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No Superiority of Stents vs Balloon Dilatation for Dominant Strictures in Patients With Primary Sclerosing Cholangitis

Short title: DILSTENT trial

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Abbreviations used in this paper: ITT, intention to treat; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; DS, dominant stricture; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreaticography; PEP, post ERCP pancreatitis; QOL, quality of life; RUQP, right upper quadrant pain; SAE, serious adverse event; ULN, upper limit of normal; BID, twice daily; UDCA, urso-deoxycholic acid; CBD, common bile duct; CHD, common hepatic duct; LHD, left hepatic duct; RHD, right hepatic duct

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ABSTRACT

Background & Aims: Dominant strictures occur in approximately 50% of patients with primary sclerosing cholangitis (PSC). Short-term stents have been reported to produce longer resolution of dominant strictures than single-balloon dilatation. We performed a prospective study to compare the efficacy and safety of balloon dilatation vs short-term stents in patients with non-end stage PSC.

Methods: We performed an open-label trial of patients with PSC undergoing therapeutic endoscopic retrograde cholangiopancreatography (ERCP) at 9 tertiary-care centers in Europe, from July 2011 through April 2016. Patients found to have a dominant stricture during ERCP were randomly assigned to groups that underwent balloon dilatation (n=31) or stent placement for a maximum of 2 weeks (n=34); patients were followed for 24 months. The primary outcome was the cumulative recurrence-free patency of the primary dominant strictures.

Results: Study recruitment was terminated after a planned interim analysis because of futility and differences in treatment-related serious adverse events (SAEs) between groups. The cumulative recurrence-free rate did not differ significantly between groups (0.34 for the stent group and 0.30 for the balloon dilatation group at 24 months; *P*=1.0). Most patients in both groups had reductions in symptoms at 3 months after their procedure. There were 17 treatment-related SAEs: post-ERCP pancreatitis in 9 patients and bacterial cholangitis in 4 patients. SAEs occurred in 15 patients in the stent group (45%) and in only 2 patients in the balloon dilatation group (6.7%) (odds ratio, 11.7; 95% CI, 2.4–57.2; *P*=.001).

Conclusions: In a multicenter, randomized trial of patients with PSC and a dominant stricture, short-term stents were not superior to balloon dilatation and were associated with a significantly higher occurrence of treatment-related SAEs. Balloon dilatation should be the initial treatment of choice for dominant strictures in patients with PSC. This may be particularly relevant to patients with an intact papilla. ClinicalTrials.gov no: NCT01398917

Key words: biliary; surgery; drainage; temporary stent

Primary sclerosing cholangitis (PSC) is a chronic fibro-inflammatory disease of the biliary tree of unknown origin. It is a progressive disease, which causes end-stage liver failure and is associated with an increased risk of cholangiocarcinoma. Transplant-free survival is estimated between 12-21 years.[1,2] Currently, therapy is limited to treatment of complications such as relieving biliary obstruction and orthotopic liver transplantation in case of end-stage liver disease. [3,4]

During the natural history of the disease many patients experience symptoms such as pruritus, right upper quadrant pain (RUQP), fatigue, and/or bouts of fever and jaundice due to impeded biliary drainage. In approximately 60% of cases dominant strictures (DS), which may be superimposed on diffuse ductal disease is the principal cause of these complaints.[5]. The incidence is estimated at 8-10% annually.[6]

The 2015 guidelines from the American Society for Gastrointestinal Endoscopy (ASGE) on the role of endoscopic retrograde cholangiopancreatography (ERCP) state that patients with PSC and a dominant strictures should undergo ERCP with biliary sampling to assess for presence of malignancy.[7] Moreover, benign strictures respond well to endoscopic therapy. Recommendations from a recent collaboration between the European Association for Study of the Liver and the European Society of Gastrointestinal Endoscopy to develop guidelines on endoscopy in PSC are in line with the ASGE statements. [8,9] The level of the evidence reviewed in both guidelines is however low, based only on retrospective series.

The best therapeutic approach to treat dominant strictures is not known. Both balloon dilatation and temporary stenting are employed. From the largest retrospective series on repetitive balloon dilatation one may infer that the recurrence-free rate at two years after a single session of endoscopic balloon dilatation is approximately 30%.[6]

Ponsioen *et al.* reported that short-term stenting with a mean duration of stent placement of 11 days is safe and effective, showing improvement of cholestatic symptoms and biochemistry in 83% of patients at 8 weeks, and a re-intervention-free

rate of 70% at two years.[5] We hypothesized that short-term stenting is superior to balloon dilatation at preventing recurrence of DS. Therefore, the aim of the present study was to compare short-term stenting versus balloon dilatation for the treatment of dominant strictures in patients with PSC with regard to cumulative recurrence-free patency, safety, as well as short-term improvement in cholestatic symptoms and biochemistry.

Methods

Study design

We undertook a multicenter, open-label, randomized, 1:1 parallel group trial with a follow-up (FU) of 24 months. Eligible patients were randomized during ERCP when a DS was identified to either balloon dilatation or short-term stenting for a maximum of 2 weeks.

