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Systematic review with meta-analysis: efficacy of balloon-assisted enteroscopy for dilation of small bowel Crohn's disease strictures

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Summary

Background: Evidence for endoscopic balloon dilation of small intestinal strictures in Crohn's disease (CD) using balloon-assisted enteroscopy is scarce.

Aim: To evaluate endoscopic balloon dilation for the treatment of small intestinal CD strictures using balloon-assisted enteroscopy.

Methods: Citations in Embase, MEDLINE, and Cochrane were systematically reviewed. In a meta-analysis of 18 studies with 463 patients and 1189 endoscopic balloon dilations, technical

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

success was defined as the ability to dilate a stricture. Individual data were also obtained on 218 patients to identify outcome-relevant risk factors.

Results: In the pooled per-study analysis, technical success rate of endoscopic balloon dilation was 94.9%, resulting in short-term clinical efficacy in 82.3% of patients. Major complications occurred in 5.3% of patients. During follow-up, 48.3% of patients reported symptom recurrence, 38.8% were re-dilated and 27.4% proceeded to surgery. On the per-patient-based multivariable analysis, that patients with disease activity in the small intestine had lower short-term clinical efficacy (odds ratio 0.32; 95% confidence interval 0.14-0.73, $P = 0.007$). Patients with concomitant active disease in the small and/or large intestine had an increased risk to proceed toward surgery (hazard ratio 1.85; 95% confidence interval 1.09-3.13, $P = 0.02$ and hazard ratio 1.77; 95% confidence interval 1.34-2.34, $P < 0.001$).

Conclusions: Balloon-assisted enteroscopy for dilatation of CD-associated small intestinal strictures has high short-term technical and clinical efficacy and low complication rates. However, up to two-thirds of patients need re-dilation or surgery.

1 | INTRODUCTION

Crohn's disease (CD) is a chronic relapsing inflammatory disorder that may affect the whole gastrointestinal tract.¹ Triggered by the chronic nature of the disease, more than one third of patients with CD develop clinically apparent intestinal strictures over time.^{2,3} In affected patients, stricture formation often results in obstructive symptoms and the necessity for hospitalisation and surgery. Up to 75% of patients with CD require surgery at least once during their life-time, with strictures being main indication.^{1,4} Most frequently, CD strictures are localised in the ileocecum where they can be reached during routine ileocolonoscopy. In contrast, CD strictures of the small intestine beyond the terminal ileum are only reliably accessible via device-assisted enteroscopy including balloon-assisted enteroscopy (BAE).^{1,5-8} BAE has been first described in 2001 by Yamamoto et al (double-balloon-enteroscopy) and was modified in 2007 by Hartmann et al (single-balloon enteroscopy).^{9,10}

The treatment of CD strictures of the small bowel is challenging.¹¹⁻¹⁴ Anti-inflammatory treatment including corticosteroids and anti-tumour necrosis factor-alpha blockers might improve obstructive symptoms; however, the CREOLE trial demonstrated that within 12 months, 40% of patients with symptomatic small-bowel stenosis treated with anti-tumour necrosis factor-alpha blockers required endoscopic balloon dilation (EBD) or surgery and within four years 50% needed a bowel resection.¹⁵ In the absence of specific anti-fibrotic drugs,¹⁶ EBD has emerged as a valuable adjunct and alternative to surgery.^{11,13,14,17} Accordingly, EBD of CD strictures is part of current guideline recommendations for the treatment of ileal strictures.^{14,18,19} However, most studies evaluated EBD for terminal ileal and ileocolic anastomotic strictures which can be reached by standard ileocolonoscopy and the evidence for EBD of small bowel strictures which can only be reached by BAE is scarce (Figure 1).^{7,8,11,19}

To address this knowledge gap, this pooled analysis of international cohort studies aimed to evaluate the efficacy and safety of BAE-based EBD of small bowel CD strictures.

Furthermore, we used individual patient data sets from 218 patients to identify risk factors that might be associated with clinical efficacy, symptom recurrence, need for repetitive EBD and surgery.

2 | MATERIALS AND METHODS

2.1 | Literature search and data selection

A formal systematic review with a comprehensive literature search to identify all relevant citations in Embase, Medline (service of the United States National Library of Medicine and the National Institutes of Health) and Cochrane library was performed using pre-defined search strategies (Supplementary Methods and Figure S1). The search included cohort studies from 01/1991 to 12/2017. Eligible studies enrolled adult patients (age >18 years) with a confirmed diagnosis of CD, strictures of the small intestine including jejunum and ileum associated with CD that was dilated through BAE using through-the-scope EBD. To ensure an adequate level of experience with EBD through BAE, case reports and small case series with less than eight patients per study were excluded from this analysis. Furthermore, records were excluded due to the following reasons: the dilated stricture was localised in nonsmall-bowel location, no EBD and no BAE was performed and records were only available in non-English language. In addition to this comprehensive literature search, conference proceedings including Digestive Disease Week, European Crohn's and Colitis Organization Congress, United European Gastroenterology Week, Advances in Inflammatory Bowel Disease, American Gastroenterological Association Congress and German Gastroenterology Congress were screened for additional data since inception until December 2017 (Figure S1). Screening conference proceedings, all above-enlisted criteria except for the "non-English language"-criterion were applied. Two reviewers (D.B. and A.B.) independently screened citations and abstracts. The full-text publications of potentially eligible studies were reviewed in duplicate by D.B. and A.B. Disagreements regarding inclusion or extraction were resolved through discussion (D.B. and A.B.), or in case of ongoing disagreement by F.R.

