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A comparison of balloon- versus stent-based approach for dominant strictures in primary sclerosing cholangitis: a meta-analysis

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Abstract

Background Approximately 10-62% of patients with primary sclerosing cholangitis (PSC) will develop dominant strictures at some point during their disease. Because of the paucity of available data, optimal endoscopic therapeutic strategies remain unclear. We performed a systematic review and meta-analysis of endoscopic balloon dilation vs. balloon dilation plus stenting of dominant strictures in PSC.

Methods A comprehensive literature search from inception to November 2020 was performed. Primary outcomes were clinical and technical success. Secondary outcomes reported were adverse events (AE). Clinical success was defined in most studies as improvement in symptoms such as fever, abdominal pain, pruritus, fatigue and/or liver enzymes. The statistical analysis was done using comprehensive meta-analysis (CMA Version 3).

Results The technical success rates for balloon and balloon plus stent were 96.8% and 91.9%, respectively. The clinical success rates for balloon and balloon plus stent were 86.5% and 70.8%, respectively. The overall AE rates for balloon and balloon plus stent were 11.2% and 26.9%, respectively. Other AE rates in balloon and balloon plus stent were cholangitis (4.8% vs. 11.4%), bile duct perforation (1.3% vs. 1.6%), post-procedural pancreatitis (2.2% vs. 9.8%), and bleeding (1.5% vs. 1.2%), respectively. Low to considerable heterogeneity was noted in our meta-analysis.

Conclusions Balloon dilation appears to be superior in terms of clinical and technical successes, with overall lower rates of AE compared to balloon dilation plus stenting for the management of PSC dominant strictures. Further trials are needed to validate our findings.

Keywords Balloon dilation, stenting, endoscopy, dominant strictures, primary sclerosing cholangitis

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease that leads to biliary cirrhosis and portal hypertension by causing obstruction of intra- and/or extrahepatic bile ducts by inflammation and fibrosis [1,2]. From 5-15% of patients with PSC have a lifetime risk of developing cholangiocarcinoma (CCA), with the annual incidence being 0.6-1.5% [3,4]. Magnetic resonance cholangiopancreatography is currently the modality of choice, given the invasive nature and increased risk of adverse events (AE) with endoscopic retrograde cholangiopancreatography (ERCP) [5].

The most common reason for endoscopic intervention in patients with PSC is dominant strictures, found in 15-20% of patients [6,7]. Anatomically, dominant strictures are defined as: 1) strictures of the common bile duct measuring <1.5 mm in diameter; or 2) strictures of the hepatic ducts with a diameter <1.0 mm within 2 cm of the bifurcation [8,9]. As the disease progresses, patients can have evidence of mechanical biliary obstruction, manifested by jaundice, pruritus,

ascending cholangitis and malabsorption, but biliary strictures are asymptomatic in most cases [10]. Approximately 25% of intrahepatic or extrahepatic duct strictures are malignant at the time of presentation [11]. The presence of a dominant stricture has been associated with a worse long-term prognosis and an increased risk of CCA [12].

ERCP is the endoscopic therapeutic modality of choice for the endoscopic management of dominant strictures. The goal is to relieve the biliary obstruction and rule out malignancy, specifically CCA. This has been associated with improved transplant-free survival and a reduced risk of CCA in patients with PSC [13,14]. A percutaneous approach is associated with high morbidity and mortality and is reserved for symptomatic patients who have failed an endoscopic approach [15]. Multiple interventions can be performed for these strictures, such as balloon dilation, balloon dilatation with stent placement, nasobiliary catheter perfusion, or injection of mitomycin C [16]. According to the recent guidelines of the American Association for the Study of Liver Diseases, endoscopic biliary stricture dilation is the initial procedure of choice for the management of dominant strictures [17]. Bile duct stenting is often reserved for cases where balloon dilation alone appears to be inadequate [10].

Balloon dilation with or without bile duct stenting for the management of dominant strictures in PSC both has certain limitations. Balloon dilatation can lead to early restenosis requiring multiple ERCPs, while with bile duct stenting there is an increased risk of stent occlusion leading to cholangitis [18]. Optimal endoscopic therapeutic strategies remain unclear because of the paucity of available data. Currently, there is no published meta-analysis of the endoscopic management of dominant strictures. This is a comprehensive meta-analysis to compare endoscopic balloon dilation vs. endoscopic balloon dilation plus stenting for management of dominant strictures in PSC.