Participants

Eligible patients had a diagnosis of PSC according to the EASL 2009 criteria,[10] ascertained with MRCP, ERCP, PTC and/or liver biopsy, were between 18-75 years of age, and fulfilled at least one of the following 5 sets of criteria: (i) serum bilirubin >3xULN; (ii) progression of right upper quadrant pain (RUQP), pruritus, fatigue, and/or fever attributed to acute bacterial cholangitis by at least 1 grade according to the Amsterdam Cholestatic Complaints Score (ACCS)[5] (see supplementary table_1) within the last month *together with* 50 % increase of total bilirubin and/or alkaline phosphatase (ALP) within the last 4 months and absolute value > 1.2xULN; (iii) increase of 20% or more of total bilirubin and/or ALP within last 4 months and absolute value >1.2xULN *together with* a documented dominant appearing stricture on MRCP or ERCP < 4 months prior to screening; (iv) progression of RUQP, pruritus, fatigue, and/or fever

attributed to bacterial cholangitis by at least 1 grade within last month: *together with* total bilirubin and/or ALP > 1.2xULN *and* a documented dominant stricture on recent MRCP or ERCP < 4 months prior to screening; (v) summed cholestatic complaints score at screening of ≥3, or pruritus ≥2, or RUQP ≥2 at screening *together with* total bilirubin and/or ALP > 1.2xULN *and* a documented dominant stricture on recent MRCP or ERCP < 4 months prior to screening. Sets iv and v were added to the eligibility criteria in order to increase recruitment after additional IRB approval in March 2013 and May 2015, respectively. All eligibility sets were designed to reflect clinical practice with regard to indication for endoscopic intervention, as well as to allow for detection of relevant changes during FU. On imaging a dominant stricture was defined as any stricture arising in the extrahepatic or left/right main ducts that was deemed functionally relevant by the treating endoscopist/radiologist.

Exclusion criteria were: prior stenting or balloon-dilatation within the previous 4 months; signs of bacterial cholangitis as defined by definite cholangitis according to supplementary table_2[11];□change of ursodeoxycholic acid (UDCA) therapy within 4 weeks; inability to give written informed consent;□biliary cirrhosis with Child-Pugh score ≥ 8;□estimated transplant-free survival < 2 years as calculated by a Mayo score > 2;□ suspicion of cholangiocarcinoma, reflected by an imaging study suggestive of metastasis, MRCP with mass lesion with contrast enhancement, or rise in CA19.9 of > 63 U/ml in the previous 4 months together with an absolute value > 130 U/ml;□signs of current malignancy other than basal cell carcinoma; life expectancy < 24 months;□use of antibiotics in previous 4 weeks;□women pregnant at the time of screening; HIV or acute or chronic hepatitis B or hepatitis C; substance (drug or alcohol) misuse within the previous 2 years.

Outcome

Primary end-point was the cumulative recurrence-free rate of the primary DS(s) within 24 months in those patients who did not experience initial failure, (see supplementary

figure 1). Ideally, assessment of recurrence of the treated DS(s) would require successive ERCPs at regular intervals during FU. Since this is not possible for obvious ethical reasons, a decision rule for re-ERCP was determined based on either (i) recurrence of serum bilirubin level back to screening level if >3xULN; (ii) increase of ALP or bilirubin ≥ baseline level *together with* increase in a cholestatic complaint ≥1 point relative to the previous visit; (iii) bouts of definitive or likely cholangitis.

In order to identify either serum bilirubin or ALP as an indicator for recurrence of the dominant stricture warranting a re-ERCP, an initial failure assessment at three months was included, (see Supplementary Appendix and supplementary figure_2). Patients who showed insufficient response with regard to improvement in cholestatic liver enzymes/cholestatic symptoms at three months would qualify as initial failure without the requirement for repeated cholangiography.

Secondary outcomes consisted of occurrence of procedure related complications, including serious adverse events (SAEs) as defined by the World Health Organisation, as well as change in symptoms assessed by the ACCS, liver enzymes, and change in quality of life as measured by the Short Form36 (SF36), both the mental component summary (MCS) and the physical component summary (PCS), at 3 months. Complications within the first 30 days after randomization were rated as not related, possibly related, or related by the treating physician. The criteria to diagnose PEP were according to the 1991 consensus report on PEP by Peter Cotton *et al*.[12] These require hospitalisation or extension of hospital admission, >3x ULN elevated amylase 24 hr post-procedure, and abdominal pain.

Sample size and interim analyses

A retrospective series from Amsterdam showed a re-intervention-free rate of 70% for short-term stenting.[5] In a previous pilot study in Amsterdam, 2-year re-intervention free survival of 50% versus 17% for short-term stenting versus balloon dilatation was observed (unpublished data). Assuming that the re-intervention free survival rate at

two years would be 60% for short-term stenting versus 30% for balloon dilatation yielded a sample size of n=42 per group. Allowing for a drop-out rate of 15% rendered a total sample size of n=100 to attain a power of 80% and a 2-sided α-level of 0.05. An interim analysis by a Data Safety Monitoring Board (DSMB) was planned when 50% of the intended total number of study subjects had passed their 3-month visit. The DSMB was assigned to advise on early termination of the trial due to safety concerns, as well as on futility.

Interventions

Patients were recruited and treated at 9 academic centers across Europe.

Eligible patients underwent ERCP after written informed consent. Periprocedural antibiotic prophylaxis consisted of cefotaxime 1000 mg i.v <1 hour before the procedure, and 12 and 24 hours thereafter, or levofloxacin 500 mg orally BID within 2 hours prior to the ERCP and 12 and 24 hours thereafter.

At ERCP patients were only randomized when, in the absence of purulent bile and fever > 38.5 °C, one or more dominant stricture(s) of the common bile duct, the common hepatic duct and/or the main left or right hepatic duct were encountered and deemed amenable to both balloon-dilatation or stenting by the endoscopist. Block-randomization in blocks of 4, to ensure even distribution among participating centers, was performed by a web-based electronic CRF. Follow-up time commenced at randomization. Prior to any intervention where possible, brush cytology was obtained of any suspicious dominant stricture. When brush cytology revealed cholangiocarcinoma or high-grade dysplasia, patient were withdrawn from the study. Sphincterotomy was performed at the discretion of the endoscopist.