18 identified studies were included in the quantitative synthesis for the study-level data meta-analysis. Furthermore, all corresponding authors of these studies were contacted and invited to contribute individual patient data. Clinical data of included patients were transferred into a detailed and anonymised secured database. Data checks were performed. Ethical approval for this data collection was obtained by each local centre and data were provided in a de-identified fashion. Nonresponding corresponding investigators were re-contacted up to two times. Four large volume centres (Division of Gastroenterology, University of Alberta, Edmonton, Alberta, Canada²⁰; Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka, Japan²¹; Inflammatory Bowel Disease Center, Fukuoka University Chikushi Hospital, Fukuoka, Japan and Department of Gastroenterology, Fukuoka University Faculty of Medicine, Fukuoka, Japan^{22,23}; Department of Gastroenterology, Fujita Health University School of Medicine, Toyoake City, Japan²⁴) provided their complete data sets resulting in a total of 218 cumulative CD patients. Ethical approval of this pooled analysis was not necessary because only published

data were provided in a de-identified fashion. Missing individual-level data were handled as described in the statistical analysis section.

Outcomes were evaluated as follows: (a) *Technical success* was defined as the ability to dilate a stricture after starting the procedure (definitions, as mentioned in the individual studies, can be found in Table S1); (b) *Short-term clinical efficacy* was defined as the improvement or relief of symptoms of intestinal obstruction (definitions, as mentioned in individual studies, can be found in Table S1); (c) *Long-term success* was defined as the absence of recurrent symptoms, re-dilation-free interval, and intervention-free period with no need for surgery after the first dilation (definitions, as mentioned in individual studies, can be found in Table S1); (d) Major complications were defined as perforation, bleeding, or dilation-related surgery and (e) Need for surgery was defined as necessary surgery at the site of the dilated stricture only and not as surgery in others areas of the intestine. For the individual per-patient analysis, a protocol was developed and items regarding demographics, disease phenotype, medications, and dilation procedures were documented for all included subjects. A detailed list depicting all assessed variables is provided in Table 2.

2.2 | Statistical analysis

Categorical factors were summarised using frequencies and percentages, while continuous measures were summarised using means and standard deviations if normally distributed or medians and quartiles if not normally distributed.

Study-level data were pooled using DerSimonian-Laird random-effects model meta-analysis which controls for heterogeneity across studies. The choice of random-effects meta-analysis was performed after assessing heterogeneity using τ^2 (between study-variance) and I^2 (the ratio of true heterogeneity to total observed variation). For this pooled per-study analysis, aggregate outcome measures obtained from the publications were used. The number of patients with small bowel strictures was provided in each study; however, in few studies numbers were not provided for each of the following categories: number of strictures, percentage of single-strictures and number of dilations. For data pooling of these categories, missing data was precisely calculated or assumed based upon the minimum number of strictures/dilations matching to the number of study patients. Proportions were analysed using a logit transformation. Inverse weighting was applied for pooling and the Clopper-Pearson method was used to estimate the confidence interval (CI). Lastly, funnel plots were used to assess publication bias; for this we plotted the effect estimates against their standard errors.

Individual patient data meta-analysis was performed using a one-step approach where data from all studies were modelled simultaneously. Regression analysis accounts for correlations between subjects within the same study and multiple dilations for same patients. Complete-case analysis was performed. Five outcomes were calculated: short-term clinical efficacy, time to symptom recurrence amongst those with short-term clinical efficacy, time to redilation, time to surgery, and time to re-intervention (first surgery or re-dilation). All outcomes except time to surgery and time to re-intervention were captured at the dilation level, while time to first surgery and time to re-intervention were captured at the patient level.

2.2.1 | Short-term clinical efficacy—Dilation-level data were used to assess factors associated with short-term clinical efficacy. Generalised linear mixed models were used with a logit link for binary data; random effects for study and subject were used to account for correlation between multiple dilations performed on the same patient and between patients seen at the same centre. Factors that were seen in 10 or more patients and those that were reported for most dilations were considered for inclusion in the multivariable model and a stepwise variable selection method was used to choose the final model. Odds ratios (OR) were calculated for 95% CI and $P < 0.05$ was considered statistically significant.

2.2.2 | Re-dilation and recurrence of symptoms—Dilation-level data were used to assess factors associated with the recurrence of symptoms and need for re-dilation. Some dilations did not have follow-up information on either re-dilation or symptom recurrence and were excluded from this part of analysis. To assess re-dilation, the follow-up time was defined as months from initial dilation to time of re-dilation; subjects were censored at the time of last follow-up visit if they had no re-dilations. Symptom recurrence was only assessed in subjects with clinical efficacy after endoscopic dilation and follow-up time was defined as months from initial dilation to time of symptom recurrence; subjects were censored at the time of re-dilation, surgery or last follow-up visit if they had no recurrence. Cox marginal model regression analysis was performed, and standard errors and P values are based on a robust (sandwich) variance estimator that accounts for patients having multiple dilations and study clustered data. Factors that were seen in 10 or more patients and those that were reported for most dilations were considered for inclusion in the multivariable model and a stepwise variable selection method was used to choose the final model. Hazard ratios (HR) were calculated for 95% CI and $P < 0.05$ was considered statistically significant.

2.2.3 | Surgery and first re-intervention—Patient-level data were used to assess factors associated with need for surgery or need of re-intervention (first surgery or re-dilation). There were some patients that had no information regarding surgery or time of first re-dilation and were excluded from this part of analysis. For time to surgery, follow-up time was defined as months from the first dilation to time of surgery; patients were censored at the time of last follow-up visit if they did not have surgery. For first re-intervention, follow-up time was defined as the months from the first dilation to either first re-dilation or surgery; patients were censored at the time of last follow-up visit if they did not have a re-intervention. Unadjusted and multivariable Cox marginal model regression analysis was performed to assess factors associated with surgery; standard errors and P values are based on a robust (sandwich) variance estimator that accounts for patient clustering. Factors that were seen in 10 or more patients and those that were reported for most dilations were considered for inclusion in the multivariable model and a stepwise variable selection method was used to choose the final model. HR were calculated for 95% CI and $P < 0.05$ was considered statistically significant.