Materials and methods

Search strategy

We performed a comprehensive review of studies published through November 2020 that reported clinical outcomes of endoscopic balloon dilation with stenting vs. balloon dilation alone for dominant strictures in patients with PSC, according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) Epidemiology guidelines [19,20]. Five databases were searched: PubMed, EMBASE, Web of Science, Google Scholar, and Cochrane. Keywords included but were not limited to: "balloon dilation", "stenting", "endoscopy", "strictures", and "primary sclerosing cholangitis".

Study selection

In this meta-analysis, studies were included that evaluated the clinical outcomes of endoscopic balloon dilation with and without stenting in patients with PSC. Studies were included irrespective of inpatient/outpatient setting and geography if they provided the appropriate data needed for the analysis.

Our exclusion criteria were as follows: 1) Conference abstracts, general reviews, or commentaries; 2) studies with sample size <10; 3) studies done in the pediatric population (age <18 years); and 4) studies not published in the English language. In the case of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained.

Data abstraction and quality assessment

Data on study-related outcomes in the individual studies were abstracted onto a standardized form by at least 3 authors (SM, YN and DR), and 2 authors (SM and DR) did the quality scoring independently. The Jadad-Oxford tool for assessing the risk of bias was used for the randomized clinical trial and the Newcastle-Ottawa scale (NOS) was used for nonrandomized studies [21,22].

Outcomes

Pooled clinical success was defined in most studies as improvement in liver enzymes or symptoms such as fever, abdominal pain, pruritus, and fatigue. Pooled technical success was defined as the successful completion of the endoscopic procedure. Pooled rate of overall AE and significant procedure-related AE subtypes, such as cholangitis, bleeding, perforation, and post-ERCP pancreatitis (PEP), were defined as complications related directly to the procedure.

Statistical analysis

Meta-analysis techniques were used to calculate the pooled estimates in each case, following the methods suggested by DerSimonian and Laird and using a random-effects model [23]. When the incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before statistical analysis. Heterogeneity between study-specific estimates was assessed using the I^2 statistic, where values of <30%, 30-60%, 61-75% and >75% were suggestive of low, moderate, substantial and considerable heterogeneity, respectively [24,25]. Publication bias was ascertained qualitatively, by visual inspection of funnel plot, and quantitatively, by the Egger test [25-27]. Comparison between the 2 treatments was performed using subgroup comparisons by the meta-analysis software. The comparison is based on 2-sided (bivariate) testing and a P-value of <0.05 to define significance between the groups compared. All analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3 (BioStat, Englewood, NJ).

Results

Search results and characteristics

From an initial 671 studies, 10 studies were included in the final analysis, 3 of which directly compared the outcomes of balloon dilation with stenting and balloon dilation alone [8,28-36]. A total of 9 studies reported on the outcomes of balloon dilation alone, and 4 studies reported on the outcomes of balloon dilation with stenting. A schematic diagram showing the study selection process is provided in Fig. 1. These studies were published between 1995 and 2018.

One study was a multicentered design. One study was a randomized controlled trial (RCT), 4 studies were prospective cohorts, and the remaining studies were retrospective cohorts. Six studies were carried out in the USA, 2 in The Netherlands, one in Europe, and 1 in Germany. There were 95 patients in the balloon dilation with stenting group and 361 patients in the balloon dilation only group. Additional study characteristics are described in Table 1.

Quality of studies

A detailed assessment of study quality can be found in Supplementary Table 1. Considerable heterogeneity was identified for clinical and technical success outcomes, moderate-to-considerable heterogeneity was identified for technical success in the balloon plus stent group, significant heterogeneity was identified for overall AE, cholangitis, bleeding, and PEP. Low heterogeneity was noted for bile duct perforation. Publication bias using funnel plots was not performed, as each study arm had less than 10 studies.

Meta-analysis outcomes

The pooled clinical success for balloon dilation was 86.5% (95% confidence interval [CI] 66.6-95.4%; I^2=79.7) compared to 70.8% (95%CI 37.7-90.7%; I^2=79.4%) for balloon plus stent, with P<0.001 for the difference between these 2 groups (Fig. 2). The pooled technical success for balloon dilation was 96.8% (95%CI 92.0-98.7%; I^2=75.9%) compared to 91.9% (95%CI