Stenting: A 10 French polyethylene stent was inserted and retrieved after 7 days (maximum time 14 days) by gastroduodenoscopy. No attempt to cannulate the biliary tree was made upon retrieval, unless the brush result was suspicious for cholanciocarcinoma or high-grade dysplasia. In case of (supra-)hilar stricturing with

imminent risk of cholangitis by closing of the contralateral system when inserting a stent an attempt should be made to insert two 7Fr stents, one to either system. If only one 7 French stent had been placed, a new ERCP was scheduled with the same perioperative antibiotic regimen and an attempt made to exchange the 7 Fr stent for a 10 French or two 7 French stents, to be retrieved after another 7 days. Balloon dilatation or Soehendra dilators to facilitate stent placement was allowed. When placement of a 10 Fr stent or at least two 7 Fr stents proved impossible after 2 ERCPs, treatment was regarded as a failure.

Balloon dilatation: DSs were dilated by placing a 4 cm 6 mm Ø biliary dilation balloon in the stricture(s). The balloon was inflated to the point that the waist disappears completely at fluoroscopy or the maximum recommended by the manufacturer for 2 minutes. Longer or serial strictures must be treated with successive dilatation down to the most distal (relative) narrowing during the same session. The use of Soehendra dilators to facilitate insertion of a balloon was allowed. If balloon dilatation with a 6 mm Ø balloon proved impossible at the first attempt, a second ERCP was scheduled after 1 week. For intrahepatic strictures a 4 mm Ø balloon was allowed. When balloon dilatation at the second attempt proved impossible, patient was regarded as an initial failure.

After the procedure patients were kept overnight for observation and iv antibiotics. Next morning vital signs were recorded, a VAS pain scale taken, and blood drawn for hemoglobin, leucocytes, C-reactive protein, and amylase. In one center, these measurements were performed 4 hour after the procedure and, if uneventful, patients were discharged, followed by a telephone interview next morning.

Patients were reviewed at one week, and 3-monthly thereafter for 24 months.

During each visit symptoms were assessed by ACCS, SF36, adverse events were recorded, and routine bloods were drawn.

When a study subject met the decision rule for secondary failure a re-ERCP was performed: if this showed a recurrence of the original stricture then the primary endpoint was met. If no or a new DS was seen, the original treatment was still deemed successful. The new stricture could be treated at the discretion of the endoscopist, but patient's FU was censored at the time of re-ERCP. When a cholangiocarcinoma was discovered during follow-up this led to study withdrawal, as did any change in UDCA therapy. Data were censored from the date of change in UDCA therapy with regard to the primary endpoint.

Data analysis

The primary endpoint was analysed on an intention-to-treat (ITT) base by log-rank testing. The ITT population consisted of all randomized subjects. Initial failure was compared by Chi-square testing, as was the occurrence of treatment related adverse events, applying Fisher's exact test where appropriate. Differences in change in bilirubin, ALP, AST and cholestatic symptoms at 3 months were assessed as per protocol. In the per protocol population one patient in each group who did not receive treatment, two patients in the balloon dilatation group who dropped out early because of high-grade dysplasia in their initial brush, one patient in the short-term stenting group who had a change in UDCA dose one month after randomization, as well as one patient in the short-term stenting group who was listed for liver transplant within 3 months, were left out. Changes in biochemistry and symptoms between groups were tested by Mann-Whitney-U. Differences in change in SF36, between groups at 3 months were tested with Student's T-test. Overall changes at 3 months in biochemical cholestasis and complaints were tested using the Wilcoxon paired samples signed-rank test. Potential confounders on the occurrence of treatment related SAEs were assessed by univariate and when appropriate multivariate logistic regression. All data analyses were performed using SPSS version 24.

Ethical issues

The trial was conducted according to the principles of the Declaration of Helsinki (version Seoul 2008) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). The study protocol and amendments were approved by the IRBs of all participating centers. The trial was monitored by an independent monitor on site from the Clinical Research Unit of the Academic Medical Center, Amsterdam. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Recruitment

From July 2011 to April 2016 80 patients were enrolled, 65 were randomized during ERCP. Recruitment is shown in Figure_1. One patient in each treatment arm was excluded from safety analysis because they did not receive treatment. Both were randomized prior to mandatory passage with a guiding catheter to show accessibility of the strictures to therapy. Also, they did not undergo a prescribed second attempt. Two patients in the balloon dilatation arm dropped out early, because their brush proved positive for high-grade dysplasia. In April 2016, recruitment was prematurely stopped at the advice of the DSMB after a planned interim analysis because of futility and a disproportionate occurrence of treatment related serious adverse events (SAEs) between groups. Table_1 shows demographics and clinical characteristic of the study population. Baseline data were balanced between groups. More patients in the balloon dilatation group had previously undergone a sphincterotomy, but this difference was not statistically significant, (p=0.12). Details of the findings during ERCP are shown in supplementary table_3. The distribution of stricture(s) found at ERCP was balanced between the two treatment arms.

Outcomes

Primary endpoint: The cumulative recurrence-free rate of the primary DS(s) is depicted in Figure_2 and was equal in both groups, (p=1.0), with almost completely overlapping confidence intervals. Overall median recurrence-free rate was 26 weeks (95% CI: 2,3-50) and 34 weeks (95% CI: 4.0-64) for the balloon dilatation and short-term stenting group, respectively.