Analysis was performed using SAS software (version 9.4; Cary, NC). A significance level of 0.05 was assumed for all tests.

3 | RESULTS

3.1 | Pooled per-study analysis

Systematically reviewing current databases, 18 studies were identified that reported 463 patients with stricturing CD being treated by EBD using BAE in a total of 1189 procedures (Table 1).²⁰⁻³⁷ The technical success of EBD was 94.9% (95% CI 86.7%-98.1%; number [n] = 13/18) and EBD resulted in symptomatic relief in 82.3% of patients (95% CI 68.1-91; n = 9/18). Major complications comprising bleeding, perforation or dilation-related surgery occurred in 5.3% of patients (95% CI 3.5%-8.1%; n = 14/18). During follow-up of 20.5 months, symptomatic recurrence was observed in 48.3% of patients (95% CI 33.2%-63.7%; n = 11/18), 38.8% of patients (95% CI 27%-52%; n = 16/18) were re-dilated and 27.4% of patients (95% CI 21.9-33.8; n = 15/18) proceeded to surgery (Table 1). For more details see Supplementary Material.

3.2 | Pooled individual patient analysis

To evaluate potential risk factors that affect the outcome of EBD including short-term clinical efficacy, symptom-recurrence, and need for re-dilation and surgery, respectively, a pooled individual patient analysis was performed. Upon request by prior identified studies, four high volume inflammatory bowel disease centres completed a detailed data sheet providing individual data for a total of 384 dilation procedures being performed in 218 patients.

A detailed description of the study cohort can be found in Tables 2 and 3. The median age at the time of small bowel stricture diagnosis was 40.6 ± 14.2 years. Most patients only presented with a single stricture (58.7%). Regarding the type of stricture, 72.6% of patients suffered from de novo and 21.3% from anastomotic strictures, while 6.1% of patients presented with both, de novo and anastomotic strictures. Dilated strictures were short with a median length of 1 cm (interquartile range [IQR] 1-2 cm); and nearly all dilated strictures were shorter than 5 cm (99.6%). Half of the patients were treated by a single dilation procedure (49.1%), while in 50.9% of patients multiple dilations were performed. In 57.1% of procedures, a graded dilation was performed, and the median of the maximum caliber of dilation was 18 mm (IQR 15-18 mm). The median follow-up time was 25.5 months (IQR 6-53 months).

Scope passing after dilation (%)	Short-term clinical efficacy (%)	Major complications per patient (%)	Follow-up time (mo)	Recurrence of symptoms during follow-up (%)	Re-dilation during follow-up (%)	Surgery during follow-up (%)
n.a.	n.a.	n.a.	14.5	60.8	60.8	48
n.a.	72.7	9.1	20.5	22.2	22.2	9.1
n.a.	41.7	8.3	71	100	75	25
100	n.a.	0	11.9	26.1	17.1	8.7
100	80	20	16	40	40	30
90.5	n.a.	4.8	n.a.	n.a.	21	26.3

Scope passing after dilation (%)	Short-term clinical efficacy (%)	Major complications per patient (%)	Follow-up time (mo)	Recurrence of symptoms during follow-up (%)	Re-dilation during follow-up (%)	Surgery during follow-up (%)
72	72	8	11.4	22.2	22.2	28
73.8	80	4.6	40.3	36.5	50	26.2
87.5	87.5	12.5	18	14.3	14.3	12.5
n.a.	n.a.	0	n.a.	n.a.	n.a.	n.a.
n.a.	94	n.a.	12	71	47.1	24
75	n.a.	n.a.	n.a.	n.a.	66.6	n.a.
n.a.	n.a.	8.1	27.1	n.a.	n.a.	48.6
96	100	0	16	31	12.5	18.8
n.a.	n.a.	1.6	9.5	n.a.	46.1	n.a.
80	60	0	10	n.a.	50	40
n.a.	n.a.	5.9	41.9	n.a.	75.3	24.7
n.a.	n.a.	n.a.	52	60.8	60.8	48
90.6 (78.5, 96.2)	82.3 (68.1, 91)	5.3 (3.5, 8.1)	20.5 (13, 28)	48.3 (33.2, 63.7)	38.8 (27, 52)	27.4 (21.9, 33.8)

In this pooled individual patient analysis, the technical success rate was 86.1%. 53% of patients reported a clinical relief of their obstructive symptoms. However, in 58.2% of these patients, symptoms re-occurred within a median follow-up time of 8 months (IQR 4-15 months). Eventually, 51.6% of patients required a re-dilation with a median time of 6 months (IQR 0.95-10 months) and 32.1% of patients (IQR 1.2%-28.9%) underwent surgery within a median time of 4.5 months (1.2-28 months; Tables 2 and 3). The overall outcome rates including symptom recurrence, need for re-dilation, surgery, and re-intervention (surgery or re-dilation) at 3, 6, 12, and 24 months are depicted in Table 4 and Figure 2A-D.