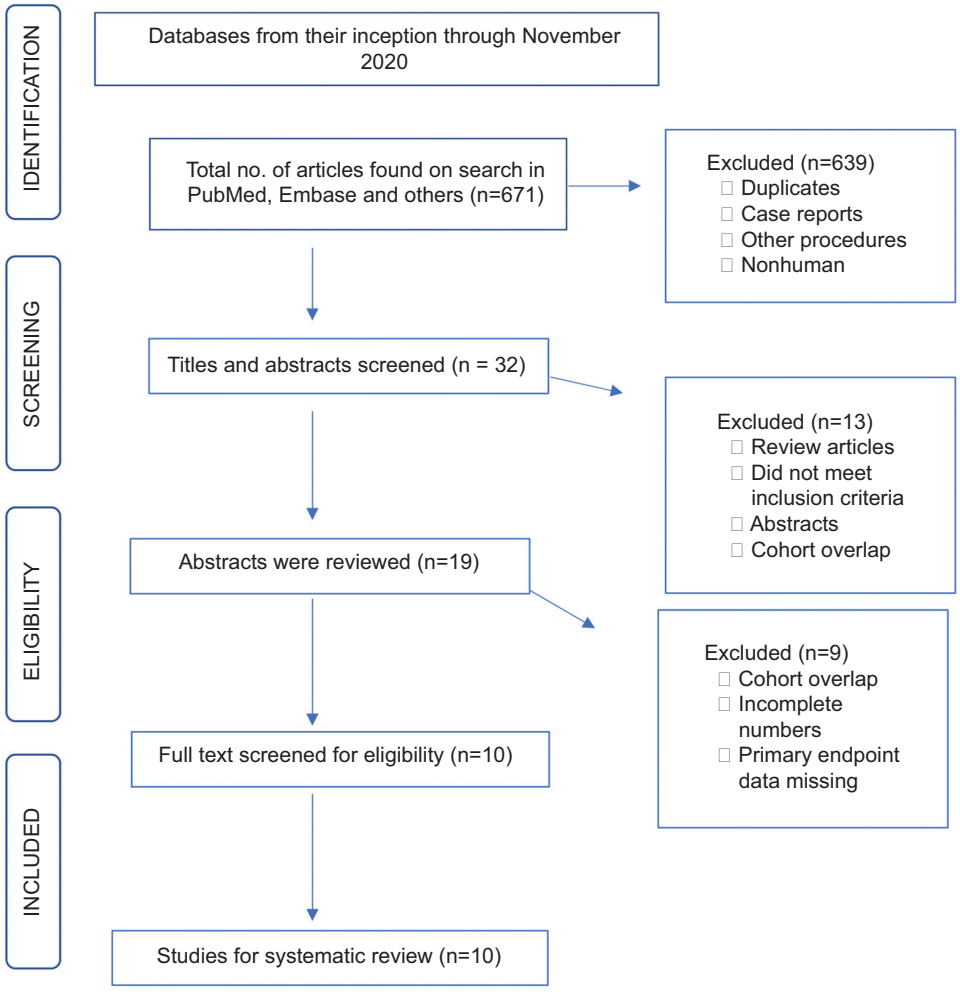

Figure 1 Preferred reporting items for systematic reviews and meta-analysis (PRISMA)

Table 1 Characteristics of the studies

Balloon dilatation plus stenting

Author [ref.]	Year	Type of study	Center	Location	Patients	Male	Female	Age	Clinical success	
Ponsioen [30]	2018	Randomized controlled trial	Multicenter	Europe	34	23	11	40	19/34	
Kaya [29]	2001	Retrospective	Single	USA	14	--	--	--	--	
Wit [8]	1996	Retrospective	Single	The Netherlands	25	12	13	42	21/25	
Lee [36]	1995	Retrospective	Single	USA	22	--	--	--	--	
Author [ref.]	Technical success	No. of ERCP procedures	Overall adverse events	Cholangitis	Perforation	PEP	Bleeding	How many pts received abx?	Post-op duration of abx	Follow up (months)
Ponsioen [30]	34/38	38	15	4	0	8	0	34	24 h	24
Kaya [29]	35/35	80	7	2	2	2	1	--	24 h	22
Wit [8]	21/25	105	15	10	0	4	1	25	24 h	29
Lee [36]	37/38	38	24	14	0	10	0	22	24 h	31

Balloon dilatation alone

Author [ref.]	Year	Type of study	Center	Location	Patients	Male	Female	Age	Clinical success	
Johnson [28]	2006	Retrospective	Single	USA	10	8	2	47	10/10	
Kaya [29]	2001	Retrospective	Single	USA	34	22	12	34	20/34	
Ponsioen [30]	2018	Randomized controlled trial	Multicenter	Europe	31	22	9	40	15/29	
Stiehl [31]	2002	Prospective	Single	The Netherlands	52	--	--	--	29/30	
Wagner [32]	1996	Prospective	Single	Germany	12	6	6	38	8/12	
Ahrendt [33]	1998	Prospective	Single	USA	35	24	11	47	--	
Gluck [34]	2008	Retrospective	Single	USA	59	--	--	48	--	
Gotthardt [35]	2010	Prospective	Single	USA	97	69	28	37	97/97	
Lee [36]	1995	Retrospective	Single	USA	31	--	--	--	31/31	

(Contd...)

