 months: EQVAS: OBS: 0.32 (0.09); Dilation: 0.36 (0.09) (p = 0.364) After 12 months: EQVAS: OBS: 0.67 (0.21); Dilation: 0.73 (0.2) (p = 0.648)	N/A	N/A
Time to re-intervention (dilation, re-stenting, ...)	N/A	N/A	N/A
Safety			
Intervention failed in n (%)	OBS: 0 Dilation: 0	OBS: 0 SEPS: 0 FCSEMS: 0	OBS: 2 (11) SEPS: 1 (5) (p = 0.49)
Total AEs (mean per patient)	OBS: 4.9 Dilation: 1 (p = 0.001)	OBS: 0.7 SEPS: 0.9 FCSEMS: 0.6 (p = 0.38)	OBS: 0.8 SEPS: 0.4
Serious AEs (in n patients)	OBS: Mean per patient: 1.8 (acute pancreatitis 1; severe pain 2; severe dysphagia 2). Dilation: 0 (p = 0.026)	OBS: Mean per patient: 0.2 (Hemorrhage 1, Severe chest pain 1) SEPS: 0 FCSEMS: 0	OBS: Mean per patient 0.2 (hemorrhage 2; retrosternal pain 2) SEPS: Mean per patient: 0.1 (p = 0.3) (hemorrhage 1; perforation 1)

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Study	**Dhar 2014** [5]	**Canena 2012** [6]	**Van Boeckel 2011** [7]
Minor AEs (in n patients)	OBS: Mean per patient: 2.8 (bleeding 3; cough 1; constipation 1; diverticulosis 1; dry mouth 1, foult taste 1; oesophageal candidiasis 1; dysphagia 5; hiccups 1; hyperglicemia 2; insomnia 1; pain 5; vomiting 1; reflux 1) Dilation: Mean per patient: 0.5 (dysphagia 2; oesophageal spasm 1)	OBS: Mean per patient: 0.5 (stent migration 2; hyperplastic tissue: 3) SEPS: Mean per patient: 0.9 (stent migration 6; reflux 1; chest pain 2) FCSEMS: Mean per patient: 0.6 (stent migration 3; globus sensation 1; reflux 1; chest pain 1)	OBS: Mean per patient: 0.6 (Nausea, vomiting 2; reflux 1: stent migration 4; food bolus obstruction 2; hyperplastic tissue 2) SEPS: Mean per patient: 0.3 (nausea, vomiting 1; stent migration 5)
Unexpected re-interventions: mean per patient (SD)	*Additional procedures:* 6 m after: OBS: 3.22 (2.91); Dilation: 0.8 (1.1) (p = 0.127) 12 m after: OBS: 4.13 (3.87); Dilation: 1.2 (0.84) (p = 0.165) *Endoscopic procedures:* 6 m after: OBS: 0.33 (0.71); Dilation: 0 (0) (p = 0.505) 12 m after: OBS: 0.63 (1.06): Dilation: 0 (0) (p = 0.417) *Balloon procedures:* 6 m after: OBS: 1.22 (1.39): Dilation: 0.4 8 (0.55) (p = 0.275) 12 m after: OBS: 1.38 (1.77); Dilation: 0.4 (0.55) (p = 0.385) *Endoscopies:* 6 m after: OBS: 1.67 (1.5); Dilation: 0.4 (0.55) (p = 0.107) 12 m after: OBS: 2.13 (1.89); Dilation: 0.8 (0.45) (p = 0.203)	OBS: 1.3 SEPS: 2.4 FCSEMS: 1.3 (p = 0.24 Kruskal-Wallis test) (p<0.05 Poisson regression)	OBS 0.9 SEPS: 1.05 Mean number of re-interventions per stent placed: OBS 0.8 (0.6); SEPS 1.3 (0.4) (p = 0.03)
Procedure-related mortality in n (%)	OBS: 0 Dilation: 0	OBS: 0 SEPS: 0 FCSEMS: 0	OBS: 0 SEPS: 0

Abbreviations: AE = adverse events; EQ5D = EuroQol 5 Dimensions; EQVAS = EuroQol Visual Analogue Scale; FCSEMS = Fully Covered Self-expandable Metal Stent; HR = Hazard Ratio; m = months; n = number, N/A = Not available; OBS = Oeosphageal Biodegradable Stent; pts = patients; QALY = Quality Adjusted Life Years; SD = standard deviation