Initial failure was observed in 16/31 (52%) and 15/34 (44%) in the balloon dilatation and short-term stenting groups, respectively (p=0.89). Reasons for initial failure are listed in supplementary table_4.

Secondary endpoints: Overall, the vast majority (40/52, 77%) of patients experienced improvement in their overall symptom score at 3 months, which mirrored a reduction in serum bilirubin, ALP, and AST, see supplementary table_5.

Table_2 shows change in ACCS, cholestatic liver enzymes, cholestatic symptoms, and SF36 MCS and PCS at 3 months as compared to baseline. No differences were observed in any of the secondary endpoints between groups.

Table_3 lists the occurrence and nature of procedure-related SAEs. There was a strikingly elevated relative risk of 6.8 (95%CI: 1.7-27.4) for developing treatment related SAEs in the short-term stenting group as compared to the balloon dilatation group, predominantly driven by PEP. The univariate analysis of potential confounders with respect to PEP and cholangitis/cholecystitis is shown in table _4. The only statistically significant association was randomization. A sensitivity analysis for PEP alone showed that in univariate analysis there was a statistically significant association of stenting with the risk for PEP as SAE, (OR=9.3, 95%CI: 1.1-79.4, p=0.04), with an –expected- strong, albeit not statistically significant protective effect of previous sphincterotomy. In multivariate analysis, carrying forward randomization and previous sphincterotomy only in order to avoid overfitting, there was a trend towards stenting being associated with PEP (p=0.07), but numbers were probably too low to demonstrate a statistically significant association, (see supplementary table_6). The risk of

developing PEP requiring hospitalization in patients who had a previous EPT was only 4% (1x stent), while this was 20% (1x balloon dilatation, 7x stent) in patients with intact papilla's OR=0.17, (95% CI:0.02-1.4, p=0.10).

Discussion

Since more than 20 years, there has been debate regarding the preferred modality to treat dominant strictures arising in PSC. [5,6,8,13] We present the first-ever randomized trial on endoscopic therapy in PSC. We could not confirm our hypothesis that short-term stenting is superior to balloon dilatation at preventing recurrence of DS. Indeed, although the study was not designed as a non-inferiority trial the results showed that cumulative recurrence-free rates of DS over 2 years FU following single session balloon dilatation or short-term stenting were comparable with Kaplan-Meier curves and 95% confidence intervals almost completely overlapping. Even though only 65% of the predefined sample size was available for interim analysis, the DSMB calculated that the likelihood of yielding a significant contrast between the two treatment arms when 100% of the sample size would have been included would be less than 5%.

On the other hand, there was a strong safety signal in the stenting group, who experienced almost 7 times more frequently SAEs such as PEP and cholangitis/cholecystitis compared to the balloon dilatation group, while in the latter the SAE rate was 6.7%, which is consistent with earlier observations. [6,14] This large contrast in occurrence of SAEs between groups was the main reason to terminate the trial prematurely. The overall rate of PEP as SAE in this trial was 14%, which is approximately twice the rate reported in several recent retrospective series[14,15], which used a similar definition of PEP, and had comparable rates of previous sphincterotomy as the major protective factor. Putative factors explaining the difference between these

series and our trial are that the former applied stenting much less to treat DSs and had a retrospective design, which may be prone to underreporting of adverse events.

The reason for the elevated risk of PEP may be the space-occupying effect of a standard 10 Fr transpapillary stent or two 7 Fr stents obstructing the pancreatic duct in an often small and retracted papilla in PSC. This is supported by our and other's observations that PEP occurred much less frequently after previous sphincterotomy.[14,16,17] Likewise, 8-10mm self-expandable metallic stents for malignant obstruction in pancreatic carcinoma or distal cholangiocarcinoma are associated with an increased risk of PEP compared to 10Fr plastic stents.[18] Furthermore, a stent may block the cystic duct or the contralateral main intrahepatic duct in the often multi-strictured biliary tree of PSC patients, precipitating bacterial cholangitis.[16,19]

Our trial also yielded the first prospective data showing that both balloon dilatation and stenting of DS leads to amelioration of symptoms and significant decrease in cholestasis in the majority of patients at three months, strengthening the -thus far- low level of evidence on which the recent ASGE, EASL, and ESGE recommendations to perform therapeutic ERC in symptomatic cases are based.

An obvious advantage of balloon dilatation is that it precludes the need for further endoscopy for stent removal. However, in the largest series of balloon dilatation for DS in PSC, 1-8 (mean 1.8 ±0.2) repeated interventions were needed for successful opening of DSs.[6]

A limitation of the trial is that patients underwent ERCs during follow-up only when they met the criteria of a predefined decision rule or when clinically indicated, to avoid the risks of unnecessary ERC. This generally mirrors clinical practice and justified this decision rule. Consequently, some recurrences of DSs may have been overlooked.

Balloon dilatation to facilitate stent insertion was allowed and applied in half of the patients that were randomized to stent placement. If the trial would have yielded a significant benefit of short-term stenting compared to balloon dilatation this could

theoretically have constituted a confounder. However, since the trial was in fact comparing two endoscopic treatment strategies, we felt that any measure to facilitate stent placement was appropriate. Another limitation is that patients with Child-Pugh score ≥8 or Mayo Risk score >2 were excluded. It is unclear if the results can be extrapolated to such more advanced cases, because these may respond less favorably, e.g. in terms of decrease of bilirubin. More than 2/3 of patients in each group used UDCA maintenance therapy. This could potentially have blunted the biochemical response at 3 months and may have had impact on the relatively high proportion of patients that did not meet the initial response criteria.

