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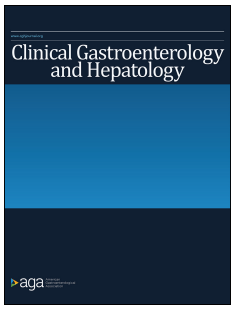

Lumen-Apposing Stents with or without Pigtail in Endosonography-Guided Biliary Drainage for Malignant Distal Biliary Obstruction

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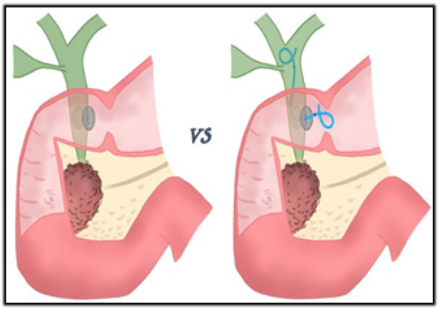
PII: S1542-3565(25)00611-1
DOI: https://doi.org/10.1016/j.cgh.2025.05.025
Reference: YJCGH 60009

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 26 May 2025

Please cite this article as: Sumalla-Garcia A, Aparicio-Tormo JR, Pedraza-Sanz R, Sanchiz-Soler V, De-la-Serna Higuera C, Andujar X, Vazquez-Sequeiros E, Puigcerver-Mas M, Martinez-Moreno B, Barbera T, Capilla-Lozano M, Martinez-Ortega A, Foruny-Olcina JR, Luna-Rodriguez D, Garcia-Lerma E, Peñafiel J, Barenys JB, Laquente-Saez B, Perez-Miranda M, Videla S, Loras C, Gornals JB, On behalf of The Spanish Working Group on Endoscopic Ultrasound Biliary Drainage, Lumen-Apposing Stents with or without Pigtail in Endosonography-Guided Biliary Drainage for Malignant Distal Biliary Obstruction, *Clinical Gastroenterology and Hepatology* (2025), doi: https://doi.org/10.1016/j.cgh.2025.05.025.

Lumen-apposing stent with vs. without coaxial pigtail for EUS-guided choledochoduodenostomy in malignant biliary distal obstruction: a multicenter randomized trial (**BAMPI study**)



N=91

LAMS 47

LAMS-Pigtail 44

Follow up 1 year

Primary Outcome
Recurrent biliary obstruction rate
(stent dysfunction parameter)

Difference: 30 vs 9%

RR 0.31 (CI95% 0.09–0.78; p=0.024)

Favouring LAMS-Pigtail group

Clinical Gastroenterology and Hepatology

TITLE PAGE

Title: Lumen-Apposing Stents with or without Pigtail in Endosonography-Guided Biliary Drainage for Malignant Distal Biliary Obstruction

Short Title: Randomized multicenter trial for EUS-BD: LAMS (pigtail vs non-pigtail).

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Funding: The BAMPI study was supported by a grant from the Spanish Society of Digestive Endoscopy (SEED) in 2020, and a grant from the Catalan Society of Gastroenterology (SCD) in 2021. The funding bodies had no role in the trial design or interpretation of the data.

Abbreviations: AE, Adverse event; ASA, American Society of Anesthesiologists' classification; BD, Biliary drainage; BRI, Biliary reintervention; CBD, Common bile duct; CDS, choledochoduodenostomy; CEIC, Clinical research ethics committees; CRF, Case report form; DPS, Double-pigtail plastic stent; EE, Electrocautery-enhanced; ERCP, Endoscopic retrograde cholangiopancreatography; EUS, Endoscopic ultrasound; EUS-BD, Endoscopic ultrasound-guided biliary drainage; GE, Gastroenterostomy; HGS, hepaticogastrostomy; LAMS, Lumen-apposing metal stent; MRI, Magnetic resonance imaging; MDBO, Malignant distal biliary obstruction; PTBD, percutaneous biliary drainage; RBO, Recurrent biliary obstruction; SEED, Spanish Society of Digestive Endoscopy; TA, Tissue acquisition.

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Conflict of interest statement: MPM is a consultant and speaker for Medtronic, Olympus, Taewoong, and M.I.Tech; EVS, JRAT, and JBG are consultants for Boston Scientific. CL is a consultant for Fuji and received a speaking fee from Boston Scientific. JBG has received research funding from Boston Scientific and Fujifilm. ASG is a PhD student in the Faculty of Medicine, University of Barcelona, and this paper is part of his doctoral project. JBG acts as a PhD supervisor. The remaining authors disclose no conflicts.