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Table 7: Characteristics of case series

Study	**Repici 2010** [58]	**Hirdes 2012** [59]
Country	The Netherlands, Italy	The Netherlands
Sponsor	No sponsor	PD Siersema serves as advisor to Boston Scientific Corp. (USA) and receives research support from Cook Medical Ltd. (Ireland)
Intervention/Product	SX-ELLA Stent Oesophageal Degradable	SX-ELLA Stent Oesophageal Degradable
Comparator	None	None
Study design	Case series	Case series
Number of pts	21	28
In-/Exclusion criteria	Inclusion criteria: RRBOS, defined as: biopsy-proven benign stenosis, absence of inflammation, inability to achieve or maintain a diameter of 14 mm despite dilation every 2 to 4 weeks. Exclusion criteria: malignancy suspicion, Barret oesophagus, dysmotility disorder, fistulae or leak, unfit for endoscopy	Inclusion criteria: Refractory benign oesophageal stenosis defined as: Kochman dysphagia score ≥2, inability to achieve a 14 mm diameter within 5 sessions at 2-weekly intervals. Exclusion criteria: malignancy suspicion, motility disorder, fistula or leak, or inflammation, unfit for endoscopy
Age of pts in years: mean (range)	59 (SD: 17)	Median 58 (22-88)
Sex of pts (M/F) in %	52/48	54/46
Stenoses etiology in n (%)	Peptic 7 (33); anastomotic 5 (24); radiotherapy 5 (24); caustic ingestion 4 (19), Boerhaave syndrome 1 (5); idiophatic 1 (5)	Peptic 9 (32), anastomosis 7 (25), radiotherapy induced 3 (11), Corrosive 2 (7), Lichen planus 1 (4), Iatrogenic 1 (4), Post ischemic 1 (4), other/unknown 4 (14)
Oesophagus location of the stenoses in n (%)	Distal 8 (38), mid 10 (47), proximal 3 (15)	Proximal 7 (25), Mid 7 (25), Distal 14 (50)
Stenoses length in cm: mean (SD)	3 (1)	3.9 (1.2)
Baseline dysphagia score (Mellow score 0-4): mean (SD)	3.30 (0.47)	Median 3 (range: 2-4)
Dilations per patient before intervention	Mean per patient month: 2.25	> 10 dilations n 20 (%: 71) > 10 dilations±previous stents n 8 (%: 29)
Time for stent degradation	Weeks range: 13.5-27	
Follow-up	Median 12.4 months (range 5.8-20.5)	Median 21 months (range: 0.7-37.4)
Loss to follow-up in n (%) patients	1 in 21 (4.8)	5 in 28 (22.7)
OUTCOMES		
Effectiveness		
Dilations per patient after intervention	Mean per patient month: 0.8	N/A
Number of patients free of dysphagia (score 0-1) after follow-up (%)	8 (40)	7 (25)
Dysphagia score(0-4) after stenting : mean (SD)	2.05 (1.15)	N/A

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Study	**Repici 2010** [58]	**Hirdes 2012** [59]
Time to recurrent dysphagia since stent placement: mean weeks (SD)	19.4 (4.7). Range 7-42	Median days 90 (range: 14-618)
Oesophageal lumen patency before stent placement and after stent degradation	N/A	N/A
Reduction of pain before/after stent	N/A	N/A
Overall mortality in n (%)	1 (4.8)	5 (22.7)
Disease related mortality in n (%)	0	1 (3.6)
Health-related quality of life	N/A	N/A
Time to re-intervention (dilation, re-stenting, ...)	N/A	N/A
Safety		
Stent technical insertion failed in n (%)	0	2 (7)
Total AEs (mean per patient)	0.3	0.5
Serious AEs (in n patients)	Mean per patient: 0.05 (Severe pain 1)	Mean per patient: 0.39 (retrosternal pain, vomiting 4; retrosternal pain 2; bleeding 2; fever, nausea, vomiting 1; hematemesis, nausea 1; aspiration pneumonia 1)
Minor AEs (in n patients)	Mean per patient: 0.29 (stent migration 2; hyperplastic tissue 1, bleeding 1;moderate pain 2)	Mean per patient: 0.14 (retrosternal pain 2; reflux 1; vomiting 1; stent migration 3)
Unexpected re-interventions (in n patients)	Mean per patient: 0.1 (second stent implantation because of stent migration 1; dilation because of stent migration 1)	Mean per patient: 0.82 (second stent implantation 13; third stent implantation 7; endoscopy 2; blood transfusion 1)
Procedure-related mortality	0	0