Table 1 (*Continued*)

Balloon dilatation alone

Author [ref.]	Technical success	No. of ERCP procedures	Overall adverse events	Cholangitis	Perforation	PEP	Bleeding	How many pts received abx?	Post-op duration of abx	Follow up (months)
Johnson [28]	66/66	68	17	17	0	0	0	10	1 week	--
Kaya [29]	73/73	73	6	1	2	0	2	34	minimum 24 h	24
Ponsioen [30]	29/31	--	2	1	0	1	0	31	24 h	24
Stiehl [31]	--	--	14	4	1	9	0	52	2 days	62.4
Wagner [32]	63/75	75	5	3	0	1	1	12	1 week	23
Ahrendt [33]	112/116	--	5	1	0	4	0	--	--	26
Gluck [34]	160/160	317	23	3	2	12	0	59	--	76
Gotthardt [35]	500/500	NA	19	7	1	11	0	97	--	60
Lee [36]	43/50	175	24	14	0	10	0	31	24 h	31

ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis; abx, antibiotics

81.3-96.8%; I^2=40.24%) for balloon plus stent, with P<0.001 for the difference between these 2 groups (Fig. 3).

The pooled rate of overall AE was 11.2% (95% CI 6.6%-18.4%; I^2=91%) for balloon dilation alone and 26.9% (95%CI 9.6-55.9%; I^2=93%) for balloon plus stent, with P<0.001 for the difference between these groups (Fig. 4). The pooled rate of cholangitis was 4.8% (95%CI 1.4-14.8%; I^2=49%) for balloon dilation alone and 11.4% (95%CI 3.7-16.2%; I^2=93%) for balloon plus stent, with P<0.001 for the difference between these groups (Fig. 5 top). The pooled rate of bile duct perforation was 1.3% (95%CI 0.5-3.7%; I^2=16%) for balloon dilation alone and 1.6% (95%CI 0.6-4.5%; I^2=43%) for balloon plus stent, with P=0.782 for the difference between these groups (Fig. 5 bottom). The pooled rate of post-procedural PEP was 2.2% (95%CI 0.6-7.4%; I^2=81%) for balloon dilation alone and 9.8% (95%CI 3.1-26.8%; I^2=81.7%) for balloon plus stent, with P<0.001 for the difference between these 2 groups (Fig. 6 top). The pooled rate of bleeding was 1.5% (95%CI 0.5-3.8%; I^2=49%) for balloon dilation alone and 1.2% (95%CI 0.04%-3.5%; I^2=43%) for balloon plus stent (Fig. 6 bottom).

Discussion

This meta-analysis demonstrates that, as a treatment modality for dominant strictures in PSC, balloon dilatation alone appears to be superior to balloon dilatation with stenting in terms of clinical and technical success. Recently, Ferreira *et al* published a meta-analysis of endoscopic therapies for dominant strictures in PSC, but reported different outcomes regarding efficacy [37]. Their study found that the balloon-based and stent-based approaches were comparable in efficacy, which was not the case in our meta-analysis. The rates of AE, however, were comparable to our meta-analysis. Two potential reasons for the differences reported by the 2 meta-analyses could be the inclusion of significantly more studies in our meta-analysis (9 vs. 5) as well as the inclusion of only full-text manuscripts in our own study.

Patients with dominant strictures in PSC had superior technical success and clinical success rates with balloon dilatation alone vs. balloon dilatation with stenting, at 96.8% and 86.5% vs. 91.9% and 70.8%, respectively. These data suggest that the clinical success in both groups may be influenced by the technical success, which highlights the importance of achieving a high technical success rate. The inability to dilate dominant strictures with balloon dilators or other dilatation catheters may lead to technical failure [30]. Technical success for biliary stenting may be inferior to dilatation alone, because of the difficulty of placing stiff stents across tight dominant strictures. Dilation balloons may be more likely to produce technical success as a result of their increased flexibility compared to stents and the higher likelihood of completely traversing tight strictures. Long-term clinical success in patients with PSC and dominant strictures is variable and can be difficult to achieve. Among the reasons why these patients may be difficult to