Author contribution to manuscript: JBG conceived the project. ASG, SV, MPM, CL, and JBG participated in the design of the study. The study design was discussed in research meetings with all the authors. ASG, JRAT, RPS, VSS, CSH, XA, EVS, MPM, TB, BMM, MCL, AMO, JRFO, DLR, EGL, JPM, JBB, BLS, MPM, SV, CL, and JBG promoted the enrolment of patients, conducted the study, and acquired the data. ASG, EGL, JP, and JBG collected, interpreted, and analysed the data, and verified the underlying data. ASG, SV, and JBG coordinated the study. ASG, EGL, JPM, and JBG did the statistical analysis. ASG and JBG drafted the manuscript. All authors read, revised, and provided a critical review of the draft manuscript. All authors approved the final manuscript. The guarantor of the article is JBG.

Collaborators: From the Spanish Working Group on Endoscopic Ultrasound Biliary Drainage. Sandra Maisterra, Julio G Velasquez-Rodriguez, Claudia F Consiglieri (Endoscopy Unit, Hospital Universitari de Bellvitge, Barcelona), who assisted in the enrolment of patients. The surgeons who assisted in cephalic duodenopancreatectomy surgeries were Angel Antonio Moya Herraiz (Hospital General Universitari de Castello), Jose Manuel Ramia (Hospital General Universitario Dr. Balmis de Alicante), Elena Muñoz Forner (Hospital Clinico Universitario de Valencia), Lluis Secanella (Hospital Universitari de Bellvitge). Cristian Tebe provided helpful initial assistance in the protocol design.

Acknowledgements: Thanks to the Asociación Española de Gastroenterología (AEG) for providing us with REDCap platform; to E. Julià for her selfless artwork; to E. Sospedra, for his advice on the responses to CEIm amendments; to the institutions and scientific societies that supported this project with grants (Sociedad Española de Endoscopia Digestiva and Societat Catalana de Digestologia); and to the CERCA Programme/Generalitat de Catalunya for institutional support.

Data Transparency Statement: If requested, de-identified data collected for the BAMPI trial, the study protocol, and informed consent form can be made available. Please contact JBG (jgornals@bellvitgehospital.cat) or bampi-trial@gmail.com. All requests will be reviewed by the members of the BAMPI trial investigators team.

ABSTRACT:

Background and Aims: EUS-guided biliary drainage, creating a choledochoduodenostomy and using lumen-apposing metal stents (LAMS), is a promisingintervention for the management of malignant distal biliary obstruction (MDBO). But concerns exist regarding its stent patency. Our aim was to determine whether the insertion of an axis-orienting double-pigtail plastic stent (DPS) through LAMS offered a clinical benefit by improving the stent dysfunction rate.

Methods: This multicenter randomized controlled trial was carried out in 7 tertiary hospitals. Patients with MDBO secondary to resectable, locally-advanced, or unresectable cancers, and indication for biliary drainage, were eligible for inclusion. Patients were randomly assigned (1:1) to either the LAMS group or the LAMS-DPS group. The primary endpoint was the rate of recurrent biliary obstruction (RBO), detected during follow-up. The secondary endpoints were technical and clinical success, safety, time-to-RBO, reinterventions, and hospitalization.

Results: Between Nov. 2020, and Oct. 2022, we screened 123 patients with MDBO, of whom 91 were randomly assigned to LAMS (n=47) or LAMS-DPS (n=44). RBO rate was lower in the LAMS-DPS group (14[30%] of 47 patients vs 4[9%] of 44 patients; relative risk0.31[95%CI 0.09–0.78];p=0.024). Hospitalization was shorter in the LAMS-DPS group (median difference 4.5[95%CI 0, 9]; p=0.016). Procedure time was longer (21 vs 32-min, p=0.018) in the LAMS-DPS-group. No differences were found among technical, clinical success, and global adverse events (19 vs 27%; relative risk,1.42[95%CI 0.67–3.18];p=0.362).

Conclusions: In patients with malignant distal biliary obstruction, EUS-guided biliary drainage using LAMS with coaxial DPS was superior to LAMS alone. It offered clinical benefits including lower recurrent biliary obstruction rate and shorter hospitalization (ClinicalTrials.gov, number NCT04595058).

Keywords: Endoscopic ultrasonography; choledochoduodenostomy; lumen-apposing metal stent; malignant biliary obstruction; pancreatic cancer.

INTRODUCTION

Malignant distal biliary obstruction (MDBO) is a common issue in pancreatico-biliary malignancies, and it can alter the oncological treatment, directly impacting the patient's quality of life.[1,2] Although treatment with endoscopic retrograde cholangiopancreatography (ERCP) remains the gold standard, it is associated with significant risk of post-ERCP pancreatitis and stent dysfunction secondary to tumor ingrowth and/or overgrowth.[3] Endoscopic ultrasound-guided biliary drainage (EUS-BD) using electrocautery-enhanced (EE) lumen-apposing metal stents (LAMS), creating a choledochoduodenostomy (CDS), has emerged as a rescue strategy after failed ERCP or even as a viable alternative to ERCP.[4-7] Findings from recent studies provide new evidence for considering EUS-CDS not only in palliative scenarios, but also as a first-line treatment for MDBO or as a bridge to surgery.[8-11]