Abbreviations: AE = adverse events; OBS = Oesophageal Biodegradable Stent; FCSEMS = Fully Covered Self-expandable Metal Stent; n = number; N/A = Not available; pts = patients; SD = standard deviation

List of ongoing and planned studies

Table 8: List of ongoing studies with oesophageal biodegradable stents for refractory or recurrent benign oesophageal stenosis

Study Identifier	Time	Study type	Number of patients	Intervention	Comparator	Patient population	Primary endpoints
NCT01337206 DESTINY – SX ELLA Oesophageal Degradable BD Stent System Sponsor: Cook Medical	2012 January-2015 January (Final data collection date for primary outcome measure)	Multicentre RCT, parallel assignment, open label	66	Oesophageal stenting with ELLA Biodegradable stent	Oesophageal Standard Dilations (Bougie Dilation, Balloon Dilation)	Recurrent benign oesophageal stricture due to all causes Over 18 years old	Average number of dilations per patient within 3-6 months following stent placement

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Risk of bias tables

Table 9: GRADE evidence profile: efficacy and safety of the OBS stent vs oesophageal dilation

Quality assessment							Results			Quality	Importance
Studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OBS**	**Dilation**	**Effect size**		
EFFECTIVENESS											
Dysphagia 3-6 months after intervention (follow-up 3-6 months; measured with: Mean of dysphagia score after 3-6 months; range of scores: 0-4)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	No serious indirectness	very serious[2]	none	1.17 (0.9 SD)	0 (0 SD)	MD 1.17 higher for OBS (p = 0.004)	⊕OOO VERY LOW	CRITICAL
Dysphagia 3-12 months after intervention (follow-up mean 3-12 months; measured with: Mean of dysphagia score after 3-12 months; range of scores: 0-4)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	1.21 (1.08 SD)	0 (0 SD)	MD 1.21 higher for OBS (p = 0.016)	⊕OOO VERY LOW	CRITICAL
Dilations 6 months after intervention (follow-up mean 6 months; measured with: Mean of additional dilations per patient 6 months after intervention)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	1.22 (1.39 SD)	0.4 (0.55 SD)	MD 0.82 higher for OBS (p = 0.275)	⊕OOO VERY LOW	CRITICAL
Dilations 12 months after intervention (follow-up mean 12 months; measured with: Mean of additional dilations per patient 12 months after intervention)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	1.38 (1.77 SD)	0.4 (0.55 SD)	MD 0.98 higher for OBS (p = 0.385)	⊕OOO VERY LOW	CRITICAL
Dysphagia-free patients											
Not reported											CRITICAL
Time to recurrent dysphagia											
Not reported											CRITICAL
Overall mortality (follow-up 6-12 months; assessed with: Number of deaths for all causes during follow-up)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0/9 (0%)	0/6 (0%)	No difference	⊕OOO VERY LOW	IMPORTANT
Disease-related mortality (follow-up 6-12 months; assessed with: Number of disease-related deaths during follow-up)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0/9 (0%)	0/6 (0%)	No difference	⊕OOO VERY LOW	IMPORTANT
Health-related quality of life (follow up 12 months; assessed with mean EQ5D 12 months after intervention; range of scores: -0.59-1)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0.66 (0.23 SD)	0.64 (0.42 SD)	MD 0.02 higher for OBS (p = 0.927)	⊕OOO VERY LOW	IMPORTANT