3.3 | Factors associated with short-term clinical efficacy after endoscopic balloon dilation

Several risk factors were linked with short-term clinical efficacy after performed EBD (Table S2; Table 5). In the univariable analysis, graded dilation (OR 2.1, 95% CI 1.1-3.8, $P=0.021$), de-novo strictures (OR 0.2, 95% CI 0.1-0.4, $P<0.001$), endoscopic active disease in the jejunum/proximal ileum (OR 0.30, 95% CI 0.15-0.61, $P<0.001$), Asian race (OR 0.06, 95% CI 0.02-0.15, $P<0.001$), body mass index (OR 1.2, 95% CI 1.1-1.3, $P<0.001$), smoking (OR 3.6, 95% CI 1.5-8.8, $P=0.005$), age at time of first stricture diagnosis (OR 1.3, 95% CI 1.1-1.4, $P<0.001$), age at first dilation (OR 1.3, 95% CI 1.1-1.4, $P<0.001$), active ileocaecal disease (OR 2.5, 95% CI 1.1-5.5, $P=0.028$), medication at dilation with aminosaliclates (OR 0.38, 95% CI 0.21-0.69, $P=0.002$), anti-metabolites (OR 3.8, 95% CI 1.5-9.6, $P=0.005$) or steroids (OR 6.6, 95% CI 2.1-20.8, $P=0.001$) were associated with clinical efficacy. In the multivariable analysis, only a few factors of these were found to be linked with clinical efficacy: graded dilation was positively associated (OR 2.0, 95% CI 1.04-3.9, $P=0.039$), while de-novo strictures (OR 0.4, 95% CI 0.17-0.9, $P=0.027$), endoscopically active disease in the jejunum/proximal ileum (OR 0.32, 95% CI 0.14-0.73, $P=0.007$) and Asian race (OR 0.1, 95% CI 0.04-0.3, $P<0.001$) were negatively associated with clinical efficacy (Table S2; Table 5). Additionally, factors associated with symptom

recurrence after EBD were assessed (Table S3; Table 5); for more details see Supplementary Material.

3.4 | Factors associated with risk of re-dilation after endoscopic balloon dilation

Furthermore, potential risk factors for the need for re-dilation were evaluated (Table S4; Table 5). The factors linked to the risk for re-dilation in the univariable analysis were active disease of the colon (HR 0.55, 95% CI 0.11-0.96, $P = 0.034$), body mass index (HR 0.96, 95% CI 0.94-0.97, $P < 0.001$), Asian race (HR 1.5, 95% CI 1.1-1.9, $P = 0.008$), smoking (HR 0.64, 95% CI 0.42-0.99, $P = 0.044$), active disease in the jejunum/proximal ileum (HR 1.3, 95% CI 1.04-1.6, $P = 0.019$), stricture location in the jejunum (HR 0.72, 95% CI 0.57-0.9, $P = 0.004$) and additional stricture location in the colon (HR 0.69, 95% CI 0.55-0.87, $P = 0.002$), associated fistula or abscesses (HR 0.29, 95% CI 0.1-0.79, $P = 0.015$), pre-stenotic dilation (HR 0.59, 95% CI 0.37-0.96, $P = 0.034$), medication at dilation with aminosaliclates (HR 1.3, 95% CI 1.06-1.6, $P = 0.014$), steroids (HR 0.69, 95% CI 0.63-0.76, $P < 0.001$) or anti-tumour necrosis factor-alpha blockers (HR 0.77, 95% CI 0.71-0.85, $P < 0.001$), abnormal mucosa at time of dilation (HR 0.66, 95% CI 0.57-0.76, $P < 0.001$) and applied stents after EBD (HR 0.62, 95% CI 0.47-0.82, $P < 0.001$). Of these, only a few factors were significantly associated in the multivariable analysis: active disease of the colon (HR 0.6, 95% CI 0.41-0.88, $P = 0.01$) and a higher body mass index (HR 0.97, 95% CI 0.93-1.00, $P = 0.041$) were protective factors, associated with a decreased risk for re-dilation (Table S4; Table 5).

3.5 | Factors associated with the need for surgery after endoscopic balloon dilation

Next, we analysed factors to be associated with the need for surgery after EBD (Table S5; Table 5). In the univariable analysis following factors were found to be significant: pre-stenotic dilation (HR 1.7, 95% CI 1.2-2.4, $P = 0.003$), active disease location in the jejunum/proximal ileum (HR 1.7, 95% CI 1.2-2.3, $P = 0.002$), active disease location in the colon (HR 1.6, 95% CI 0.97-2.6, $P = 0.063$), Asian race (HR 1.7, 95% CI 1.3-2.1, $P < 0.001$), proton-pump-inhibitor therapy (HR 0.58, 95% CI 0.47-0.71, $P < 0.001$), female gender (HR 1.2, 95% CI 1.01-1.3, $P = 0.038$), smoking (HR 0.69, 95% CI 0.51-0.93, $P = 0.014$), de-novo strictures (HR 2.0, 95% CI 1.5-2.7, $P < 0.001$), medication at dilation with steroids (HR 0.68, 95% CI 0.55-0.83, $P < 0.001$), abnormal mucosa at time of dilation (HR 1.7, 95% CI 1.2-2.5, $P = 0.003$), maximum caliber of dilation (HR 0.85, 95% CI 0.74-0.98, $P = 0.025$) and the use of stents after dilation (HR 0.67, 95% CI 0.54-0.83, $P < 0.001$). Of these, only a few factors were significantly associated in the multivariable analysis: pre-stenotic dilation (HR 1.7, 95% CI 1.07-2.71, $P = 0.026$), active disease location in the jejunum/proximal ileum (HR 1.85, 95% CI 1.09-3.13, $P = 0.022$), active disease location in the colon (HR 1.77, 95% CI 1.34-2.34, $P < 0.001$) and Asian race (HR 2.13, 95% CI 1.6-2.84, $P < 0.001$) were associated with an increased risk for surgery during follow-up, while proton-pump-inhibitor therapy at the time of dilation was associated with a reduced risk for surgery (HR 0.58, 95% CI 0.48-0.7, $P < 0.001$; Table S5; Table 5).

