# Biodegradable Stents in Resistant Peptic Oesophageal Stricture: Is It the Right Way to Go?

Tom Richardson[1], Gerlin Naidoo[1], Namal Rupasinghe[1], Howard Smart[2] and Sayantan Bhattacharya[1,3,4]

[1]Department of Digestive Diseases, Warrington Hospital, Warrington and Halton Hospitals NHS Foundation Trust, Warrington, UK. [2]Endoscopy Unit, Royal Liverpool University Hospital, Liverpool, UK. [3]Consultant Upper GI Surgeon, Warrington, UK. [4]Department of General Surgery, Warrington Hospital, Warrington and Halton Hospitals NHS Foundation Trust, Warrington, UK.

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**ABSTRACT:** Peptic oesophageal stricture can be considered as the end result of prolonged gastro-oesophageal reflux. The 'gold standard' treatment for peptic stricture is endoscopic dilatation with balloon or bougie. It is predicted that up to 40% of patients remain symptomatic with dysphagia due to refractory (resistant to treatment) or recurrent strictures, needing frequent interventions at short intervals. Such patients have poor nutritional status due to the primary disease and are susceptible to complications related to repeated endoscopic dilatation such as bleeding and perforation. This general review aims to analyse existing published evidence and address the role of biodegradable stents in resistant peptic strictures as an alternative treatment to provide long-term dysphagia-free intervals.

**KEYWORDS:** Biodegradable stent, oesophageal stents, peptic stricture, resistant oesophageal stricture

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**CORRESPONDING AUTHOR:** Sayantan Bhattacharya, Department of General Surgery, Warrington Hospital, Warrington and Halton Hospitals NHS Foundation Trust, Lovely Lane, Warrington WA5 1QG, UK. Email: sayan.bhattacharya@whh.nhs.uk

## The Problem of Resistant Peptic Stricture

Peptic oesophageal stricture is the end result of long-term gastro-oesophageal reflux disease (GORD). A competent lower oesophageal sphincter and active peristalsis, clearing small amounts of oesophageal refluxate, normally protects oesophageal mucous membrane. Breakdown of this mechanism along with prolonged mucosal exposure to irritant gastric acid, bile, or pancreatic enzymes leads to erosive changes with inflammation, ulcers, healing by fibrosis, and finally stricture formation[1] (defined as oesophageal diameter <13 mm, restricting passage of food and or fluids). A stricture results in dysphagia, traditionally scored by 5-point Mellow and Pinkas (score 0-4) scoring system.[2] A variable but significant proportion of patients with long-term GORD progress to develop oesophageal strictures. Although most of these are simple strictures allowing easy passage of an endoscope through them, some may have a complex nature (>2 cm, tortuous and narrow enough not to allow endoscope passage). It is the latter variety that has a higher recurrence rate and is more difficult to treat.[3] For most obvious reasons, peptic strictures start at the squamo-columnar junction and progress proximally.[4–6] Endoscopic dilatation is a standard treatment offered to these patients.[7] However, up to 33% of patients need repeated dilatations, sometimes as frequently as twice every month.[8,9] A varied proportion of these patients would present with 'refractory' or treatment-resistant stenosis (inability to achieve a diameter of at least 14 mm by dilatation over 5 sessions performed at 2-weekly intervals) or as 'recurrent' stenosis (failure to maintain a luminal diameter of 14 mm for a minimum of 4 weeks, even after this has been achieved once).[7,10,11] Strictures that are longer than 2 cm, have a narrower diameter, and are tortuous have greater propensity towards being recurrent or refractory. Unsurprisingly, patients with long-term strictures have poor nutritional status and weight loss,[12] they may require repeated dilatation with a small (up to 0.4%) but significant risk of oesophageal perforation. Needless to say, frequent endoscopic procedures have a huge financial burden on current health care systems.[13–15]

Current guidance (2018) from the British Society of Gastroenterology (BSG) acknowledges the challenge of managing refractory strictures, calling for further studies to help clarify the role and outcomes of stent use in this cohort. Although the BSG recommends the use of self-expanding metal stents (SEMS) for selected patients with refractory disease, their use is limited by associated complications. Biodegradable stents (BDS) have emerged in the past few years as an attractive alternative and may also reduce the frequency of serial dilatation[7]; however, it is not clear whether they provide long-term symptom relief and whether the benefits achieved in these situations outweigh the risks associated with BDS. This review aims to analyse contemporary evidence for the role of BDS in managing refractory peptic oesophageal strictures.