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Quality assessment							Results			Quality	Importance
Studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OBS**	**Dilation**	**Effect size**		
Health-related quality of life (follow up 12 months; assessed with mean EQVAS 12 months after intervention; range of scores: -0.59-1)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0.67 (0.21 SD)	0.73 (0.2 SD)	MD 0.06 higher for dilation (p = 0.648)	⊕OOO VERY LOW	IMPORTANT
Pain reduction											
Not measured											IMPORTANT
SAFETY											
Technical failure (assessed with: number of patient with intervention technical failure)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0/9 (0%)	0/6 (0%)	No difference	⊕OOO VERY LOW	IMPORTANT
Total adverse events (follow-up 6-12 months; measured with: Mean of adverse events per patient)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	4.9	1	MD 3.9 higher for OBS (p = 0.01)	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up 6-12 months; measured with: Mean of serious adverse events per patient)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	1.8	0	MD 1.8 higher for OBS (p = 0.026)	⊕OOO VERY LOW	CRITICAL
Unexpected re-interventions (follow-up 6 months; measured with mean of additional procedures after intervention per patient)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	3.22 (2.91 SD)	0.8 (1.1 SD)	MD 2.42 higher for OBS (p = 0.127)	⊕OOO VERY LOW	IMPORTANT
Unexpected re-interventions (follow-up 12 months; measured with mean of additional procedures after intervention per patient)											
Dhar 2014	randomised trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	4.13 (3.87 SD)	1.2 (0.84 SD)	MD 2.97 higher for OBS (p = 0.165)	⊕OOO VERY LOW	IMPORTANT
Procedure-related mortality (follow-up 6-12 months; measured with: number of procedure-related deaths during follow-up)											
Dhar 2014	randomise d trial	very serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0/9 (0%)	0/6 (0%)	No difference	⊕OOO VERY LOW	IMPORTANT

[1] See Cochrane risk of bias table; [2] Very small sample size or wide confidence interval or lack of statistical significance; MD: Mean Difference; OBS: Oesophageal Biodegradable Stent

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Table 10: GRADE evidence profile: efficacy and safety of the OBS stent vs SEPS

Quality assessment							Results			Quality	Importance
Studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OBS**	**SEPS**	**Effect size**		
EFFECTIVENESS											
Dysphagia 4 weeks after intervention (follow-up mean 4 weeks; measured with: Mean of dysphagia score after intervention; range of scores: 0-4)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0.4 (0.52 SD)	0.7 (0.48 SD)	MD 0.3 higher for SEPS (p = N/A)	⊕OOO VERY LOW	CRITICAL
Dysphagia 4 weeks after intervention (follow-up mean 4 weeks; measured with: Median of dysphagia score after intervention; range of scores: 0-4)											
Van Boeckel 2011	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0.0	0.0	MD 0.0 (p = 0.91)	⊕OOO VERY LOW	CRITICAL
Dilations after intervention (follow-up median 18.5-42.7 months; assessed with: Number of patients with oesophageal dilations after intervention)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	3/10 pts (30%)	1/10 pts (10%)	20% higher for OBS (p = N/A)	⊕OOO VERY LOW	CRITICAL
Dysphagia-free patients (follow-up median 5.5-43 months; assessed with: Number of patients free of dysphagia (score 0-1) after follow-up)											
Canena 2012; Van Boeckel 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/28 pts (32.1%)	7/30 pts (23.3%)	8.8% higher for OBS (p = 0.58)	⊕OOO VERY LOW	CRITICAL
Time to recurrent dysphagia (follow-up median 18.5-42.7 months; measured with: Hazard ratio of dysphagia recurrence)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	10 pts	10 pts	HR: 1.34 higher for SEPS (IC 95%: 0.50-3.58)	⊕OOO VERY LOW	CRITICAL
Overall mortality (follow-up median 5.5-42.7 months; assessed with: Number of deaths for all causes during follow-up)											
Canena 2012; Van Boeckel 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/28 (0%)	0/30 (0%)	No difference	⊕OOO VERY LOW	IMPORTANT
Disease-related mortality (follow-up median 5.5-42.7 months; assessed with: Number of disease-related deaths during follow-up)											
Canena 2012; Van Boeckel 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/28 (0%)	0/30 (0%)	No difference	⊕OOO VERY LOW	IMPORTANT
Health-related quality of life before vs after intervention – not measured											
Not measured											IMPORTANT
Pain reduction											
Not measured											IMPORTANT