3.6 | Factors associated with the need for re-intervention (re-dilation or surgery) after endoscopic balloon dilation

Finally, potential risk factors associated with the need for re-intervention (re-dilation or surgery) after EBD were analysed (Table S6; Table 5). Factors linked to the risk for re-intervention in the univariable analysis were smoking (HR 0.75; 95% CI 0.68-0.81, $P < 0.001$), age at time of first stricture diagnosis (HR/decade 0.97; 95% CI 0.96-0.98, $P < 0.001$), age at first dilation (HR/decade 0.97; 95% CI 0.96-0.97, $P < 0.001$), active disease in the jejunum/proximal ileum (HR 1.4; 95% CI 1.1-1.8, $P = 0.005$), de-novo stricture (HR 1.2; 95% CI 1.09-1.3, $P < 0.001$), length of stricture (HR 1.3; 95% CI 1.03-1.6, $P = 0.025$), medication with steroids at dilation (HR 0.92; 95% CI 0.87-0.98, $P = 0.015$) and medication with anti-tumour necrosis factor-alpha blockers at dilation (HR 0.73; 95% CI 0.58-0.93, $P = 0.010$). Of these, only two factors were significantly associated in the multivariable analysis: active disease in the jejunum/proximal ileum increased the risk of intervention after EBD (HR 1.29; 95% CI 1.03-1.60, $P = 0.026$) and medication with anti-tumour necrosis factor-alpha blockers at dilation reduced the risk of re-intervention (HR 0.78; 95% CI 0.63-0.96, $P = 0.019$; Table S6; Table 5).

3.7 | Complication rates following endoscopic balloon dilation

Regarding the safety of EBD performed via BAE, the occurrence of major complications after EBD including bleeding, perforation or dilation-related-surgery was assessed. Major complications occurred in 1.82% per performed EBD procedure, corresponding to an overall complication rate of 3.21% in the per-patient-based analysis (Table 6). Risk factors following EBD via BAE were not assessable due to the limited number of patients.

4 | DISCUSSION

We provide the results from a pooled per-study analysis including 1189 dilation procedures through BAE for small bowel CD strictures. Additionally, we present the largest available investigation of individual-level data from 218 patients with 384 performed EBD to identify predictive risk factors of beneficial short- and long-term outcomes.

In the per-study analysis, we found a high technical success rate (94.9%) which resulted in a short-term clinical efficacy in the vast majority of patients (82.3%). During follow-up, 48.3% of patients suffered from recurrent obstructive symptoms, 38.8% needed repetitive stricture dilation and 27.4% proceeded to surgery, while acceptable complication rates were observed. The high pooled technical success rate emphasises that EBD is highly successful, when performed in trained hands. In most studies, technical success was defined as the ability to pass the stricture after performed EBD^{20,24,25,27,29,32,35}; however, not all studies provided an unequivocal definition for technical success.^{21,26,28,30,31,33,34,36,37} This finding is in line with results from earlier meta-analyses on EBD for ileocecal and gastroduodenal strictures, in which technical success rates of 90 and 100%, respectively, were reported.^{11,13} Following EBD, nearly 80% of patients experienced relief of obstructive symptoms, which we classified as short-term clinical efficacy. Noteworthy, included studies applied slightly different definitions including “complete disappearance”²²⁻²⁴ as well as “improvement”^{26,27,29,33-35} of obstructive symptoms after performed EBD. Again, as

compared to gastroduodenal and ileocecal CD strictures (87% and 80.8%), using similar definitions, short-term clinical success rates obtained through BAE were comparable.^{11,13} With regard to long-term clinical efficacy, 48% of those patients with short-term clinical efficacy developed recurrent symptoms, while 27.4% of patients eventually required surgery during two years of follow-up. These results are also comparable to the long-term efficacy of EBD for ileocecal and gastroduodenal strictures (47.5% and 70.5%; surgery: 28.6% and 30.8%).^{11,13} We observed higher complication rates following BAE EBD as compared to EBD for ileocecal and gastroduodenal strictures (5.3% vs 2.8% and 2.9%).^{11,13} This finding may be partly related to the generally more invasive and more challenging procedure of a BAE as compared to endoscopy using a conventional gastroscope or colonoscope. Nevertheless, this higher complication rate highlights the necessity to closely monitor patients after EBD using BAE and have this procedure performed in high-volume centres and by trained endoscopists. Noteworthy, stricture and dilation characteristics slightly differed in our pooled individual patient analysis compared to our pooled per-study analysis. It is conceivable that higher volume centres performed endoscopic balloon dilations in a slightly different manner and in slightly different patient cohorts; however, we can only speculate about this.

Identification of predictive factors for the long-term success of EBD could help clinical decision-making and facilitate an individualised treatment approach of patients with stricturing CD. Our per-patient analysis found that patients with inflammatory disease activity on endoscopy were at a higher risk for an unfavourable outcome accompanied by a lower short-term clinical efficacy, a higher risk to undergo surgery, and a higher risk to have a re-intervention (surgery or re-dilation). Likewise, the application of anti-inflammatory drugs (anti-tumour necrosis factor- α blockers) lowered the risk of re-intervention (surgery or re-dilation). CD patients with predominantly fibrotic strictures and the absence of inflammatory disease activity elsewhere in the gastrointestinal tract had the best prognosis regarding the long-term efficacy of EBD through BAE.