In conclusion, endoscopic treatment of dominant strictures is efficacious in ameliorating symptoms in patients with PSC. Short-term stenting was not superior to balloon dilatation and associated with a much higher occurrence of treatment related SAEs. Balloon dilatation should be the initial treatment of choice for dominant strictures in PSC. This may be particularly relevant in patients with an intact papilla..

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Legends

Figure 1. DILSTENT flow diagram

Table 1. Baseline characteristics

* data missing for 1 patient

** data missing for 2 patients

*** data missing for 3 patients

Figure 2. Cumulative recurrence-free patency of treatment

Short-term stenting: n=34; balloon dilatation: n=31

Log-rank test: p=1.0

Table 2. Changes in bilirubin, ALP, AST and cholestatic symptoms at baseline, 3 months, and changes thereof between groups.

analyses were performed in the per protocol population

'n' denotes the number for which the pertaining parameter was available.

* Mann-Whitney U test

** Fisher's exact test.

*** independent samples T-test

Table 3. Procedure-related serious adverse events

[*]one patient in each group was left out from the comparison because they did not receive an attempt at their allotted treatment due to failure to pass the dominant stricture with a guidewire

Table 4. Univariate analyis for risk factors of procedure-related serious adverse events

Table 1. Baseline characteristics

	balloon dilatation n=31	short-term stenting n=34
mean age (years ± STD)	40 ± 14	40 ± 11
male	22 (71%)	23 (68%)
median disease duration (years, IQR)	7 (3-10)	4 (2-8)
concurrent IBD	25/31 (80%)	25/33 (76%)*
UC	*23 (74%)*	*19 (58%)*
Crohn	*1 (3%)*	*5 (15%)*
IBD-U	*1 (3%)*	*1 (3%)*
previous EPT	15 (48%)	10 (29%)
UDCA use	21 (68%)	26 (76%)
anti-pruritic medication	3 (10%)	5 (15%)
median bilirubin (µmol/L, N≤17)) (IQR)	38 (15-108)*	24 (12-57)*
median ALP (U/L, N 40-120) (IQR)	312 (259-470)*	302 (214-475)*
median AST (U/L, N≤40) (IQR)	110 (48-170)**	70 (41-111)***

Table 2. Changes in bilirubin, ALP, AST and cholestatic symptoms at baseline, 3 months, and changes thereof between groups.

	balloon				stent				
	baseline	t=3 mth	Δ (t0->t3)	relative change	baseline	t=3 mth	Δ (t0->t3)	relative change	P-value
bili median, (IQR) µmol/L	39 (16-108) n=30	14 (11-58) n=28	*-10 (0-45) n=28*		24 (12-57) n=33	14 (9-24) n=28	*-3 (1-33) n=28*		*0.35**
($bili_0$-$bili_{3mth}$)/$bili_0$ (IQR)				*-0.30 (0-0.67) n=28*				*-0.22 (0-0.53) n=27*	*0.54**
ALP_0 median, (IQR) U/L	312 (259-470) n=30	306 (153-446) n=29	*-31 (-47-115) n=29*		302 (215-475) n=33	280 (157-390) n=27	*-35 (-21-131) n=26*		*0.67**
(ALP_0-ALP_{3mth})/ALP_0 (IQR)				*-0.09 (-0.17-0.41) n=29*				*-0.10 (-0.12-0.36) n=26*	*0.97**
AST median, (IQR) U/L	110 (48-171) n=29	64 (43-175) n=29	*-12 (-5-55) n=28*		70 (41-111) n=31	44 (32-83) n=27	*-15 (2-39) n=25*		*0.73**
(AST_0-AST_{3mth})/AST_0 (IQR)				*-0.14 (-0.11-0.49) n=28*				*-0.25 (0.06-0.43) n=25*	*0.32**
pruritus median, (IQR)	1.5 (0-2) n=30	0.0 (0-1) n=28	*-1.0 (0-2) n=28*		1.0 (0-3) n=33	0.5 (0-1) n=28	*0.0 (0-2) n=27*		*0.70**
fatigue median, (IQR)	1.0 (0-2) n=30	0.5 (0-1) n=28	*-1.0 (0-1) n=28*		1.0 (0-2) n=33	0.0 (0-2) n=27	*0.0 (0-1) n=26*		*0.60**
fever N, (%)	1 (3) n=30	*2 (7) n=28*			4 (12) n=33	*1 (3) n=28*			*1.0***
RUQP median, (IQR)	1.0 (0-1) n=30	0.0 (0-1) n=28	*0.0 (0-1) n=28*		0.0 (0-2) n=33	0.0 (0-0) n=28	*0.0 (0-1) n=27*		*0.68**
ACCS median, (IQR)	4.0 (2-4) n=30	1.0 (0-3.5) n=28	*-1.5 (0.25-3) n=28*		4.0 (2-5) n=33	1.0 (0-3) n=27	*-2.0 (1-3) n=27*		*0.61**
SF36 MCS mean (SD)	43.2(10.3) n=29	49.4 (8.5) n=20	*6.5 (11.4) n=20*		41.7 (11.4) n=28	49.5 (8.3) n=16	*6.5 (8.1) n=14*		*0.99****
SF36 PCS mean (SD)	46.4 (8.5) n=29	51.4 (5.0) n=16	*4.7 (8.3) n=20*		47.2 (8.7) n=28	49.4 (8.9) n=16	*0.9 (9.4) N=14*		*0.23****