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Quality assessment							Results			Quality	Importance
Studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OBS**	**SEPS**	**Effect size**		
SAFETY											
Technical failure (assessed with: number of patient with intervention technical failure)											
Canena 2012; Van Boeckel 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/28 (7.1%)	1/30 (3.3%)	3.8% higher for OBS (p = N/A)	⊕OOO VERY LOW	IMPORTANT
Total adverse events (follow-up mean 5.5-42.7 months; measured with: Mean of adverse events per patient)											
Canena 2012; Van Boeckel 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0.79	0.57	MD 0.22 higher for OBS (p = N/A)	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up mean 5.5-42.7 months; measured with: Mean of adverse events per patient)											
Canena 2012; Van Boeckel 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0.21	0.07	MD 0.14 higher for OBS (p = N/A)	⊕OOO VERY LOW	CRITICAL
Unexpected re-interventions (follow-up median 5.5-42.7 months; measured with: Mean of unexpected re-interventions per patient)											
Canena 2012; Van Boeckel 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1.03	1.5	MD 0.47 higher for SEPS (p = N/A)	⊕OOO VERY LOW	CRITICAL
Procedure-related mortality (follow-up median 5.5-42.7 months; measured with: Number of procedure-related deaths during follow-up)											
Canena 2012; Van Boeckel 2011	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/28 (0%)	0/30 (0%)	No difference	⊕OOO VERY LOW	IMPORTANT

[1] See New Castle – Ottawa risk of bias table; [2] Very small sample size or wide confidence interval or lack of statistical significance; HR: Hazard Ratio; MD: Mean Difference; N/A = Not available; OBS: Oesophageal Biodegradable Stent; SEPS: Self-Expanding Plastic Stent

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Table 11: GRADE evidence profile: efficacy and safety of the OBS vs FCSEMS

Quality assessment							Results			Quality	Importance
Studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OBS**	**FCSEMS**	**Effect size**		
EFFECTIVENESS											
Dysphagia 4 weeks after intervention (follow-up mean 4 weeks; measured with: Mean of dysphagia score 4 weeks after intervention; range of scores: 0-4)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0.4 (0.52 SD)	0.5 (0.53 SD)	MD 0.1 higher for FCSEMS (p = N/A)	⊕OOO VERY LOW	CRITICAL
Dysphagia after follow-up (follow-up median 10-18.5 months; measured with: Mean of dysphagia score after intervention; range of scores: 0-4)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	2 (0.82 SD)	1.6 (1.26 SD)	MD 0.4 higher for OBS (p = N/A)	⊕OOO VERY LOW	CRITICAL
Dilations after intervention (follow-up median 10-18.5 months; assessed with: Number of patients with oesophageal dilations after intervention)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	3/10 (30%)	2/10 (20%)	10% higher for OBS (p = N/A)	⊕OOO VERY LOW	CRITICAL
Dysphagia-free patients (follow-up median 10-18.5 months; assessed with: Number of patients free of dysphagia (score 0-1) after follow-up)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	3/10 (30%)	4/10 (40%)	10% higher for FCSEMS (p = 0.64)	⊕OOO VERY LOW	CRITICAL
Time to recurrent dysphagia (follow-up median 10-18.5 months; assessed with: Hazard ratio of dysphagia recurrence)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	10 pts	10 pts	HR 1.15 higher for OBS (0.39-3.41)	⊕OOO VERY LOW	CRITICAL
Overall mortality (follow-up median 10-18.5 months; assessed with: Number of deaths for all causes during follow-up)											
Canena 2012	observational studY	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0/10 (0%)	0/10 (0%)	No difference	⊕OOO VERY LOW	IMPORTANT
Disease-related mortality (follow-up median 10-18.5 months; assessed with: Number of disease-related deaths during follow-up)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0/10 (0%)	0/10 (0%)	No difference	⊕OOO VERY LOW	IMPORTANT
Health related quality of life before vs after intervention											
Not measured											IMPORTANT
Pain reduction											
Not measured											IMPORTANT

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Quality assessment							Results			Quality	Importance
Studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OBS**	**FCSEMS**	**Effect size**		
SAFETY											
Technical failure (assessed with: Number of patients with intervention technical failure)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0/10 (0%)	0/10 (0%)	No difference	⊕OOO VERY LOW	IMPORTANT
Total adverse events (follow-up mean 10-18.5 months; measured with: Mean of adverse events per patient)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0.7	0.6	MD 0.1 higher for OBS (p = N/A)	⊕OOO VERY LOW	CRITICAL
Serious adverse events (follow-up median 10-18.5 months; measured with: Mean of adverse events per patient)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0.2	0	MD 0.2 higher for OBS (p = N/A)	⊕OOO VERY LOW	CRITICAL
Unexpected re-interventions (follow-up median 10-18.5 months; measured with: Mean of unexpected re-interventions per patient)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	1.3	1.3	No difference	⊕OOO VERY LOW	CRITICAL
Procedure-related mortality (follow-up median 10-18.5 months)											
Canena 2012	observational study	serious[1]	Only 1 study	no serious indirectness	very serious[2]	none	0/10 (0%)	0/10 (0%)	No difference	⊕OOO VERY LOW	IMPORTANT