## Oesophageal Stents: Pros and Cons

Stents used to treat benign oesophageal stenoses are of metal, plastic, or biodegradable variants. Self-expanding metal stents are made of shaped memory alloys and may be 'fully covered' (with silicone or polytetra-fluoro-ethylene), 'partially covered',

or 'uncovered' (bare).[16–18] Given the mechanical irritation produced by the stent, partially covered and uncovered metal stents can embed in oesophageal mucosa because of tissue ingrowth 1 to 4 weeks after placement. This ingrowth is mostly granulation tissue, but with time, fibrosis leads to new onset stricture formation making removal of the stent difficult. Apart from this, migration, bleeding, pain, fistula, and worsening reflux may occur following SEMS insertion.[3,19,20] Fully covered SEMS show resistance to tissue ingrowth, especially when used for shorter periods. However, migration rates remain high when compared with partially covered stents (36% versus 12%).[15,21] Current BSG guidelines dissuade use of uncovered or partially covered SEMS. They recommend fully covered SEMS as second-line for resistant strictures ahead of other stent subtypes.[7] In practice, SEMS are employed in the palliative setting or temporarily for benign conditions, especially for patients with short life expectancy, where previous stents have failed or repeated procedures are not feasible. When used for refractory benign conditions as second-line treatment, their removal is recommended after a period of 3 months and no sooner than 6 weeks to achieve maximum benefit, on one hand, and to prevent tissue ingrowth, on the other.[22,23]

Self-expanding plastic stents (SEPS) are used temporarily in several benign conditions including peptic strictures and are cheaper than their metal counterpart and are easily deployed. The Polyflex (Boston Scientific Corp., Natick, MA, USA, made of polyester in silicone membrane) is licensed for this but has shown poor outcomes and is difficult to place in a complex stricture due to a wider delivery system of 39 to 42 F; sometimes requiring pre-stenting dilatation. A major drawback of the plastic stent is their high frequency of migration, occurring in almost 80% of cases. They are also more traumatic to remove (due to absence of a purse string). These factors are responsible for associated poor long-term outcome.[11,15,24–27]

Biodegradable stents are made of degradable synthetic material, and disintegrate by random hydrolysis, and therefore do not need removal. They potentially cause mechanical irritation of tissues too, but this is time-limited by their dissolution. SX-ELLA Stent Esophageal Degradable BD – BD Stent (Hradec Kralove, Czech Republic), made of PDX/polydioxanone monofilament, is currently marketed and is indicated in resistant cases of benign oesophageal strictures and inoperable achalasia which has not responded to conventional therapy. Radial force is maintained for up to 6 weeks and the stent disintegrates gradually about 12 weeks after placement by hydrolysis, a process that is accelerated by increased acid exposure. Breakdown products are inert and are largely excreted through bowel. This stent has flared ends designed to reduce migration.[28,29] Again, distal migration into stomach enhances stent disintegration by increased exposure to gastric acid, causing stent hydrolysis. This prevents distal bowel injury or obstruction-related complications and potential morbidity.[30]