In addition, we identified prestenotic dilation in imaging reports as a significant risk factor to proceed to surgery following EBD. Independent of this, prestenotic dilation is routinely evaluated in imaging and one of the most important criteria for small bowel CD stricture diagnosis.³⁸ While prestenotic dilation on its own may not result in worse dilation outcome, it may trigger the surgeon to perform surgery assuming a more advanced stage of stricture. Interestingly, CD patients with an Asian origin had a lower short-term clinical efficacy rate, a lower risk of symptom recurrence and an increased risk of surgery after EBD using BAE. These findings may be partly explained by different local disease phenotypes, varying strategies for the usage of EBD and different management for proceeding to surgery in varying geographical regions. Noteworthy, in a previous meta-analysis on EBD of gastroduodenal CD strictures, Asian race was likewise identified as a risk factor for surgery during follow-up.¹¹ Furthermore, PPI therapy was found to slightly reduce the risk for surgery after EBD. Because PPI therapy is part of the medical therapy for gastroduodenal Crohn's disease, we included PPI therapy as one possible outcome-relevant factor in our analysis. Although PPI, indeed, slightly reduced the risk for surgery after EBD, based on our data, we cannot provide a causal explanation for this finding.

Concerning the technical performance of EBD, we identified several factors that impacted the outcome. A graded dilation was on the one hand associated with a higher clinical short-term efficacy, but on the other hand linked to 60% higher risk of symptom recurrence after EBD. In most procedures (57.1%) a graded dilation was performed which confirms previous results from a survey study, in which 126 endoscopists indicated that over 90% of investigators preferred graded- over one-sized balloons for dilation.¹⁷ If a graded dilation is also associated with lower complication rates is currently unclear: in our study complications were observed in 3.2% of patients after graded dilations and in 0.7% after one-step dilations; however, these complication rates did not differ significantly ($P=0.246$), likely due to the overall low event rate. In addition, balloon size was slightly lower in graded dilation compared to one-step dilations (15.8 mm vs 17.2 mm; $P<0.001$). Future prospective studies need to address whether a graded or one-step dilation approach is rational in terms of efficacy and safety.

Stricture length is an important factor for the outcome of EBD. In our previous meta-analysis on ileocecal strictures, the main long-term predictor of successful EBD was a stricture length of ≤ 5 cm.^{13,19} Our current analysis on EBD using BAE was limited as only one patient was treated endoscopically for a stricture longer than 5 cm. All other patients suffered from strictures of ≤ 5 cm, with a median length of 1 cm. Therefore, we hypothesise that also for EBD of small bowel strictures using EBD the most probable standard of care is to dilate stricture with a length of ≤ 5 cm.^{19,39}

There is an ongoing debate on the efficacy of EBD for de novo vs *anastomotic* CD strictures. In our study, we report that EBD of de novo strictures was associated with a lower short-term clinical efficacy. Concerning the long-term outcomes including the frequency of symptom recurrence, re-dilation, and surgery there was no difference identified in the multivariable analysis; similarly to the results from ileocecal strictures.¹³ A recent survey amongst inflammatory bowel disease experts reports that endoscopists prefer to dilate anastomotic over de novo strictures.¹⁷ Considering our results, this perception might partly be supported by our data that at least short-term clinical efficacy of EBD in *anastomotic* strictures is more successful.

Concerning the risk of re-dilation, we identified that patients with a higher body mass index had a lower risk of re-dilation. This finding is in line with published studies demonstrating a strong impact of the body mass index and therapeutic outcomes in CD patients.⁴⁰ For stricturing CD, it might be speculated that an advanced stricture might cause particularly severe obstructive symptoms leading to weight loss and that advanced strictures might need repetitive dilation therapies. Furthermore, patients with an active, extensive disease phenotype including active colonic disease received less frequently re-dilations of their stricture during the follow-up period. This observation might be owed to the fact that endoscopists less frequently preferred to perform re-dilations in patients with an active disease phenotype and that these should be primarily treated with anti-inflammatory drugs.^{38,39}

Our study has several limitations. First, we collected data from multiple studies which applied heterogeneous definitions for outcomes including technical success, short-term

success, long-term success and complications and furthermore, not all studies assessed each of these outcomes. Especially the outcome “symptom recurrence” was the least firm one given the heterogeneity in reporting why we preferred to present this outcome only in the supplementals. Second, we cannot exclude publication or reporting bias: for example, patients in whom a dilation therapy could not be technically performed may have been under-represented in available studies and although in most patients EBD was performed because of a symptomatic stricture, few EBDs might have been performed in asymptomatic patients. Third, the evaluation of clinical efficacy and long-term outcome was not measured at a specified time-point. Fourth, our analysis has all potential biases of retrospective cohort studies; however, according to the Amstar-Checklist to assess the methodological quality of systematic reviews, our work is a *high quality review*.⁴¹ Fifth, while our study is not a classical meta-analysis, the employed approach of a pooled-analysis was successfully performed in similar clinical conditions.^{13,42} Additionally, reporting bias might have been occurred due to this pooled analysis of already published literature.

Taken together, this large multicentre study demonstrates that EBD of CD-associated small bowel strictures using BAE achieves high short-term technical and clinical efficacy rates. Considering the acceptable complication rate, EBD of small bowel strictures using BAE is a valuable adjunct and alternative to surgery in selected patients; however, up to two-thirds of patients might need re-dilation or surgery in the mid-term.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX 1

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FIGURE 1.

Principle of endoscopic balloon dilation of small bowel Crohn's disease strictures by balloon-assisted enteroscopy. (A) The balloon-assisted enteroscope can be inserted via oral or anal pathway to reach the site of the bowel stricture. (B) After identification of the small bowel stricture, a through-the-scope balloon can be used to dilate the stricture

FIGURE 2.