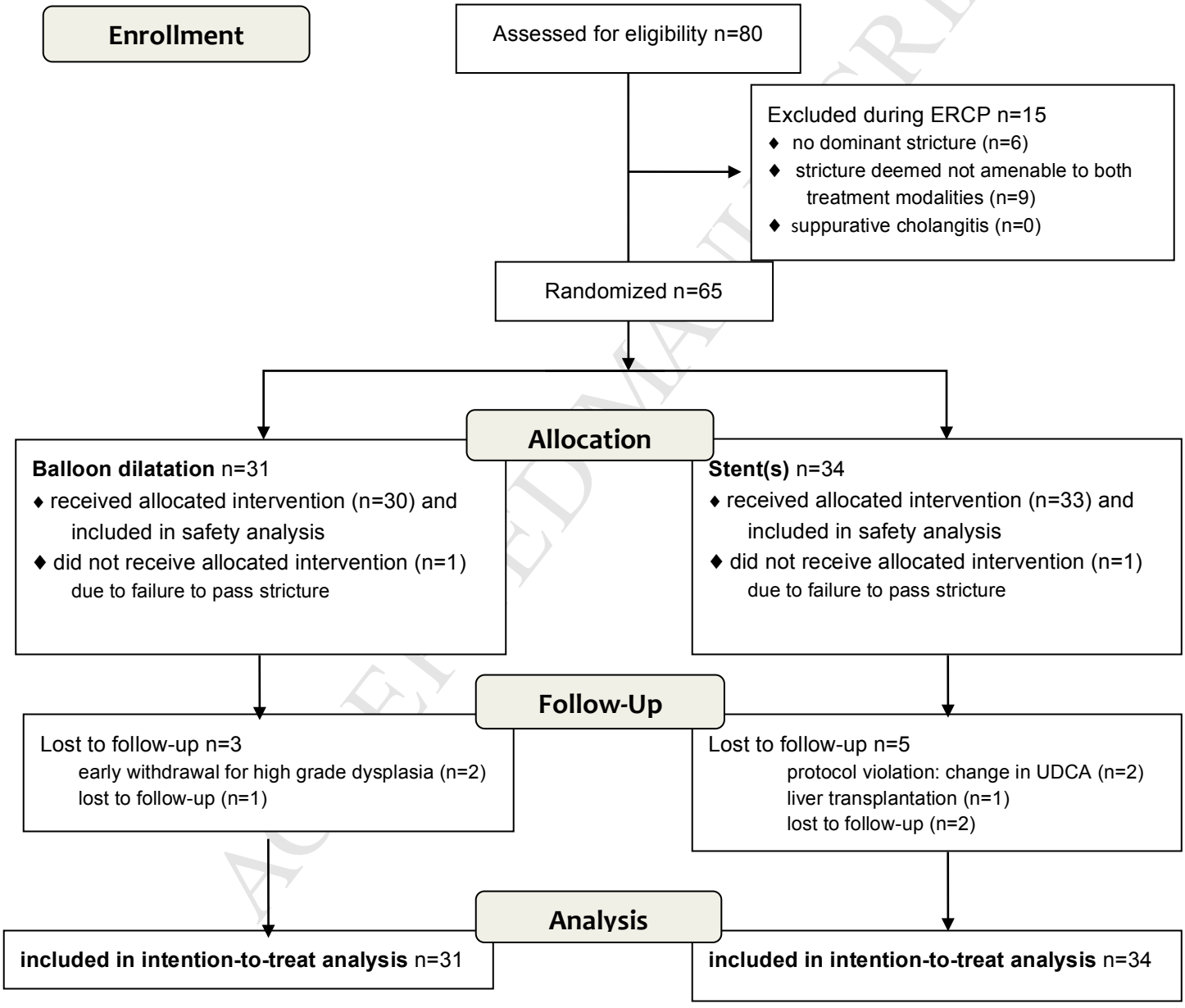
Table 3. Procedure related serious adverse events