Current meta-analysis and trials have shown that EUS-BD using LAMS offers technical benefits, and its shorter procedure time makes it preferable when difficult ERCPs are anticipated.[12-15] But concerns still exist regarding its safety, as non-negligible rates of adverse events (AE) have been described, and recurrent biliary obstruction (RBO), as a stent dysfunction parameter, occurs frequently.[16-19] In this setting, a classification of different types of biliary LAMS dysfunction has been proposed, with some rescue options.[20]

There is a basic limitation in LAMS design, as the short length of the stent causes the distal flange to become impacted against the opposing biliary wall. The insertion of a coaxial double-pigtail plastic stent (DPS) has been postulated to improve LAMS patency and bile flow, by maintaining a vertical orientation in the common bile duct (CBD),reducing the risk of stent occlusion and backflow of alimentary material.[20,21]

Because of this lack of evidence to support the routine use of coaxial DPS, a multicenter randomized controlled trial was designed to assess whether a coaxial DPS within a biliary LAMS was superior to a single LAMS in EUS-BD (CDS_type) for MDBO in terms of stent dysfunction.

METHODS

Study design

The BAMPI(*Biliary_Apposing_Metal_Pigtail*) trial was a multicenter, industry-independent, parallel-group, randomized controlled trial designed to test two strategies (LAMS-alone vs LAMS-plus-DPS) of EUS-BD for MDBO. The protocol was published previously and is available online(**Supplement-1)**.[22] This study was approved by the research and ethics committee(ref.ICPS024/20).[22] Study recruitment was initiated in

November-2020 and ended in October-2022, in 7 Spanish centers(**Supplement-2,TableS1**).

An independent data monitoring committee (DMC) evaluated the progress and safety of the trial with one planned meeting (after consecutive enrolment of the first half of included patients was completed).

The trial protocol followed the SPIRIT guidelines, and the study was conducted in accordance with CONSORT guidelines, the principles of the Declaration of Helsinki, and the guidelines for Good Clinical Practice.[22]

All authors had access to the study data and reviewed and approved the final manuscript.

Participants

Patients with MDBO (secondary to resectable, locally advanced, or unresectable cancers) and clinical criteria justifying EUS-BD were candidates for either a first-line BD method or a rescue method, after failed ERCP. Patients with CBD diameter<10mm, severe coagulation disorder (INR>1.5 not correctible, and/or platelets<50.000/mm^3), or with another type of BD at the time of the index procedure (e.g., percutaneous), were excluded. The inclusion and exclusion criteria are listed in **Supplement-2(TableS2**).

The informed consent form was signed in the presence of participating personnel knowledgeable about the study before inclusion in the study.

Randomization and masking

Potential candidates were assessed for eligibility by study personnel at each participating site. Selected participants were randomly assigned using a computer-generated random sequence (using R-software) at a 1:1 ratio to LAMS-DPS (experimental group) or LAMS-alone (control group), stratified by trial site, age (<or>65 years old), and presence of liver metastases. The block size was four. The random sequence was created by an independent researcher who was not involved in the trial.

The randomization process was carried out on the day of the intervention by a study member (not involved in the procedure) in the same endoscopy unit and during the procedure. The Research_Electronic_Data_Capture_software (REDCap) platform was used, and the result of the randomization was transferred to the circulating nurse. Endoscopist remained blinded until the moment of the LAMS placement when the nurse informed them about the participant's assigned group.

Endoscopists and researchers were not masked to the treatment allocation, given the difference between the two stent types. However, the independent data monitoring committee re-evaluated the efficacy endpoint (RBO) in blinded conditions to randomization. In case of discrepancy, the final decision remained with this committee.

Procedures

Interventions were performed by endoscopists with previous experience in EUS-guided transmural drainage. A minimum requirement of at least 12 LAMS placed annually for any indication, including a minimum experience of seven EUS-CDS, was required of the endoscopists.[22]

A general description of the technique is detailed in **Supplement-2(Methods)** and **Figure1.**

Follow-up

Data were collected by the participating investigators in charge at each center. The data was introduced into an electronic database. Remote supervised monitoring was done at the hospital of the PI by one physician research coordinator. Patients were assessed (visit and telephone call) on days 1 and 14, and at 1,3,6,9, and 12 months, with the aim of obtaining clinical data pointing to the primary and secondary endpoint data(**Supplement-2**,**FigureS1**).

Outcomes

The primary outcome was the rate of RBO after the index procedure detected during follow-up (one year).

The secondary outcomes included technical and clinical success, safety data, time-to-RBO, number of biliary reinterventions (BRI), procedural time, hospitalization, surgery data (if done), related-mortality, and survival time.