## Resistant Peptic Stricture: Options Available

*Endoscopic dilatation and steroid injection*

Endoscopic dilatation with balloon or bougie remains the 'gold standard' treatment offered to patients with peptic oesophageal stricture.[7] No significant differences were found between the success, recurrence, or complication rates of these 2 techniques.[31,32] However, based on the current evidence, it is predicted that up to 40% of patients will need ongoing dilatation for recurrent symptoms of dysphagia because of refractory or recurrent stenosis.[33–35] Investigations are ongoing to find ways to reduce the recurrent or resistant stenoses and establish more viable alternatives to repeated endoscopic dilatation. Dilatation combined with steroid injection has been shown to have some added benefit over dilatation alone in this respect. A randomised trial compared the effects of dilatation with added 4-quadrant triamcinolone injection against dilatation alone in a cohort of 30 patients with peptic oesophageal stricture (15 patients in each arm), all of whom had at least 1 failed dilatation in the past 18 months. The authors reported significant decrease in need for repeated dilatation episodes (13% versus 60%; $P = .01$) and significant increase in symptom-free period in the steroid arm added with acid suppression therapy.[36] In a similar randomised study involving a smaller cohort (n = 21 patients) with oesophageal strictures from different causes (peptic, caustic, anastomotic, and postradiotherapy; only 29% patients in this cohort had peptic strictures), the effects of intra-lesional steroid injection was assessed with or without bougie dilatation. Although this study dealt with a small group of patients and did not specifically look at peptic strictures, the mean symptom-free period in the steroid arm was found to be significantly longer ($24 \pm 12.75$ months versus $5.18 \pm 5.06$ months; $P < .001$) with fewer number of dilatations (significantly lower periodic dilatation index, defined as the ratio of number of dilatation episodes and follow-up duration in months; $P < .05$). However, there was no statistically significant difference between the 2 groups in achieving sufficient postdilatation oesophageal diameter ($P = .28$).[37] Benefit of adding steroid injections with dilatations was demonstrated in other non-randomised studies in peptic strictures.[38,39] Non-peptic strictures, however, were found to be more resistant to this technique.[40,41] In addition, no definite dose of injected steroid has been optimised and has been largely empirical in different studies, hence still in experimental phase.[42] Steroids are known to decelerate the inflammatory process and reduce fibroblast action. This may be the mechanism of action. However, a major downside of using steroids is a possibility of delayed perforation.[43] In summary, although marginal benefit has been demonstrated by combining steroid injections with dilatations, the studies were limited either by their cohort size or were non-randomised, had heterogeneous cohorts with strictures from several causes, and sometimes had conflicting results; hence, no robust evidence is available to routinely support this treatment.

*Metal (SEMS) and plastic (SEPS) stents*

Stents (SEMS, SEPS, and BDS) have been used in resistant cases of peptic oesophageal stenosis as a second-line treatment. Self-expanding metal stents have several drawbacks, including tissue ingrowth causing embedding of the stent with the chance of fibrosis and more resistant stenosis. Fully covered SEMS are preferred over partially covered or bare-stents for this reason.[7] Studies using covered SEMS have demonstrated good success with complete relief of dysphagia in 40%[44]; however, migration remains problematic with high rates of 30%[44] and recurrence occurring in 69% following SEMS removal.[45] Partially covered SEMS have a place in 'stent in stent technique', used as a salvage procedure in situations, whereas fully covered SEMS are inserted in the lumen of a pre-existing embedded stent. The new internal stent is slightly longer and has a slightly bigger diameter than the embedded outer stent. Due to pressure necrosis of the hyperplastic tissue ingrowth caused by the inner stent in 10 to 14 days, both stents can be removed.[44,46,47] The Polyflex (SEPS) stent has FDA (Food and Drug Administration) approval for use in benign oesophageal stricture. Although it performed well in malignant oesophageal stenosis in 90% of cases (major complications were dysphagia due to migration of stent, embedding, and impacted food bolus), results in benign disease were variable.[48] Effects of expandable polyester silicone covered plastic stent placed temporarily for 6 weeks were studied in a small cohort of 15 patients with resistant benign oesophageal stricture. After removal of stents, relief of dysphagia (assessed by pre- and post-treatment dysphagia scores) was found to be statistically significant ($P < .0005$). Long-term resolution of stricture was reported in 80% cases in this cohort.[49] A retrospective study by Holm et al reported 98.8% success from SEPS placement in a mixed group of benign oesophageal conditions (stenosis from reflux, ischaemia, idiopathic, radiation, anastomotic stricture, and oesophageal fistula/leak). Nearly 80% of stents placed in benign strictures in this study were found to have migrated, and only 6% of cases experienced long-term improvement after stents were removed.[26] A meta-analysis from 2010 assessed 10 studies and 128 patients who underwent SEPS insertion with a variety of benign oesophageal strictures at different levels, of which only 12% of patients had peptic strictures. Although this study does not comment about the success rate in peptic strictures in particular, the overall success in relieving dysphagia was 52% at a median follow-up period of 13 months. Early migration rates (defined in this study as migration in less than 4 weeks) and major complication rates were low (24% and 9%, respectively). The limitations of this meta-analysis are quite apparent. First, given most of the analysed studies were retrospective with small sample size and reporting bias, possibility of further magnification of this bias cannot be excluded. Second, given the median follow-up of 13 months is very small, long-term success rates with SEPS are still unclear. Finally, this meta-analysis reports the success rates in a heterogeneous group of benign strictures (from several causes: peptic, post-surgical, corrosive, radiation), previous evidence points towards the fact that strictures from different pathologies (reflux versus other pathologies) react differently to different forms of treatment.[50] The relationship between cause of stricture and clinical success rate of treatment used was further strengthened by a meta-analysis.[51] In summary, the current evidence points towards moderate success rates of plastic stents in benign stenosis in general with complications mostly related to migration, but not specifically in peptic oesophageal stricture. As most of the current evidence is from heterogeneous cohort and with varying results, rationale for using SEPS to achieve long-term relief of dysphagia in peptic stricture is still weak.