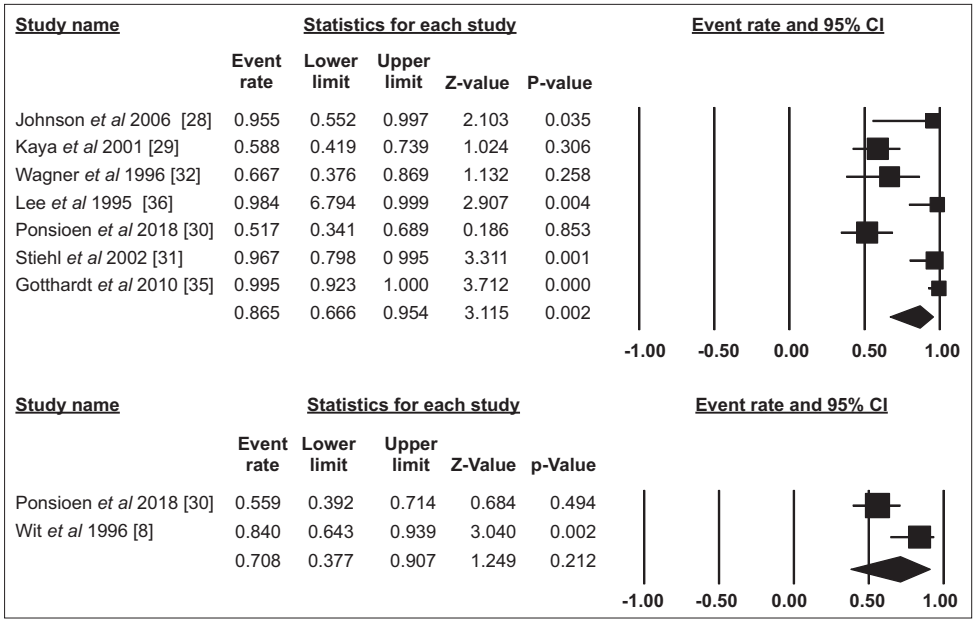

Figure 2 Forest plots for the clinical success of balloon dilation alone (top) and balloon plus stent (bottom)

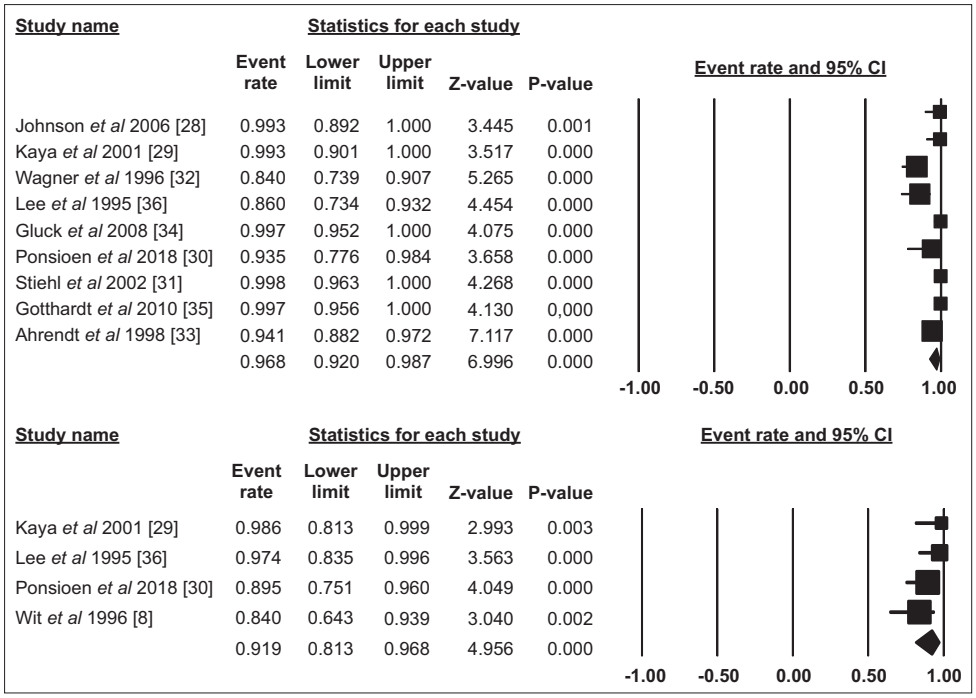

Figure 3 Forest plots for the technical success of balloon dilation alone (top) and balloon plus stent (bottom)

treat may be the variable number of dominant strictures, or having the disease for a longer time [30-32]. These patients often require repeated dilations, consistent with the chronic progressive nature of the disease. In a study by Kaya *et al*, stents were placed in patients in whom balloon dilation was thought by the endoscopist to be insufficient, suggesting a more severe disease that progressed to refractory dominant strictures. The clinical outcome in that study showed that more than 50% of patients still had the same symptoms despite balloon dilation plus stenting. However, in the other balloon plus stent studies, greater clinical success rates were reported with the intervention [8,29,30,32,36].