RBO was defined as a composite endpoint of stent dysfunction (either occlusion or migration) detected during follow-up (mainly based on Tokyo guidelines, to avoid the risk of bias linked to subjectivity).[23] This endpoint was diagnosed in case of clinical recurrence (jaundice, cholangitis) with evidence of biliary obstruction on imaging (dilation) or endoscopic findings confirmed as follows: stent migration was defined as presence of completely/partially migrated stent at the time of endoscopic reintervention; causes of stent occlusion were tumor ingrowth/overgrowth, sludge, food, an haemobilia. AEs were classified in accordance with both the ASGE lexicon and the latest AGREE classifications.[24]

All other definitions are explained in detail in **Supplement-2(eMethods)** and in the published protocol. [22]

Statistical analysis

Prior data indicated that the RBO rate was 20% vs 1% for the LAMS alone and LAMS-DPS groups, respectively.[21,25,26] A total of 80 subjects (40 in each group) were required in order to be able to reject the null hypothesis that the RBO rates for LAMS and LAMS-DPS groups were equal with 80%power. The type I error probability associated with this test was 5%. Considering a dropout rate of 10%, a final sample of 88 patients (44 in each arm) was required. This dropout rate was adjusted, in relation to the rate reported in the

published protocol(5%), to account for a more acceptable percentage in a multicenter study.

Demographic characteristics were described by the study group. Categorical variables were presented as the number of non-missing cases and percentages, and continuous variables were presented as the mean and standard deviation (SD) or median with interquartile range. The primary efficacy analysis was performed in the intention-to-treat population. The cumulative incidence of trial outcomes was compared at the individual level using a chi-squared test. Relative risk (RR) and its 95% confidence interval (CI) were estimated to quantify the magnitude of the observed differences. Survival curves according to the trial group for time-to-event outcomes were compared with the log-rank test, and hazard ratios were estimated using a Cox proportional-hazards model. The significance threshold was set at a two-sided alpha value of 0.05. Statistical analyses were performed using R(version_4.1.2).

RESULTS

Baseline characteristics

Between Nov 16, 2020, and Oct 24, 2022, 123 patients with MDBO were assessed for eligibility, of whom 32 were ineligible/excluded. Ninety-one patients were randomly assigned to treatment—47 to the LAMS group and 44 to the LAMS-DPS group. In these treatment groups, three and four patients, respectively, discontinued treatment for different reasons (investigator decision, patient conditions, or protocol violation; **Figure2**).

Most patients were female (64% in LAMS vs 59% in LAMS-DPS) with a mean (SD) age of 74(9) years. Pancreatic cancer with palliative status was the most common etiology in both groups, and obstructive jaundice (94%) was the most common indication for endoscopic BD. All oncological statuses were included (palliative 82%, borderline 13%, resectable 5%). Gastric outlet obstruction (GOO) and liver metastases were present in 26% and 36% of all included cases, respectively. EUS-CDS was decided upon after failed ERCP (68%) or as first-line approach (32%).

Baseline characteristics were distributed equally between groups(**Table1**;**Supplement-2,TableS3,eResults**).

Outcomes

The RBO rate, as primary outcome, was lower in the LAMS-DPS group (14 [30%] of 47 patients vs four [9%] of 44 patients; RR, 0.31[95%CI 0.09–0.78];p=0.02). In addition, using Kaplan-Meier analysis, a significant difference in terms of time to RBO was found in favor of the LAMS-DPS group (hazard ratio 0.21[95%CI 0.07-0.63];log-rank p=0.002;**Figure3**). A post-hoc analysis stratified for RBO and palliative vs non-palliative

patients was made, and the benefit of DPS remained consistent(**Supplement-2,FigureS2).**

Furthermore, a non-significant difference was observed for the number of biliary reinterventions (12 [26%] patients in the LAMS-group vs five [11%] patients in the LAMS-DPS group; RR 0.46[95%CI 0.16-1.12];p=0.10).

Concerning hospitalization, a significantly longer stay length (median difference, 4.5d [95%CI 0, 9];p=0.01) was encountered in the LAMS group(**Supplement-2,FigureS3**).

No differences were found in technical success (85 vs.84%;RR, 0.99 [95%CI 0.82-1.19]; p=0.89) or clinical success (81vs.77%;RR, 0.96[95%CI 0.76-1.19];p=0.67) for the LAMS vs LAMS-DPS groups, respectively. Procedure time was shorter in the LAMS group (median difference, -11min[95% CI -29, -2];p=0.01).

Outcomes by intention-to-treat analysis are available in **Table2**. Similar results were noted in the *per protocol* analysis (**Supplement-2,TableS4**).

More procedural details and a detailed RBO case-by-case analysis are provided in **Supplement-2,TableS5**,**TableS6,eResults.**

Concerning global SAEs, similar rates were found (RR,1.42[95%CI 0.67–3.18];p=0.36) between the two groups (**Supplement-2,TableS7**). Regarding related-SAEs, in the LAMS group, there were two (4%) bleedings, two abdominal sepsis, two non-obstructive cholangitis, and one (2%) cholecystitis. In LAMS-DPS group there were four (9%) cholecystitis, two (4%) bleedings, two non-obstructive cholangitis, one (2%) abdominal sepsis, and one perforation.