*Biodegradable stents*

Biodegradable stents have shown some promising results in animal models.[52,53] Initial clinical experience in treatment of benign oesophageal strictures involved the use of PLLA (poly-L/D-lactic acid) BDS (InStent, Eden, MN, USA) in 1996. Following placement, PLLA-BDS stents expanded to its design diameter (14-16 mm; 6-10 mm long), providing radial force and degraded in 3 to 6 months. Initial results were somewhat unsatisfactory as radial force provided by the stent was lower than SEMS. There were 3 cases of spontaneous stent collapse causing recurrent dysphagia.[54] Scientific reports with improved PLLA-BDS (Tanaka-Marui stent) showed some initial promising results.[55] A retrospective study reported use of this BDS in a small cohort of 13 patients, none of whom had peptic stricture. This demonstrated a very high proportion of stent migration (76.9%/10 of 13 patients) within 3 weeks of placement and only 3 stents (23%) successfully relieved dysphagia without any episodes of re-stenosis (range of follow-up 7 months to 2 years).[56] A further case series with the same stent in 2 patients with oesophageal stenosis after endoscopic submucosal dissection demonstrated no recurrence in symptoms for 6 months.[57] Currently, SX-Ella BD stent, made of PDX, is the only BDS licensed for use in patients for treating oesophageal strictures and its role has been studied extensively (Table 1) in the benign setting.[66] This stent is available in 4 diameters (18, 20, 23, and 25 mm), variable length (6-13.5 cm), and is assembled on a 28-F delivery unit. The stent needs to be mounted on this delivery system by the operator immediately before deployment. Once deployed, under endoscopic and fluoroscopic guidance, the stent gradually expands laterally to achieve the desired diameter within 1 to 2 days. Complete radial force and integrity is maintained for the initial 6 weeks. Following this, it possesses two-thirds and one-thirds of its integrity until approximately 9 and 12 weeks, respectively. The degradation process following this period is gradual and by ester bond hydrolysis, accelerated by gastric acid exposure. This process can be slowed down by proton pump inhibitor therapy and stent life can be increased. A prospective report from Repici et al studied effects of BDS in 21 patients, 7 of whom