[1] See New Castle – Ottawa risk of bias table; [2] Very small sample size or wide confidence interval or lack of statistical significance; FCSEMS: Fully Covered Self-expandable Metal Stent; HR: Hazard Ratio; MD: Mean Difference; N/A= Not available; OBS: Oesophageal Biodegradable Stent

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Table 12: Risk of bias table for RCT. Cochrane quality assessment tool

Study: Dhar 2014 [5]		
Bias	**Author's judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	The random sequence generation was appropriate (web-based stratified by hospital site with a block size of four, allocating patients in a 1:1 ratio).
Allocation concealment (selection bias)	Low risk	The recruiting clinician was blinded. To ensure concealment of allocation the recruiting clinician provided patient details before allocation was disclosed
Blinding of participants and personnel (performance bias)	High risk	Clinicians and patients were not blinded
Blinding of outcome assessment (detection bias)	Low risk	The observer was blinded
Incomplete outcome data (attrition bias)	Unclear risk	The authors do not describe the reasons for exclusion of 35 patients. Lost to follow- up: OBS group 1 in 9 patients, dilation group 2 in 6. Sensitivity analysis was performed to assess impact of missing values
Selective reporting (reporting bias)	Low risk	No selective reporting was detected when the manuscript was compared with the trial protocol
Other bias	High risk	The comparability between groups is not warranted. We found the following risk of bias regarding comparability between groups: • Very small sample size • Dilations. In the RCT, according to the number of previous dilations required by the patients, the OBS group included more severe patients than the dilation group. The mean number of dilations was 6.2 (5.1 SD) in the OBS group; and 3.2 (2.3 SD) in the dilation group. High variance in the standard deviation but also in the range. The OBS group included patients with a range between 1 dilation and 16; and the dilation group between 1 and 6. • Comorbidities: The number of comorbidities was different between groups, counting 15 in the dilation group and 23 in the OBS group. The authors reported the statistical difference in comorbidities but only for each comorbidity individually. They did not provide a statistical analysis for ascertain differences in comorbidities globally between groups. • Concomitant medication: The statistical difference was not analysed but table 6 shows important differences. • The RCT does not describe the etiology and the location of the stenoses. Potential differences between groups in the etiology could explain differences in the response to the intervention. In addition several ambiguities were detected in the RCT: • The mean dysphagia score at 3 months in the dilation group is 0.25 (figure 2), however the table 3 reported for the same group a dysphagia score of 0 (range 0 to 0) at 3 and 6 months and for 3, 6 and 12 months. One of these results must be wrong. • The headlines in tables 5 and 6 mention the number of patients but they do not correspond with the rest of the manuscript. This was clarified with the authors, who said that the correct numbers are: "Endoscopic balloon dilation: 6; Biodegradable stent: 9. • The article reported that the luminal diameter of the oesophagus at endoscopy prior to the intervention in the OBS groups ranged from 6 to 80 mm. A diameter of 80 mm before the stent insertion is malpractice or a mistake.

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Table 13: Risk of bias table for observational studies.
Newcastle-Ottawa scale for quality assessment of cohort studies