A total of six patients experienced fatal events; there were no significant differences between the two groups. In the LAMS-DPS group there were: one sepsis immediately after EUS-CDS and EUS-Gastroenterostomy (GE), two late cholecystitis (48 and 81 days after the index procedure), one intraprocedural CBD perforation, and one non-obstructive cholangitis (8 days later). In LAMS group there was one late bleeding (53 days). Related-mortality rate and survival rate were similar for the two groups (**Table2**; **Supplement-2,TableS4**).

A detailed description of all related-SAEs in the groups is provided in **Supplement-2** (**TableS8;FigureS4**).

Twenty-four cases suffered GOO. Most patients were managed conservatively (13 patients, 54%), but other patients were treated with an EUS-GE in 8 cases, surgical GE in one, and enteral stent in one. In all but two cases, EUS-CDS was performed (22 patients). An exploratory analysis was made of this selected population (EUS-CDS plus EUS-GE). More details in **Supplement-2(eResults;TableS9/S10;FigureS5**).

Seven patients underwent surgery (7%), with a similar figure for the two groups. In all but one patient, a cephalic duodenopancreatectomy was performed without incident. Details in (**Supplement-2**,**TableS11**).

DISCUSSION

This multicenter, randomized trial provides evidence in support of placing a coaxial DPS for EUS-CDS using LAMS in patients with biliopancreatic malignancies. To our knowledge, this is the first trial comparing these two stenting options for the management of MDBO and including all oncological status.

Our results have demonstrated the expected superiority of LAMS-DPS over LAMS-alone in terms of lower rate of RBO. Furthermore, benefit was shown in secondary outcomes, as the LAMS-DPS group had shorter hospitalization.

In this trial, EUS-CDS was performed as a rescue after failed ERCP and as a first-line approach. Currently, EUS-BD is reported to be an effective and safe rescue technique in patients with failed ERCP.[14,15,27] Two recent trials have been designed to assess EUS-CDS as a primary treatment modality for MDBO over ERCP.[12,13] Both studies yielded evidence in favor of adopting EUS-CDS as a complementary first-line option for ERCP.

The preference for using EE-LAMS is not shared by all endoscopists. Recent papers show that LAMS and SEMS are comparable in terms of efficacy and call for further research, above all regarding safety.[25]

Concretely, stent dysfunction of LAMS in EUS-CDS is one of the main concerns, and it has been reported in 12-55%.[21,25,26,28] Moreover, a recent prospective study (SCORPION-p) concluded that a high incidence of stent dysfunction might limit EUS-CDS using LAMS alone as a valid alternative to ERCP; further studies on the benefit of coaxial DPS are necessary.[28]

The prophylactic placement of a DPS within a LAMS offers two hypothetical advantages to prevent RBO: an axis-orientation of the stent to maintain a non-perpendicular LAMS in the CBD, and a lower migration rate. This suggestion has been tested in retrospective studies, but solid evidence is lacking.[21,26, 28]

In the present study, RBO rate as primary outcome was significantly different, confirming our initial hypothesis that inserting a coaxial DPS improves LAMS patency. Independent of the heterogeneity of the patient population, this benefit was consistent across the overall population and the palliative subgroup.

The RBO rate for the LAMS-group differs from the recent ELEMENT trial[13]. The reported stent dysfunction rate was lower but the definition of rate for this outcome always required re-interventions.[13]

Recently, Vanella et al. reported 93 EUS-CDS using LAMS, and stent dysfunction occurred in 32% of patients, but almost all of them could be managed by endoscopic reinterventions. Although a minority received a coaxial-DPS, the authors suggested its potential benefit, but noted a randomized trial was needed.[20] As in that study, in our trial most RBO cases were caused by food impaction. Cleaning the LAMS using a balloon and inserting a new DPS (LAMS_group) or a second DPS (DPS_group), followed by SEMS placement through LAMS, were the most frequently used interventions.

Concerning secondary outcomes, the delay in time-to-RBO between groups was significant using the Kaplan-Meier analysis. BRI rate was not significantly lower in the DPS-group; this was surely due to some fragile cases having a favorable outcome with only the initial conservative measures. Perhaps the current sample size might have underestimated the effect of DPS in producing a significant reduction in BRI.

Apparently, hospitalization seems excessive but comprehensive if most included patients are palliative. Stay length was several days less in the LAMS-DPS group, offering new clinical data in terms of quality-of-life assessments.

Almost a third of the included cases suffered GOO, and an exploratory analysis was carried out. The potential benefit of coaxial DPS was not proved, but a significant reduction in hospitalization was detected. As in the Leuven-Amsterdam-Milan study, a combination of GOO and EUS-CDS might increase the risk of RBO, especially when an enteral stent is deployed.[20] In this trial, only one enteral stent was reported. Most cases of GOO were managed with conservative measures, with EUS-GE in one third.