**Table 1.** Outcome of stents in different studies.

| NO. | AUTHOR | YEAR | TYPE OF STUDY AND REFERENCE NUMBER | AIMS | RESULTS | DEFINITION OF CLINICAL SUCCESS AND FOLLOW-UP |
|---|---|---|---|---|---|---|
| 1 | Saito et al | 2007 | Retrospective[56] | Poly-lactic acid knitted BDS in benign non-peptic strictures (n = 13) | 1. Clinical success 23%<br>2. Migration rate 76% | Not clearly defined but follow-up was from 7 mo to 2 y |
| 2 | Repici et al | 2010 | Prospective, 'BEST' Study[58] | Assess efficacy and safety of BDS (n = 21, 33% had peptic strictures) | 1. Clinical success 33% in peptic sub-group and 45% in entire cohort<br>2. Significant improvement in post-stenting dysphagia score ($P < .01$)<br>3. Migration 16.7% in peptic group and 10% in entire cohort | No recurrence of dysphagia at the end of at least 6 mo follow-up (median 53 wk for entire cohort) |
| 3 | van Boeckel et al | 2011 | Prospective[59] | Compared effects of BDS (n = 18) versus temporary SEPS (n = 20) 33% and 5% had peptic strictures, respectively | 1. Clinical success in BDS versus SEPS was 33% and 30%, respectively ($P = .83$).<br>2. Migration rates were 22.2% and 25%, respectively ($P = .30$) | No recurrence of dysphagia at the end of follow-up.<br>For BDS, median was 166 d (range 21-559 d)<br>For SEPS, median was 385 d (range 77-924 d) |
| 4 | Griffiths et al | 2012 | Prospective[60] | Assess efficacy of BDS in benign (n = 7, none with true benign peptic strictures) and malignant strictures | 1. 45% success in entire cohort (median follow-up 20 wk).<br>2. Re-intervention rates high after stent dissolves. | Dysphagia free till end of follow-up, median follow-up was 20 wk (range 13 to 111 wk) |
| 5 | Canena et al | 2012 | Prospective multi-centre[61] | Compare SEPS, BDS, and fully covered SEMS (n = 10 in each arm) in benign strictures; peptic strictures were in 1, 3, and 3 patients (total 23.3%), respectively | 1. Overall success 26.7% (very low)<br>2. No difference in dysphagia-free periods ($P = .67$), re-intervention ($P = .24$), clinical success ($P = .24$), and complication rates ($P = .38$)<br>3. Migration of stents in 36.7% cases (n = 6, 2, and 3 respectively; $P = .16$) | Dysphagia free till end of long-term follow-up. Median follow-up was 23.4 mo (range 8-66 mo) |
| 6 | Hirdes et al | 2012 | Prospective[62] | Assess effects of single and sequential biodegradable stents in 28 patients (59 stents), peptic strictures in 9 patients (32%), clinical success defined as dysphagia-free period for 6 mo | 1. Median dysphagia-free periods after first, second, and third stents (90, 55, and 106 d)<br>2. Clinical success rate after first stent was 25%<br>3. Clinical success rate after second stent was reduced to 15%<br>4. Clinical success rate after third stent was 0% | Dysphagia free for at least 6 mo |
| 7 | Dhar et al | 2014 | Multi-centre randomised trial[63] | Compare BDS (n = 9) versus repeated endoscopic dilatation with CRE balloon (n = 6), 46.7% with peptic stricture (n = 3 and 4 patients, respectively) | 1. Significantly higher post-intervention dysphagia score in stent group after both 6 and 12 mo ($P = .029$ and $P = .05$, respectively)<br>2. Mean adverse outcome higher in stents ($P = .024$)<br>3. Results of BDS inferior to repeated dilatation | Follow-up in 6 and 12 mo |
| 8 | Sigounas et al | 2016 | Retrospective[64] | Assess results of BDS in benign and malignant strictures of oesophagus, 17 stents inserted in 10 patients with benign (80% peptic) stricture | 1. Interval between BDS insertion and first post-stenting intervention was significantly longer than pre-stenting dilatation intervals ($P < .05$)<br>2. 80% cases needed multiple dilatation<br>3. Quoted 20% (2 of 10) success but both these patients died before presenting with recurrent symptoms | Dysphagia free till end of follow-up from March 2011 till July 2015 or till death. Median follow-up was for 171.5 wk for benign group |

**Table 1.** (Continued)

| NO. | AUTHOR | YEAR | TYPE OF STUDY AND REFERENCE NUMBER | AIMS | RESULTS | DEFINITION OF CLINICAL SUCCESS AND FOLLOW-UP |
|---|---|---|---|---|---|---|
| 9 | McCain et al | 2016 | Retrospective[65] | Efficacy and safety of BDS in benign (n = 9, % of peptic strictures not specified) and malignant (n = 11) strictures | 1. Significant improvement in dysphagia scores in benign sub-group ($P < .001$)<br>2. 55.6% patients in benign group were symptom free at follow-up (clinical success)<br>3. Migration rate was 0% | Not clearly defined |
| 10 | Fuccio et al | 2016 | Meta-analysis[51] | Compared SEMS (n = 227) versus SEPS (n = 140) versus BDS (n = 77) in 444 patients from 18 studies (17.8% with peptic stricture) | 1. Overall clinical success 40.5% with stents. Higher heterogeneity in studies involving SEMS and SEPS<br>2. BDS had lower success rate (32.9%) as compared with SEMS and SEPS (40.1% and 31.5%, respectively, difference was statistically not significant)<br>3. Overall migration rate was 28.6%. BDS had lower migration rates (15.3%) as compared with SEMS and SEPS (46.2% and 33.3%, respectively, difference was statistically not significant)<br>4. Overall adverse events 20.6%, no significant difference between 3 stents<br>5. Strictures due to anastomosis (post-surgical) and radiotherapy induced may be more sensitive to stents than other types | 1. Clinical success defined as dysphagia free till end of follow-up<br>2. Clinical heterogeneity regarding length of follow-up noted.<br>3. Follow-up for entire cohort was from 86 to 1281 d (median follow-up 455d) in different studies |