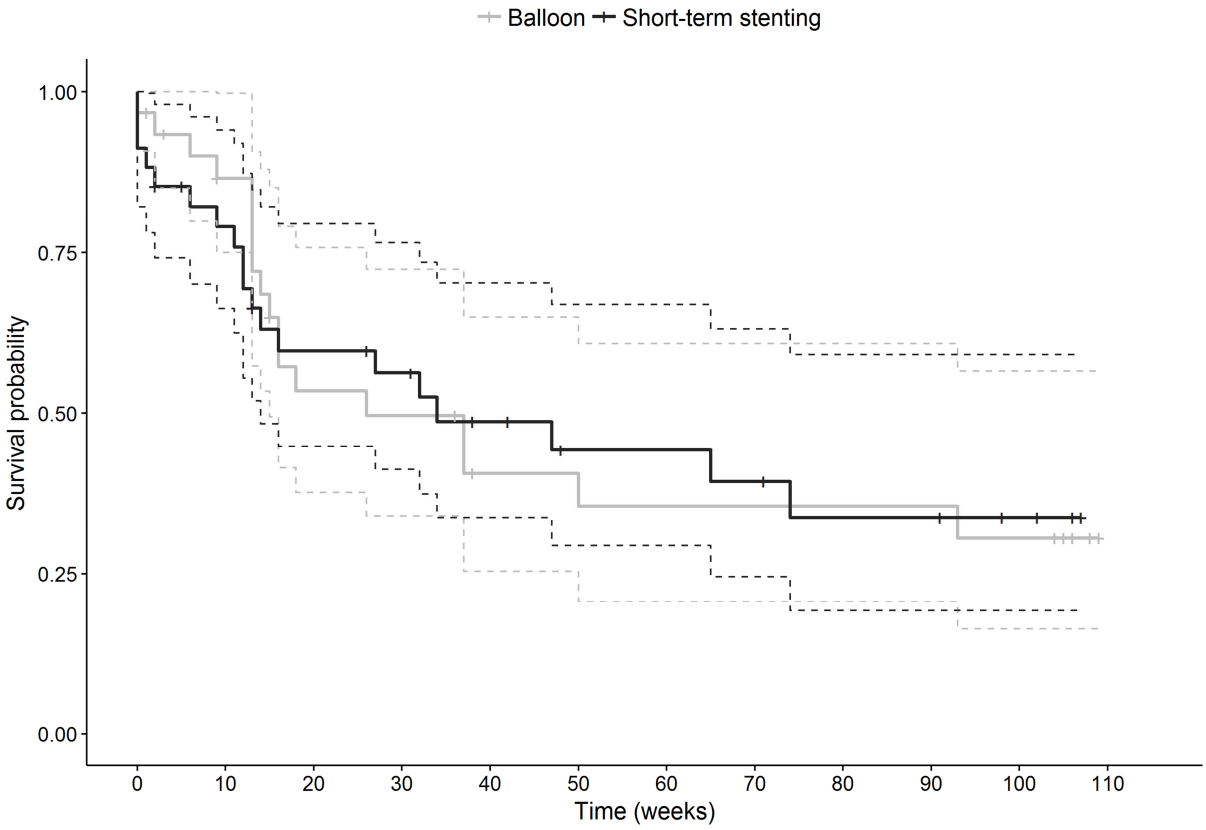
	balloon dilatation n=30*	short-term stenting n=33*	OR (95% CI)	p-value
all cause n (%)	2 (6.7)	15 (45.4)	11.7 (2.4-57.2)	0.001
cholangitis/cholecystitis n (%)	1 (3.3)	4 (12)	4.0 (0.42-38.0)	0.36
Post ERCP Pancreatitis n (%)	1 (3.3)	8 (24)	9.3 (1.1-79.4)	0.03
post-procedural pain n (%)	0	2 (4.5)	n.a.	
ascites	0	1(3)	n.a.	

Table 4. Univariate analyis for risk factors of procedure-related serious adverse events

	univariate analysis		
	OR	95% CI	p-value
age	1.0	0.9-1.03	0.42
sex	1.2	0.4-4.0	0.71
disease duration	1.0	0.9-1.1	0.83
randomization	11.2	2.4-57.2	0.002
centre	0.8	0.6-1.1	0.16
previous sphincterotomy	0.6	0.2-2.0	0.39
baseline serum biluribin	1.0	0.99-1.01	0.43
procedure time	1.0	0.99-1.02	0.79
NSAID prophylaxis	1.0	0.3-3.1	0.99
sphincterotomy	0.7	0.2-2.15	0.48

DILSTENT Flow Diagram





Supplementary Appendix

Initial failure criteria:

Whichever biochemical level of either ALP or bilirubin dropped more than 30% was subsequently used as indicator for recurrence during the remainder of the FU. If biochemical parameters dropped by less than 30%, the treatment was designated as initial failure. This threshold of 30% was chosen on the basis of data from 1999 in the pre-UDCA era, where we found that successful treatment of a dominant stricture with a stent was commonly associated with a drop in ALP and/or bilirubin of 30% or more.[5] However, in the trial most eligible patients used UDCA, which may be responsible for blunted dynamics in cholestatic liver enzyme levels. Planned evaluation of the first 15 patients who passed their 3 month FU learned that there were 3 patients who clearly improved with regard to their cholestatic complaints but dropped only 24-28% in ALP level, so they should be designated as initial failure, despite obvious clinical improvement. In order to bring the initial response criteria in line with the entry criteria it was decided to request an amendment from the IRB to add to the 30% biochemical improvement requirement the following: 20%-30% improvement *together with* improvement of at least 1 point in ACCS, (see supplementary figure 2). This became effective after IRB approval in May 2013 and had no bearing on the aforementioned 3 study subjects, since these were still in FU. Other reasons for initial failure were procedure related complications necessitating early re-intervention, assigned treatment failure, and recurrence or persistence of the treated stricture upon early re-ERCP.

Supplementary table 1.

Amsterdam Cholestatic Complaints Score.[5]

Table 1. Semiquantitative Scoring of Cholestatic Complaints

	0	1	2	3	4
Pruritus	None	Sometimes	Daily	Wakes me up/need medication	Intolerable
Fatigue	None	Cannot do everything	Have to rest	<50% daytime in bed	Fully bedridden
Cholangitis	No fever	Fever			
RUQ pain	None	Sometimes	Daily	Wakes me up/need analgesics	Intolerable

RUQ = right upper quadrant.

Supplementary table 2.

Criteria for bacterial cholangitis according to Bilhartz[11]

Major criteria

- Body temperature > 38° Celsius
- At least one positive blood culture
- Clinical signs of sepsis syndrome (chills, hypotension (systolic blood pressure <90 mmHg, diastolic blood pressure < 60 mmHg)
  and tachycardia (heart rate >100 beats per minute)

Minor criteria

- A rise in cholestatic enzymes (elevation in total bilirubine or alkaline phosphatase or gamma glucuronyl transferase
  more than 1.5 times compared to the pre-ERCP values or upsloping of these values after initial improvement above 1.5 times of the lowest value measured)
- No symptoms pointing to infection outside the biliary tree
- Pain in the right upper quadrant of the abdomen
- Leucocytosis (defined as > 12x10e9 leukocytes/L)

Definition of cholangitis

- Definite cholangitis: 3 major or at least 2 major + 2 minor criteria
- Likely cholangitis: 2 major + 1 minor criteria
- Possible cholangitis: 1 major + at least 1 minor criteria or 2 major criteria without any minor criteria
- Cholangitis unlikely: all other

Supplementary table 3.