The overall AE rate was significantly lower in the balloon dilation group compared to the balloon plus stent group, at

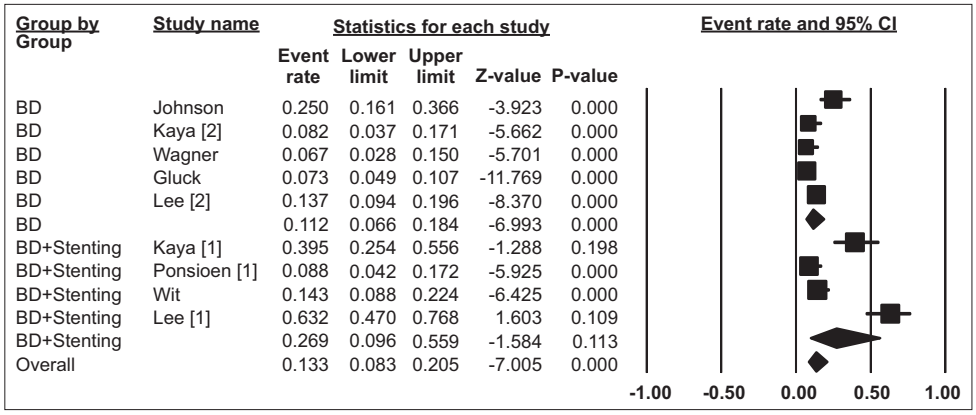

Figure 4 Forest plots for overall adverse events associated with balloon dilation and balloon dilation plus stent

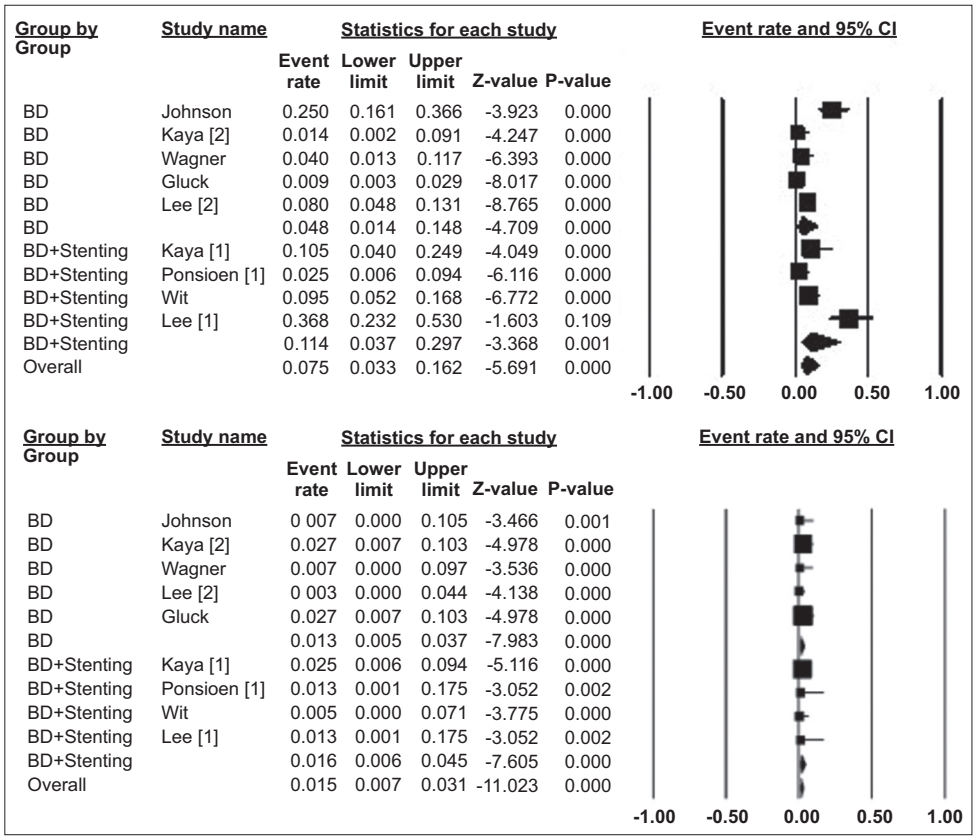

Figure 5 Forest plots for cholangitis in balloon dilation and balloon dilation plus stent (top). Forest plots for biliary perforation in balloon dilation and balloon dilation plus stent (bottom)

11.2% vs. 26.9% (P<0.001). While the AE rate in the balloon dilatation group may have been due to lower rates of bleeding, perforation, and pancreatitis, this difference may also be attributable to the smaller sample size in one of the 2 cohorts in the meta-analysis (95 vs. 361 patients).