Risk for symptomatic recurrence, re-dilation, surgery or re-intervention (surgery or re-dilation) following endoscopic balloon dilation (EBD) of Crohn's disease-associated small bowel strictures through balloon-assisted enteroscopy over time. (A) The recurrence of symptoms was observed in 24.8% and 46.8% of patients within 6 and 12 months after EBD, respectively. (B) Endoscopic re-dilation was performed in 31.2% and 45.7% of patients within 6 and 12 months, respectively, while (C) surgery was needed in 19.3% and 22% of patients within 6 and 12 months after EBD, respectively. (D) Re-intervention including endoscopic re-dilation or surgery was needed in 43.0% and 54.8% of patients within 6 and 12 months, respectively

TABLE 1

Pooled per-study analysis of available studies including Crohn's disease patients with small bowel strictures in whom a balloon-assisted enteroscopy and endoscopic balloon dilation was performed

Author, year (Ref. No)	CD patients with small bowel strictures (no)	Strictures (no)	Anastomotic stricture (%)	Dilations (no)	Mode of enteroscopy (SBE vs DBE)	Mean calibre of dilation (mm)	Technical success(%)
Deepak, 2016 ³⁷	23	69	n.a.	69 ^a	n.a.	n.a.	n.a.
Despott, 2009 ²⁶	11	18	n.a.	18	DBE	15.4	81.8
Ding, 2015 ³⁴	12	12	n.a.	22	DBE	n.a.	100
Fukumoto, 2007 ²⁵	23	23	n.a.	35	DBE	n.a.	100
Gill, 2014 ²⁷	10	10 ^a	0	18	DBE	13.3	100
Halloran, 2013 ²⁰	21	77	14.3	77 ^a	DBE	12	90.5
Hirai, 2010 ²²	25	48	12	55	DBE	n.a.	72
Hirai, 2014 ²³	65	105 ^a	15.3	105 ^a	DBE	n.a.	80
Kim, 2016 ³⁵	8	30	n.a.	30	SBE	15	87.5
Milewski, 2013 ³⁰	8	8 ^a	n.a.	8 ^a	DBE	n.a.	n.a.
Morishima, 2009 ³¹	17	32	52.9	35	DBE	n.a.	94
Navaneethan, 2014 ³²	8	8	n.a.	10	DBE	n.a.	75
Nishida, 2017 ²¹	37	59	16.2	72	DBE	n.a.	n.a.
Ohmiya, 2009 ²⁴	16	16 ^a	n.a.	18	DBE	n.a.	96
Ohtsuka, 2016 ³⁶	60	91	0	91	SBE	n.a.	100
Pohl, 2007 ²⁹	10	13	0	15	n.a.	17	80
Sunada, 2016 ²⁸	85	201	4	473	DBE	12.4	n.a.
Yamada, 2012 ³³	27	35	54.3	35	DBE	n.a.	n.a.
Overall	463	837	16 (4.8, 41.8)	1189		14.7 (13.3, 16.1)	94.9 (86.7, 98.1)

Note: Overall estimates are obtained using DerSimonian-Laird random effect model meta-analysis; pooled variables are presented with 95%-confidence interval.

Abbreviations: CD, Crohn's disease; DBE, double balloon enteroscopy; mm, millimeter; n.a., not available; No, number; Ref, reference; SBE, single balloon enteroscopy.

^aIn few studies numbers were not provided for each of the following categories: number of strictures, percentage of single-strictures, and number of dilations. For data pooling of these categories, missing data were precisely calculated or assumed based upon the minimum number of strictures/dilations matching to the number of study patients.

TABLE 2

Patient characteristics of pooled individual patient data

Factor	Total (N = 218)	
	N	Statistics
Female gender	218	59 (27.1)
Race/ethnicity	218	
Caucasian		41 (18.8)
African-American		1 (0.46)
Asian		176 (80.7)
Body mass index (kg/m ²)	195	20.2 [18.6, 23.4]
Family history of Crohn's disease	200	6 (3.0)
Smoking	198	
Never		164 (82.8)
Current		18 (9.1)
Former		16 (8.1)
Age of CD diagnosis (y)	205	27.4 ± 11.5
Age at time of first stricture diagnosis (y)	167	40.6 ± 14.2
Age at first dilation (y)	167	40.8 ± 14.2
Disease location: upper gastrointestinal tract	218	4 (1.8)
Disease location: jejunum/proximal ileum	218	51 (23.4)
Disease location: ileocaecal	218	182 (83.5)
Disease location: colon	218	43 (19.7)
Disease location: rectum	218	2 (0.92)
Extraintestinal CD manifestation—any	218	9 (4.1)
Number of strictures	189	
1		111 (58.7)
2		43 (22.8)
3		18 (9.5)
4+		17 (9.0)
<i>Patient outcomes</i>		
Follow-up (mo)	218	25.5 [6.0, 53.0]

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Total (N = 218)		
Factor	N	Statistics
Number of redilations	218	
0		107 (49.1)
1		56 (25.7)
2		24 (11.0)
3		9 (4.1)
4		4 (1.8)
5+		18 (8.3)
Stricture surgery	218	70 (32.1)
Months to surgery	70	4.5 [1.2, 28.0]
Surgery or re-dilation ^a	215	144 (67.9)
Months to surgery or re-dilation	144	4.0 [0.60,10.5]

Note: Continuous variables are presented as mean with standard deviation or median with interquartile ranges [P25, P75]. Frequencies and percentages are reported for categorical variables.

Abbreviation: N, number.