Findings during ERCP

	balloon dilatation n=31		**short-term stenting n=34**		**p value**
duration of intervention, minutes ± STD	58 ± 34	(n=28)	69 ± 36	(n=34)	0.20
second attempt needed , n (%)	2 (6)	(n=31)	3 (9)	(n=34)	0.92
sphincterotomy, n (%)	12 (39)	(n=31)	12 (35)	(n=34)	0.78
periprocedural NSAID, n (%)	18 (58)	(n=31)	21 (62)	(n=34)	0.76
distribution of stricture(s):					0.72
CBD, n (%)	*16 (52)*	(n=31)	*23 (68)*	(n=34)	
CHD, n (%)	*15 (48)*	(n=31)	*17 (50)*	(n=34)	
hilar, n (%)	*13 (45)*	(n=29)	*13 (38)*	(n=34)	
LHD, n (%)	*10 (34)*	(n=29)	*13 (38)*	(n=34)	
RHD, n (%)	*11 (38)*	(n=29)	*9 (26)*	(n=32)	
brush:		(n=28)		(n=27)	
not suspicious (n)	*26*		*27*		
HGD or CCA (n)	*2*		*0*		
Soehendra dilatation, n (%)	4 (13)	(n=31)	4 (12)	(n=34)	1.00
balloon dilatation prior to stent insertion, n (%)			18 (53)	(n=33)	
stents:				(n=34)	
1x 10 Fr, n (%)			*26 (76)*		
2x 10 Fr, n (%)			*1 (3)*		
1x 7 Fr, n (%)			*1 (3)*		
2x 7 Fr, n (%)			*4 (12)*		
per-procedural complications:		(n=31)		(n=34)	
significant bleeding (n)	*0*		*0*		
perforation (n)	*0*		*0*		
false route (n)	*1*		*1*		
second attempt needed, n (%)	2 (6)	(n=31)	4 (12)	(n=34)	0.67

(n) in grey indicate numbers of patients for which this particular feature was known

Supplementary table 4.

Reasons for initial failure

	balloon dilatation n=29*	short-term stenting n=32**
total bilirubin or alkaline phosphatase insufficiently decreased	10	7
assigned treatment failure	1	2
procedure related complications	0	2
recurrence/persistence DS	3	2

*) 2 additional patients dropped out early because of HGD finding in the brush
**) 1 additional patient was referred for liver transplant within 3 months and 1 additional patient was censored early because his UDCA dose was reduced 1 month after randomization

Supplementary table 5.

Changes in bilirubin, ALP, AST and cholestatic symptoms at baseline, 3 months, and changes thereof in all patients as per protocol.

	T=0 months	**T=3 months**	**Ratio (0–3mth)/0mth**	**Δ (0 ->3mth)** (paired samples)	**P-value***
Bilirubin (µmol/L) median (IQR)	28 (13–79) n=63	14 (11–26) n=56	0.29 (0-0.55) n=55	-5 (0-40) n=55	<0.001
ALP (U/L) median (IQR)	312 (227-471) n=63	293 (158-444) n=56	0.09 (-0.15-0.39) n=55	-31 (-35-126) n=55	0.013
AST (U/L) median (IQR)	99 (45-146) n=60	56 (35-133) n=56	0.16 (0-45) n=53	-15 (0-50) n=53	<0.001
Pruritus median (IQR)	1.0 (0-3) n=63	0 (0-1) n=56		-1.0 (0-2) n=55	<0.001
Fatigue median (IQR)	1.0 (0-2) n=63	0.0 (0-2) n=55		0.0 (0-1) n=54	0.004
RUQ pain median (IQR)	1.0 (0-1) n=63	0.0 (0-0.75) n=56		0.0 (0-1) n=55	0.01
ACCS total median (IQR)	4.0 (2-5) n=63	2.0 (1-3) n=55		-2.0 (1-3) n=55	0.001
SF-36 – MCS score mean (SD)	47.0 (8.1) n=57	50.1 (6.9) n=36		3.1 n=34	0.047**
SF-36 – PCS score mean (SD)	43.2 (9.7) n=57	49.7 (7.8) n=34		6.5 n=34	0.001**

* Wilcoxon Rank test, **paired samples T-test

'n' denotes the number for which the pertaining parameter was available.

Supplementary table 6.

Univariate and multivariate analysis of risk factors for post-ERCP pancreatitis

	univariate analysis			multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
age	1.0	0.92-1.04	0.45			
sex	1.1	0.24-4.9	0.91			
disease duration	0.8	0.62-1.02	0.07			
randomization	9.3	1.1-79.4	0.04	7.5	0.9-66.1.	0.07
centre	0.9	0.6-1.3	0.65			
previous sphincterotomy	0.2	0.02-1.4	0.10	0.2	0.03-21	0.19
baseline serum biluribin	1.0	0.99-1.01	0.44			
procedure time	1.0	0.98-1.02	0.80			
NSAID	0.7	0.15-3.0	0.60			
sphincterotomy	0.8	0.2-3.8	0.80			