Regarding safety, in our study reported SAEs were comparable for the two groups. The SAE rate was slightly higher than in previous trials comparing EUS-CDS with ERCP.[12-15]Surely, the ASA_status and Charlson_comorbidity cases with considerable scores, indicating a higher burden of coexisting conditions, contributed to the increase.

Some late cholecystitis cases were reported, all of them treated with antibiotics and some percutaneously drained. While rare, two fatal cholecystitis occurred in the DPS group, in elderly-palliative patients after a poor clinical course leading to sepsis. A potential factor, such as the changed LAMS axis after DPS placement compressing the cystic duct opening, cannot be ruled out. Clinicians should weigh this risk against benefits, especially in frail patients. This aspect needs to be evaluated in future studies, as no solid explanations were found.

A major concern in this study is that a total of six patients experienced fatal events. It must be noted that three of them were within 8 days: two diagnosed with sepsis after excluding local complications by imaging, and one perforation directly related to the procedure. All related fatalities occurred in palliative patients, and in comparing with previous trials, the results are similar.[11-15]

As expected, and as in other reports, a longer procedure time was observed in the LAMS-DPS group.[12]In our opinion, this extra procedural time, although it may impact workflow, is acceptable, considering the benefits of using a coaxial DPS.

In addition, this trial included pancreaticoduodenectomy outcomes after EUS-CDS. No differences were noted in terms of safety or surgical feasibility. It must be noted that in one case it was not possible to complete the surgical resection due to severe retroperitoneal fibrosis. This generated doubts about the role of EUS-CDS in this issue. Recently, a French study reported a significant number of pancreaticoduodenectomy outcomes after EUS-CDS using LAMS vs. ERCP, showing better outcomes with EUS-CDS.[11]

Finally, as in other studies, technical success was excellent[12,13,26]. Dilation intra-stent generally was avoided to prevent the risk of dislodgement. LAMS misdeployment requiring a salvage drainage occurred in only five cases (5%). It must be noted that other non-procedure related causes occurred in both groups, impacting on the global technical failure rates and included in the outcomes to better reflect daily clinical practice. Otherwise, clinical success was acceptable, although perhaps lower than expected. Surely the inclusion of elderly/frail patients with liver metastases may partly explain this.

Limitations. Firstly, different oncological statuses were included which may have led to heterogeneity, and the palliative population (majority) might have benefited more. Second, competing risks such as tumor progression or delays in chemotherapy were not contemplated; therefore, future studies need to evaluate DPS in resectable/borderline patients. Three, endoscopists and treating physicians were unmasked and working at seven centers (without central adjudication of failed ERCP); this could have led to potential bias (e.g.hospitalization,heterogeneity). Fourth, either as a first-line BD method and as a rescue method after failed ERCP were included. And lastly, although this trial was sufficiently powered to confirm the RBO hypothesis, it was not powerful enough for other secondary outcomes such as BRI, GOO sub-group, and survival rate.

The multicenter design, randomization nature, and adequate power to test the hypothesis strengthen the quality and generalizability of the results. Furthermore, the 12-month follow-up strengthens the reliability of RBO/AEs data collection. With the purpose of avoiding a potential bias related to a learning curve, the endoscopists had proven experience in EUS-CDS.[22] In addition, this trial offers new information regarding pancreaticoduodenostomy outcomes after an EUS-CDS. Lastly, the novelty of including resectable/borderline cancers, and using EUS-CDS as a first-line option in a considerable percentage of patients, provides new data. But the primary applicability of findings is for palliative patients, given the small resectable/borderline subgroup.

In clinical practice, EUS-BD is gaining popularity in patients with MDBO as a rescue strategy after failed ERCP. If insertion of DPS within a LAMS improves stent patency, it might prevent delays in oncological management. Surely this would have an impact on oncological outcomes, as interruption of chemotherapy due to stent dysfunction could be avoided.

In summary, this multicenter randomized trial proved the superiority of LAMS-DPS, offering clinical benefits in terms of a lower RBO rate and shorter hospitalization. These findings will probably help to provide support for considering placing a coaxial DPS, for EUS-CDS using LAMS, in patients with MDBO. Future research is needed to confirm these clinical benefits and to better explain the cholecystitis events.

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Table legends

Table_1: Baseline characteristics of patients and lesions.

Table_2: Primary and secondary outcomes. Intention-to-treat analysis.

Figure legends

Figure_1: Illustrative figure.

Figure_2: CONSORT flowchart.

Figure_3: Time to recurrent biliary obstruction (RBO).

Table 1. Baseline characteristics of patients and lesions according to group.