Study: Van Boeckel 2011 [7]		
Bias	**Author's judgment**	**Support for judgment**
Representativeness of the exposed cohort	Low risk	No suspicion of limited representativeness of the exposed cohort
Selection of the non-exposed cohort	High risk	There are differences between the cohorts. The cohorts were not simultaneously enrolled, with the control group being a historic control. SEPS was used first by all the centres, and OBS was used there after. Then, once the centre began using OBS, all new patients received BOS.
Ascertainment of exposure	Low risk	Doubtless exposure
Demonstration that outcome of interest was not present at start of study	Low risk	No bias suspicion
Comparability of cohorts on the basis of the design or analysis	High risk	There is *no* control for counfounding factors
Assessment of outcome	Low risk	No bias suspicion
Was follow-up long enough for outcomes to occur	Low risk	The follow up was enough long. Median follow up in days: BOS: 166; SEPS: 385
Adequacy of follow-up of cohorts	Low risk	No loss to follow-up
Study: Canena 2012 [6]		
Bias	**Author's judgment**	**Support for judgment**
Representativeness of the exposed cohort	Low risk	No suspicion of limited representativeness of the exposed cohort
Selection of the non-exposed cohort	High risk	There are differences between the cohorts. The cohorts were simultaneously enrolled. The stent used was chosen accordingly with the practice at that time in the participating centre.
Ascertainment of exposure	Low risk	Doubtless exposure
Demonstration that outcome of interest was not present at start of study	Low risk	No bias suspicion
Comparability of cohorts on the basis of the design or analysis	High risk	There is control for relevant factors but the follow-up was longer for the SEPS group than for the other 2 groups. Median follow-up was: 18.5 months (OBS), 10 months (FCSEMS) and 42.7 months (SEPS)
Assessment of outcome	Low risk	No bias suspicion
Was follow-up long enough for outcomes to occur (0-1)	Low risk	The follow up was enough long. Median follow-up was: 18.5 months (OBS), 10 months (FCSEMS) and 42.7 months (SEPS)
Adequacy of follow up of cohorts	Low risk	No loss to follow-up

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Table 14: Quality assessment of the case series

Criterion (Yes/No)	**Repici 2010** [58]	**Hirdes 2012** [59]
STUDY OBJECTIVE		
Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction or methods section?	Yes	Yes
STUDY POPULATION		
Are the characteristics of the participants included in the study described?	Yes	Yes
Were the cases collected in more than one centre?	Yes	No
Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate?	Yes	Yes
Were participants recruited consecutively?	Yes	Yes
Did participants enter the study at a similar point in the disease?	Yes	Yes
INTERVENTION AND CO-INTERVENTION		
Was the intervention clearly described in the study?	Yes	Yes
Were additional interventions (co-interventions) clearly reported in the study?	Yes	No
OUTCOME MEASUREMENT		
Are the outcome measures clearly defined in the introduction or methodology section?	Yes	Yes
Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	No
Were outcomes measured before and after intervention?	Yes	No
STATISTICAL ANALYSIS		
Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes
RESULTS AND CONCLUSIONS		
Was the length of follow-up reported?	Yes	Yes
Was the lost to follow-up reported?	Yes	Yes
Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	No	No
Are adverse events reported?	Yes	Yes
Are the conclusions of the study supported by results?	Yes	Yes
COMPETING INTEREST AND SOURCE OF SUPPORT		
Are both competing interest and source of support for the study reported?	Yes	Yes
TOTAL PUNCTUATION (0-18)	17/18	13/18

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Applicability tables

Table 15: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The number of patients included in the comparative studies is too small to estimate precise results. The enrolled cohorts included between 6 and 20 patients. Each of the 3 comparative studies applied a different definition for refractory and recurrent oesophageal stenosis. This resulted in an heterogeneous population
Intervention	The intervention described is consistent with the routine use of Oesophageal Biodegradable Stents in Europe. All the selected studies inserted the same device SX-ELLA Stent Oesophageal Degradable.
Comparators	The considered comparators are appropriate. The oesophageal dilation procedures, as bougie and balloon dilation, are most commonly used in routine practice, although SEPS and FCSEMS are also an acceptable alternative.
Outcomes	The studies reported dysphagia scores at specific points in time, but none of the studies analysed the reduction in dysphagia score before vs after the intervention. The dysphagia recurrence risk was measured for the comparison of OBS with SEPS and OBS with FCSEMS. However, the quality of evidence was very low and was affected by imprecision.
Setting	Only 3 comparative studies were identified. They included a very limited number of patients. One of the studies is a cohort study including overall 38 patients, which was performed in a single centre located in The Netherlands. The other study is a cohort study with 10 patients in each of 3 groups that was performed in 4 Portuguese centres. In the RCT 17 patients were recruited in several British centres, but the authors do not specify the centres. The surgeon's technical expertise is relevant to determine effectiveness and safety results. The device is being introduced as a new treatment method in European hospitals, so the learning curve could improve the current results in the future.

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APPENDIX 2: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparators require organisational changes?	Yes
2.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be organisationally relevant?	Yes
It is likely that OBS would be introduced in hospitals that are already using oesophageal stents (SEPS or SEMS). In that case no organisational changes would be required to move from other oesophageal stents to OBS.	
3. Social	
3.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be socially relevant?	No
4. Legal	
4.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be legally relevant?	No

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