(33%) had peptic (distal oesophageal) strictures. This small cohort had all undergone previous dilatations and re-presented with recurrent dysphagia (scores of 3 and 4). One patient died before follow-up was completed. In the remaining patients (median follow-up was 67.5 weeks for the peptic sub-group and 53 weeks for the entire cohort), clinical success was observed in only 2 (33.3%) patients in the peptic sub-group and in 9 out of 20 patients (45% with significant improvement of dysphagia score after stenting; $P < .01$) in the entire living cohort, not needing any further interventions. The rest of the cases needed repeated dilatations for further dysphagia. In this study, no major complications were attributed to the stenting procedure. Stent migration was observed in 1 (16.7%) patient in the peptic sub-cohort and in 2 (10%) patients in the entire living cohort. Although the cause for high failure rate of BDS was not entirely clear, the authors proposed early disintegration of stent as a possible explanation. However, it is worth noting that BDS would offer longer duration of a radial force to the stricture even if disintegration occurs sooner than expected when compared with balloon dilation which typically lasts for a few minutes. The obvious limiting factor in this study was its non-randomised model, small heterogeneous cohort, and room for selection bias.[58] A further prospective study compared effects of BDS versus temporary (removed after 6 weeks) SEPS in a cohort of 38 patients (n = 18 for BDS and n = 20 for SEPS) with resistant benign oesophageal strictures. Seven patients in this group (n = 6 or 33% and n = 1 or 5%, respectively) presented with stricture due to reflux. The authors reported that only 33% (6 patients) in the BDS group were free from dysphagia after a median follow-up of 166 days (range 21-559). A third of this group needed further treatment for recurrent stricture. Migration of stent was found to be higher than expected in 22.2% (4/18) cases and major complications were reported in 4 (22.2%) patients. Results from temporary SEPS arm (n = 6 or 30% patients were free from dysphagia at the end of median follow-up of 385 days; $P = .83$; 5 patients or 25% patients had recurrent stricture, 25% stents migrated, and major complications were noted in 2 patients or 10%; $P = .30$) were almost similar, without any statistical significance. Although this was one of the first studies to have compared BDS and temporary SEPS in parallel groups of resistant oesophageal strictures in the setting of a tertiary centre, several limitations come forward: non-randomised design leading to sampling bias, smaller cohort size, heterogeneous nature of strictures with proportionately more peptic strictures on BDS arm, and absence of sub-group (based on cause of stricture) analysis.[59] Another prospective study by Griffiths et al assessed the effects of BDS in a mixed cohort of benign and malignant strictures. Of the benign sub-group (n = 7), only 1 patient was initially stented with a diagnosis of peptic-related stricture and was later found to have adenocarcinoma. Of the rest of the patients (perforation-related stricture, Barrett's-related stricture, achalasia, anastomotic, and postradiotherapy stricture), post-stenting