	LAMS group (N=47)	LAMS-DPS group (N=44)
Patient characteristics and clinical details		
Age, years - mean (SD)	74 (10)	73 (10)
Sex - n (%)		
Male	30 (64)	26 (59)
Female	17 (36)	18 (41)
Etiology of biliary obstruction - n (%)		
Pancreatic cancer	40 (85)	41 (93)
Cholangiocarcinoma	2 (4)	2 (4)
Other ł	5 (11)	1 (2)
Initial laboratory values, mean (SD)		
Total bilirubin, mg/dL	12.9 (7)	13.5 (6)
ALT, U/L *	331 (378)	172 (128)
ALK U/L ǂ	676 (350)	732 (531)
White cell count x10^9 cells/L ¶	7.5 (6)	8.7 (7)
Platelet count x 10^9 cells/L ǁ	255 (111)	283 (124)
ASA -I / II / III /IV - n (%)	2 (4) / 27 (57) / 18 (38) / 0	1(2) / 16 (36) / 25 (56) /2 (4)
Charlson comorbidity score – median (p25-p75) **	9 (7-11)	10 (7-12)
Staging – n (%)		
Resectable	3 (6)	1 (2)
Locally advanced/Borderline	5 (11)	7 (16)
Unresectable or palliative	39 (83)	36 (82)
GOO (due to tumor infiltration)– n (%)	13 (28)	11 (25)
Liver metastases – n (%)	19 (40)	14 (32)
Reason for EUS-BD – n (%)		
Rescue after failed ERCP	25 (56)	31 (76)
First-line	20 (44)	9 (24)
Diameter of common bile duct, mm - mean (SD) ǂǂ	17 (3)	17 (3)
LAMS size - n (%)		
6 x 8 mm	20 (45)	13 (32)
8 x 8mm	23 (51)	25 (63)
10 x 10 mm	2 (4)	2 (5)

Data are median (IQR), mean (SD), n (%), or n/N (%). ł Other etiologies included (n=6) duodenal cancer (n=3), metastases (n=2), ampullary cancer (n=1). *Data missing for 18 patients. ǂ Data missing for 15 patients. ¶ Data missing for 12 patients. ǁ Data missing for 15 patients. ** Charlson comorbidity scores range from 0 to 37 (plus 1 point for each decade of age starting at 50 years), with higher scores indicating a greater burden of coexisting conditions. ǂǂ Data missing for 2 patients.

ALK, alkaline phosphatase; ALT, alanine transaminase; ASA, American Society of Anesthesiologists; DPS, double-pigtail plastic stents; EUS-BD, endoscopic ultrasound-guided biliary drainage; GOO, gastric outlet obstruction; LAMS, lumen-apposing metal stents.

Additional baseline characteristics are provided in Table S3.

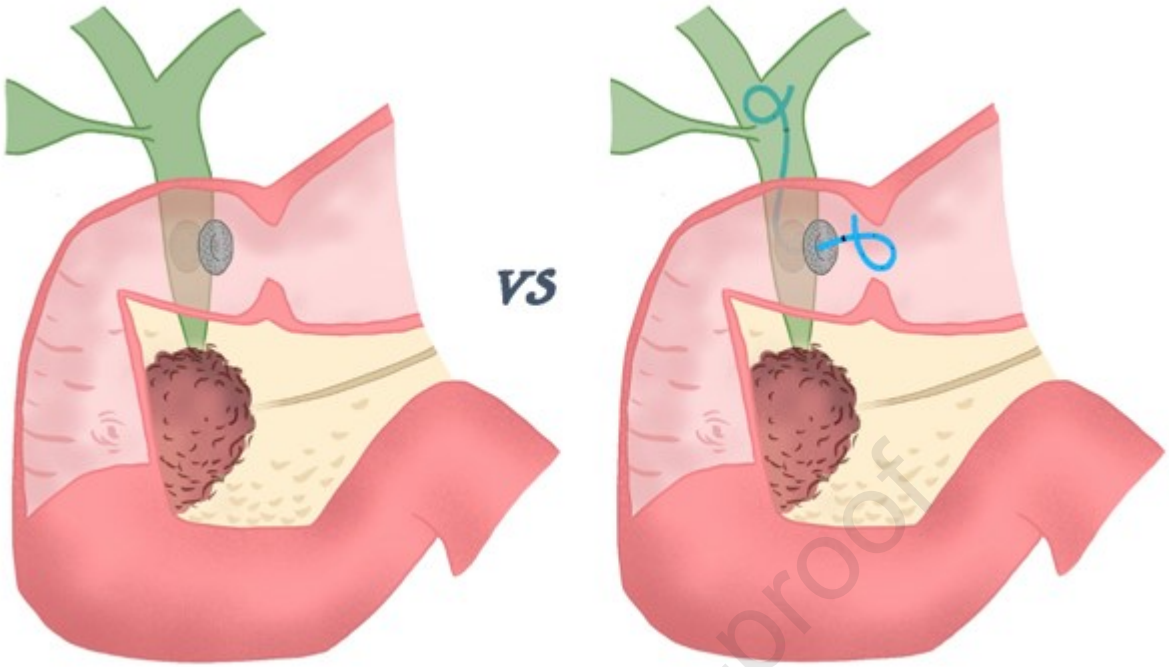
Table 2: Primary and secondary outcomes according in terms of intention-to-treat analysis.