The pooled rate of cholangitis in the balloon dilation group was lower than in the balloon plus stent group, at 4.8% vs. 11.4%. This could be attributed to the higher risk of bile duct stent occlusion in the latter group [29,38]. Ponsioen *et al* demonstrated the lowest rates of cholangitis when compared to the other 3 balloon plus stent studies in our meta-analysis. This may be attributed to the shorter duration of stent placement (7-14 days compared to 3 months) [8,29,30,36]. Similar findings were also reported in 2 other studies, which found that stenting for a median of 9-11 days led to greater clinical success and lower AE rates when compared to stenting for 90 days [39,40]. Based on clinical observation, we know that stent therapy for longer than 3 months without an exchange or removal is at risk for occlusion, which can lead to cholangitis. The optimal duration for stent therapy to achieve effective dilation has yet to be established [8]. Often in clinical practice, patients may not

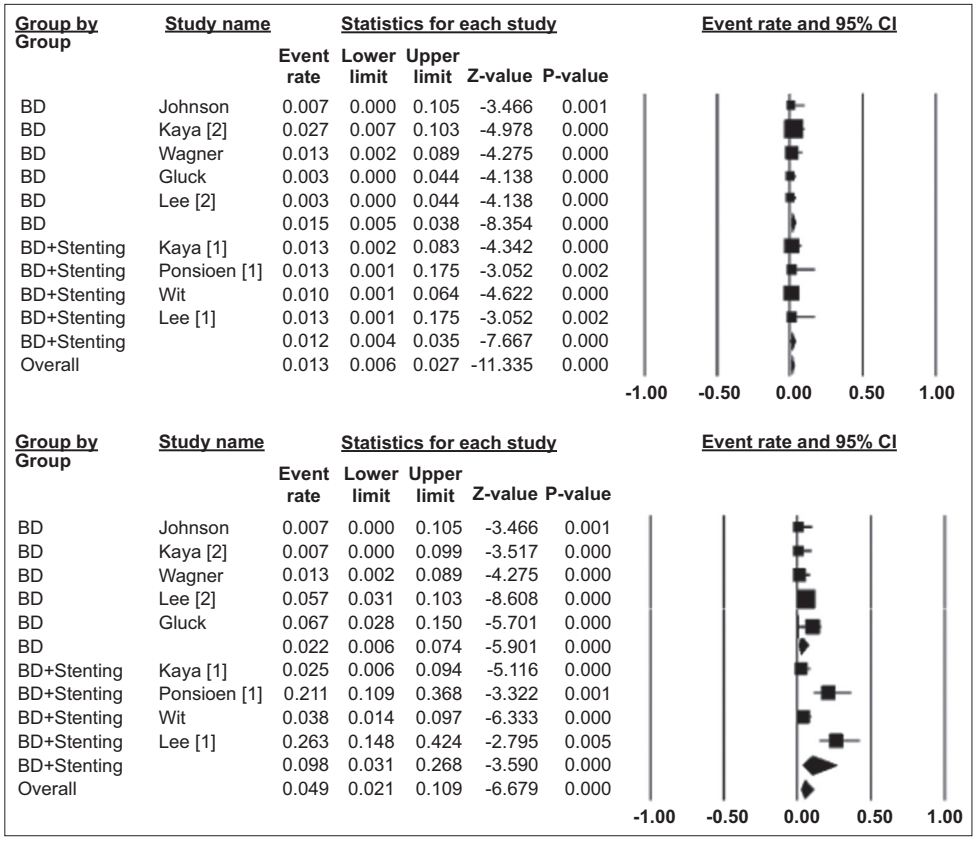

Figure 6 Forest plots for post-ERCP pancreatitis associated with balloon dilation and balloon dilation plus stent (top). Forest plots for bleeding associated with balloon dilation and balloon dilation plus stent (bottom)
ERCP, endoscopic retrograde cholangiopancreatography

be able to have a repeat ERCP in a short time frame, which can contribute to an increased risk of stent occlusion.