dysphagia scores were better and 45% patients did not require any further intervention after a median follow-up of 20 weeks. While considering the entire cohort, the authors concluded that re-intervention rates are high after the stent dissolves.[60] A prospective multi-centre non-randomised study by Canena et al compared the effects of SEPS, BDS, and fully covered SEMS in a cohort of 30 patients (10 in each arm) having benign strictures with only 23.3% cases being reflux related (n = 1, 3, and 3, respectively). No statistically significant difference was observed in dysphagia-free periods (11.1, 19.5, and 23.1 months, respectively; $P = .67$), re-intervention rates ($P = .24$), clinical success rates (1, 3, and 4 cases, respectively; $P = .24$, defined as absence of dysphagia after long-term follow-up) and complication rates ($P = .38$) in between any of these 3 treatment modalities (median follow-up for entire cohort was 23 months and median follow-up of 3 arms were 42.7, 18.5, and 10 months, respectively). Migration of stents were seen in 36.7% cases (n = 6, n = 2, and n = 3, respectively; $P = .16$). This study had obvious limitations; small cohort size, non-randomised model, susceptibility to selection bias, and median follow-up in SEPS being longer than both BDS and SEMS. Again, no cause-based sub-group analysis was performed. Furthermore, overall success rate of stenting was reported to be very low (26.7%) in benign strictures making this a less favoured option.[61] In a prospective study, the concept of single and sequential BDS was investigated by Hirdes et al in a cohort of 28 patients (59 stents) with recurrent dysphagia from benign stricture. Sequential stents were placed in a sub-cohort of 13 patients. The authors reported that (median dysphagia-free period after first, second, and third sequential stents were 90, 55, and 106 days, respectively) the success rate, defined as being dysphagia free for 6 months after stenting, steadily declined from 25% after first BDS to 0% after third sequential stent was inserted.[62] A multi-centre randomised trial by Dhar et al compared BDS (SX-ELLA) versus repeated endoscopic (CRE) balloon dilatation in a cohort of 15 patients (n = 9 and n = 6, respectively) with recurrent oesophageal stricture, of which 46.7% (7 of 15, n = 3 and n = 4, respectively) participants had peptic stricture. Although both treatments offered improvement in symptoms, in contrast to other studies, the authors noted that patients in stent arm had significantly higher mean dysphagia scores over the other sub-group after both 6 months (difference in mean scores was 1.17, 95% confidence interval [CI] = 0.63-1.78; $P = .029$) and 12 months (difference = 1.21, 95% CI = 0.56-2; $P = .05$) of intervention. Mean adverse outcome per patient related to intervention was also higher in stent group as compared to balloon dilatation (1.4 versus 0; $P = .024$). No difference was, however, found in post-intervention additional endoscopic procedures in either group. An obvious limitation in this study was its small sample size and hence being underpowered. Again, the authors did not clearly sub-classify the cohort according to their stricture causes, a factor known to influence outcome. However, given the relatively higher dysphagia scores, this study did not support routine use of BDS over repeated dilatation in recurrent benign stenosis.[63] In a recent retrospective study by Sigounas et al, 17 BDS were inserted in a very small cohort of 10 patients with benign oesophageal stricture, 80% of which were peptic in origin. In this cohort, the time between BDS insertion and first post-stenting intervention was significantly longer than pre-stenting dilatation intervals ($P < .05$). However, 50% cases need more BDS inserted, 20% required further SEMs, and 80% came back for multiple episodes of dilatation. Although the authors quoted 20% success of BDS, 2 patients who did not need any further intervention after stenting died (at 65 and 188 days) before presenting with recurrent dysphagia.[64] A retrospective study by McCain et al assessed the efficacy and safety of BDS in a small cohort of benign and malignant oesophageal strictures. Although it was not clear what proportion of benign strictures were from acid peptic reflux, the authors quoted significant improvement in dysphagia scores in benign sub-group (mean scores 2.65-1 before and after stenting, respectively; $P < .001$) with 5 of 9 patients (55.6%) being symptom free at follow-up and 4 patients (44.4%) needing multiple BD stents; median re-stenting time was 260 days. It was not, however, clear what proportion of peptic strictures was in the group not needing intervention.[65] A meta-analysis by Fuccio et al reviewed the role of different stents in benign oesophageal strictures. This meta-analysis assessed 444 patients with benign strictures from different causes (17.8% peptic) who underwent stenting by SEMS (n = 227), SEPS (n = 140) and BDS (n = 77, 38.9% were with peptic stricture). Clinical success was defined as proportion of patients being dysphagia free at the end of follow-up (median 455 days, range 86-1281 days). Overall pooled success rate with stents was found to be 40.5%. A high level of heterogeneity was noted in studies involving SEMS and SEPS as opposed to those reporting use of BDS. Patients who underwent insertion of BDS, had lower success rates (32.9%, 95% CI = 23.1%-44.1%) and lower migration rates (15.3%, 95% CI = 8.3%-25.4%), as compared with success and migration rates of SEMS and SEPS (40.1%, 31.5% and 46.2%, 33.3%, respectively). No significant differences were noted in between stents regarding stent-related adverse events (overall 20.6% for the entire cohort). Although no robust conclusion could be drawn regarding superiority of one type of stent over another due to absence of any statistically significant difference and high levels of heterogeneity in studies involving SEMS and SEPS, the authors indicated the possibility that anastomotic and postradiotherapy strictures may respond better to stent dilatation than other varieties of benign strictures.[51]