^aExcludes three patients with a re-dilation of unknown timing and no surgery.

TABLE 3

Stricture and dilation characteristics of pooled individual patient data

Factor	Total (N = 384)	
	N	Statistics
Stricture		
Stricture location: duodenum	380	1 (0.26)
Stricture location: jejunum	380	24 (6.3)
Stricture location: ileum	380	342 (90.0)
Stricture location: colon	380	33 (8.7)
Type of stricture	380	
Anastomotic		81 (21.3)
de novo stricture		276 (72.6)
Both		23 (6.1)
Length of stricture (cm)	246	1.00 [1.0, 2.0]
Length of stricture	259	
Less than or equal to 5 cm.		258 (99.6)
Over 5 cm.		1 (0.39)
Associated fistula or abscess	380	13 (3.4)
Prestenotic dilation	380	71 (18.7)
Medication at dilation: PPI	379	38 (10.0)
Medication at dilation: aminosaliclates	379	213 (56.2)
Medication at dilation: steroids	379	40 (10.6)
Medication at dilation: anti-tumour necrosis factor-alpha Blockers	379	161 (42.5)
Medication at dilation: anti-Metabolites	379	55 (14.5)
Medication at dilation: methotrexate	379	8 (2.1)
Medication at dilation: no therapy	379	58 (15.3)
Dilation		
Graded dilation	329	188 (57.1)
Abnormal mucosa at time of dilation	369	83 (22.5)
Maximum calibre of dilation (mm)	307	18.0 [15.0, 18.0]
Length of balloon (cm)	231	5.5 [5.5, 5.5]

Factor	Total (N = 384)	
	N	Statistics
Time of inflation (min)	202	1.00 [1.00, 2.0]
Pressure of dilation (psi)	214	44.0 [44.0, 65.0]
Steroid injection post dilation	366	6 (1.6)
Cutting techniques used	367	2 (0.54)
Stent used	367	10 (2.7)
Outcomes of dilation		
Technical success	375	323 (86.1)
Scope passing after dilation	365	267 (73.2)
Clinical efficacy	372	197 (53.0)
Major complications	380	7 (1.8)
Re-dilation	380	196 (51.6)
Months to re-dilation	196	6.0 [0.95, 10.0]
If clinical efficacy, symptom recurrence	170	99 (58.2)
Months to symptom recurrence	99	8.0 [4.0, 15.0]

Note: Continuous variables are presented as mean with standard deviation or median with interquartile ranges [P25, P75]. Frequencies and percentages are reported for categorical variables.

Abbreviation: N, number.

TABLE 4

Post-dilation event rates in the pooled individual patient data analysis

Outcome	Post-dilation follow-up (mo)	Cumulative rate (95% CI)
Surgery	3	14.0 (18.4, 9.2)
	6	19.3 (24.4, 13.9)
	12	22.0 (27.4, 16.2)
	24	24.9 (30.6, 18.7)
Re-dilation	3	20.3 (24.4, 16.0)
	6	31.2 (36.4, 25.7)
	12	45.7 (51.3, 39.5)
	24	55.4 (60.6, 49.7)
Symptom recurrence	3	13.7 (18.9, 8.3)
	6	24.8 (31.3, 17.7)
	12	46.8 (54.8, 37.3)
	24	67.2 (75.0, 57.0)
Surgery or re-dilation	3	30.6 (36.3, 24.5)
	6	43.0 (49.1, 36.2)
	12	54.8 (61.1, 47.6)
	24	65.5 (71.6, 58.0)

Note: Values are presented as the cumulative rate (95% confidence interval [CI]).

TABLE 5

Factors significantly associated with outcomes (short-term clinical efficacy, symptom recurrence, re-dilation, surgery, and re-intervention [re-dilation or surgery]) after endoscopic balloon dilation of small bowel Crohn's disease strictures as identified by both, uni- and multivariable cox regression analysis

Outcome	Factor	OR (95% CI)	HR (95% CI)	P value
Short-term clinical efficacy	Asian race	0.10 (0.04, 0.30)	-	<0.001
	Disease location: jejunum/proximal ileum	0.32 (0.14, 0.73)	-	0.007
	De novo stricture	0.40 (0.17, 0.90)	-	0.027
	Graded dilation	2.0 (1.04, 3.9)	-	0.039
Symptom recurrence	Asian race	-	0.36 (0.24, 0.54)	<0.001
	Graded dilation	-	1.65 (1.10, 2.46)	0.015
Re-dilation	Body mass index (kg/m ²)	-	0.97 (0.93, 1.00)	0.041
	Disease location: colon	-	0.60 (0.41, 0.88)	0.010
Surgery	Asian race	-	2.13 (1.60, 2.84)	<0.001
	Disease location: jejunum/proximal ileum	-	1.85 (1.09, 3.13)	0.022
	Disease location: colon	-	1.77 (1.34, 2.34)	<0.001
	Prestenotic dilation	-	1.70 (1.07, 2.71)	0.026
	Medication at dilation: PPI	-	0.58 (0.48, 0.70)	<0.001
	Disease location (jejunum/proximal ileum)	-	1.29 (1.03, 1.60)	0.026
Re-dilation or surgery	Medication at dilation: anti-TNF	-	0.78 (0.63, 0.96)	0.019

Note: Here, only results of the multivariable cox regression analysis are depicted, for complete uni- and multivariable analyses, please see the supplemental's section.

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio.

TABLE 6

Complication rates following endoscopic balloon dilation of small bowel strictures in Crohn's disease patients in the individual patient data analysis

Factor	%
Complication rate (per dilation)	1.82
Complication rate (per patient)	3.21

Note: Frequencies and percentages are reported for categorical variables.