The pooled rate of PEP was lower in the balloon dilatation group in comparison to the balloon dilatation plus stent group, at 2.2% vs. 9.8%, respectively; P<0.001. PEP is a known complication of ERCP and is seen in 3-15% of patients [41,42]. It is hypothesized that PEP is a risk in PSC because the complexity of ERCP in these patients results in a longer procedure time, repeated procedures and difficult cannulations [16,43]. It is unclear why PEP rates were lower in the balloon dilatation group. The difficulty of the ERCP and risk factors for PEP were not specified in the included studies.

The pooled rates of bile duct perforation were comparable between the balloon dilation cohort (1.3%) and the balloon dilation with stent cohort (1.6%). When performed by experienced endoscopists in specialized centers, the overall rate of perforation associated with ERCP is thought to be comparable to that in patients without PSC [43,44].

The overall rate of bleeding was slightly higher in the balloon dilation cohort (1.5%) than in the balloon dilation with stent cohort (1.2%). Bleeding was most commonly due to sphincterotomy, but could also be seen in those undergoing tight stricture dilations [43,44].

Regarding the recurrence-free rate of dominant strictures, one study reported recurrence at 34 weeks with stent placement, in comparison to 26 weeks with balloon dilation alone [30]. Two other studies reported a recurrence-free rate of dominant strictures in balloon dilatation alone that ranged from 9-12 months [31,32]. Given the paucity of studies reporting this outcome, a pooled analysis could not be performed.

Regarding transplant-free survival, one study reported comparable rates at 1 year in those undergoing balloon dilatation alone vs. balloon dilation with stenting, at 97% and 100%, respectively [30]. In another study undergoing balloon dilatation alone, transplant-free survival was reported to be 91% at 1 year and 68% at 5 years [33]. Transplant-free survival in another study undergoing balloon dilatation alone was reported to be 81% at 5 years and 52% at 10 years [35]. These endoscopic interventions may make it possible to delay the need for liver transplantation [38,39,45]. Given the paucity of studies reporting this outcome, a pooled analysis could not be performed.

Limitations of this study include the small patient sample size and the presence of only one RCT. However, given the rarity of PSC and the paucity of the existing data, it is difficult to implement RCTs. Most of the studies were also retrospective in nature, which may have contributed to selection bias and may also under-represent AE as there was less control over the reporting of events. Another limitation was the moderate to significant heterogeneity, probably due to the variability in study designs. Most of the studies were undertaken in advanced single centers and may not be generalizable to the general community.

In conclusion, balloon dilation alone appears to be superior in terms of both clinical and technical success. In addition, balloon dilatation with stent placement had an overall higher rate of AE, including, cholangitis and PEP rates. Further randomized clinical studies should be carried out to validate our findings.

Summary Box

What is already known:

- Dominant strictures are not an uncommon complication in patients with primary sclerosing cholangitis
- Endoscopic treatment provides a short-term benefit in terms of symptoms, bloodwork, and longer predicted survival
- Currently, balloon dilation with endoscopic retrograde cholangiopancreatography (ERCP) is the treatment of choice, with balloon plus stenting in cases difficult to treat

What the new findings are:

- Balloon dilation alone was found to be superior to balloon plus stent in terms of both clinical and technical success
- Adverse event rates of cholangitis and post-ERCP pancreatitis were higher in the balloon plus stent group.
- Endoscopic therapy may allow longer periods of transplant-free survival

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Supplementary material

Supplementary Table 1 Quality assessment of the studies with Newcastle-Ottawa Scale and Jadad-Oxford Scale

Newcastle-Ottawa Scale					
Study [ref.]	Year	Type of study	Selection	Comparability	Outcome
Wit [8]	1996	Retrospective	***	*	***
Johnson [28]	2006	Retrospective	***	*	***
Kaya [29]	2001	Retrospective	***	*	***
Stiehl [31]	2002	Prospective	***	*	**
Wagner [32]	1996	Prospective	***	*	***
Ahrendt [33]	1998	Prospective	***	*	***
Gluck [34]	2008	Retrospective	***	*	**
Gotthardt [35]	2010	Prospective	***	*	***
Lee [36]	1995	Retrospective	***	*	***
Jadad–Oxford Scale for randomized controlled trials					
Study	Year	Type of study	Randomization	Blinding	Withdrawals
Ponsioen [30]	2018	Randomized controlled trial	2	2	1