## Discussion

Primary recommended treatment for benign peptic stricture of oesophagus is endoscopic dilatation with balloon or bougie in specialist centres under the care of experienced endoscopists. In

cases where the stricture is severe enough not to allow passage of the endoscope (<10 mm luminal diameter), endoscopic dilatation should be performed. This should be graded; the initial dilatation restricted to a diameter of 10 to 12 mm (30-36 F) only. Use of fluoroscopic guidance and carbon dioxide insufflation, as opposed to simple wire-guided dilatation, blind bougie dilatation, and air insufflation, respectively, adds to the safety of this procedure. It is recommended that 3 or less diameter increments should be targeted in each dilatation session to decrease chances of perforation which has been reported to be approximately 1% in peptic strictures. The BSG guidelines recommend weekly or twice monthly dilatations until 15 mm luminal oesophageal diameter is achieved with symptomatic improvement of dysphagia, following which intervals may be increased accordingly. Intensive follow-up is advised for these high-risk patients. There is poor evidence regarding role of surgery in treating benign strictures.[7] Patients, who fail to respond to endoscopic dilatations with refractory or recurrent stenosis as defined above, pose a serious challenge to the clinician. These patients are mostly in their extremis and malnourished, prone to complications from factors both related and unrelated to interventions.[12-15] Hence possible alternative or secondary treatments which reduce number of invasive interventions or increase their intervals are worth exploring. In quest for this, investigators have tried steroid injection with endoscopic stretching and stents of different varieties including BDS. Endoscopic steroid injection to the stricture site was reported initially as a better option over endoscopic dilatation alone, however, in absence of a specified dose of injection, set regime and added risk of delayed perforation[36-39,43] are still under review.

Following several initial reports of complications and low success rates in benign setting with metal and plastic stents (embedding, migration, and need for re-intervention),[15,26,67-71] BDS came forward as a more viable alternative. However, studies failed to show success rates of more than 55% with BDS (Table 1). Most of these studies were non-randomised, prospective, or retrospective, with small cohorts and affected by several types of bias. Moreover, most used heterogeneous cohort comprising strictures from different causes (peptic strictures ranging from 0% to 80% of the cohort size in different studies), although a meta-analysis[51] suggested association between cause and outcome of treatment in benign strictures. Different follow-up periods were used to define clinical success in these studies, ranging from 3 to 264 weeks (median follow-up ranging from 20 to 94 weeks in different studies). Thus, inferences drawn about success rates were difficult to compare between reports.

Furthermore, a randomised trial[64] reported inferior performance of BDS with respect to mean number of adverse outcomes, post-intervention dysphagia score at 6 and 12 months as compared with endoscopic dilatation alone, in benign setting. This was in clear contradiction to reports from non-randomised studies claiming superiority of BDS in providing greater dysphagia-free intervals.[65] The cumulative risk reduction in perforation achieved using BDS, with not having multiple dilatations (up to 6 per patient and each adding 0.4% risk of perforation), needs to be considered here.[14,15] A recent meta-analysis,[51] after analysing results from 444 patients and 18 studies, reported no significant difference between results from SEMS, SEPS, and BDS in benign strictures. The authors warned about high levels of heterogeneity in participant studies, especially those involving plastic and metal stents. There was also the obvious risk of amplification of bias from several participant studies which were largely non-randomised. Again, stents may be liable to cause more strictures at its ends for reasons not entirely clear to us. A possible mechanism is direct mechanical irritation by keeping the gastro-oesophageal junction open promoting continued reflux. This may result in proximal migration and increased length of strictures with poorer prognosis and progressively shorter dysphagia-free interval along with need for sequential stenting.[63,72]

Therefore, on one hand, after comparing several secondary treatments (SEMS versus SEPS versus BDS) in patients where primary treatment of endoscopic dilatation has failed, BDS emerges with marginal benefit only. But, on the other hand, it may also be argued that in patients with failure of primary treatment, a success rate of 45% may be acceptable and should be considered after careful discussion of associated risks and benefits. Although based on very weak evidence and classed as 'low level' recommendation, this later view has been reflected in the recent BSG guidelines.[7]

In summary, although several studies have reported advantages in obtaining longer dysphagia-free intervals with BDS in peptic strictures, many refute the notion. Success rates differ widely, so do complication rates, making these reports contradict each other. In the light of this, routine use of BDS as first choice in resistant peptic stricture is not yet an established option. It may only be considered in a small subset of patients unfit for regular frequent endoscopic interventions and poor life expectancy. Furthermore, its routine use in benign conditions as a secondary treatment modality needs further investigation through targeted studies with larger, non-heterogeneous cohorts, longer follow-up periods, and more robust evidence base.

## Author Contributions

SB, TR and GN compiled evidences and wrote the main manuscript. NR and HS completed an extensive review of this manuscript and contributed towards updating manuscript in lines with reviewers' queries. SB was the team lead in this project.

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