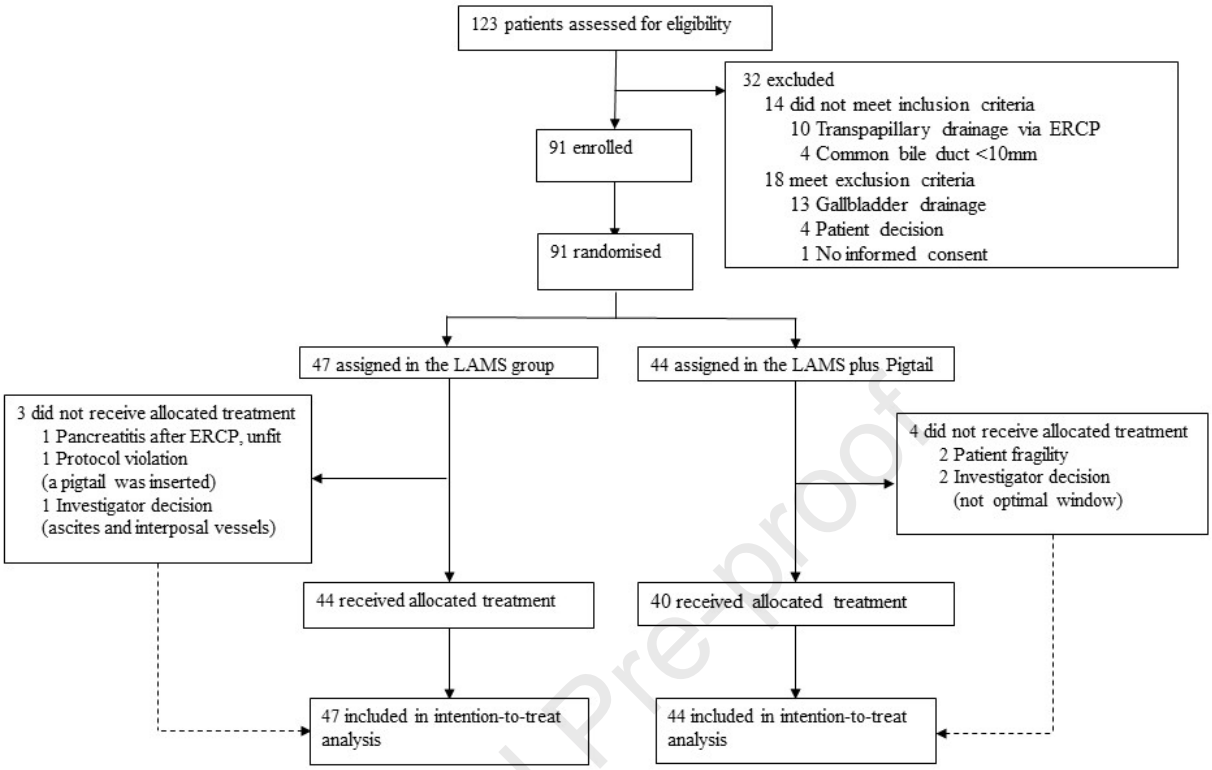
	LAMS group (N=47)	LAMS-DPS group (N=44)	Effect [1,2]	P value
Primary outcome				
Recurrent biliary obstruction (RBO) - n (%)	14 (30)	4 (9)	0.31 (0.09-0.78)[1]	0.02
Secondary outcomes				
Time-to RBO, days – median (IQR)	70 (30-160)	155 (63-242)	-85 (-146,0)[2]	0.09
Biliary re-intervention – n (%)	12 (26)	5 (11)	0.46 (0.16-1.12)[1]	0.10
Technical success – n (%)	40 (85)	37 (84)	0.99 (0.82-1.19)[1]	0.89
Clinical success – n (%)	38 (81)	34 (77)	0.96 (0.76-1.19)[1]	0.67
Procedure time, mins ɬ				
Median (IQR)	21 (16-37)	32 (20-60)	-11 (-29.5, -2)[2]	0.02
Length of hospital stay, days *				
Median (IQR)	9 (4-18)	5 (3-10)	4.5 (0, 9)[2]	0.02
Safety, global SAEs – n (%)	9 (19)	12 (27)	1.42 (0.67-3.18)[1]	0.36
Other outcomes				
Fluoroscopy assistance – n (%)	32 (68)	36 (82)	1.27 (0.95-1.56) [1]	0.13
Rate of pancreaticoduodenostomy - n (%)	4 (8.5)	3 (6.8)	..	..
Related mortality rate – n (%)	1 (2.1)	5 (11.4)	5.5 (0.94-1.03)[1]	0.10
Survival time, days - median (IQR)	131 (56-228)	164 (63-260)	-33 (-143, 62)[2]	0.70

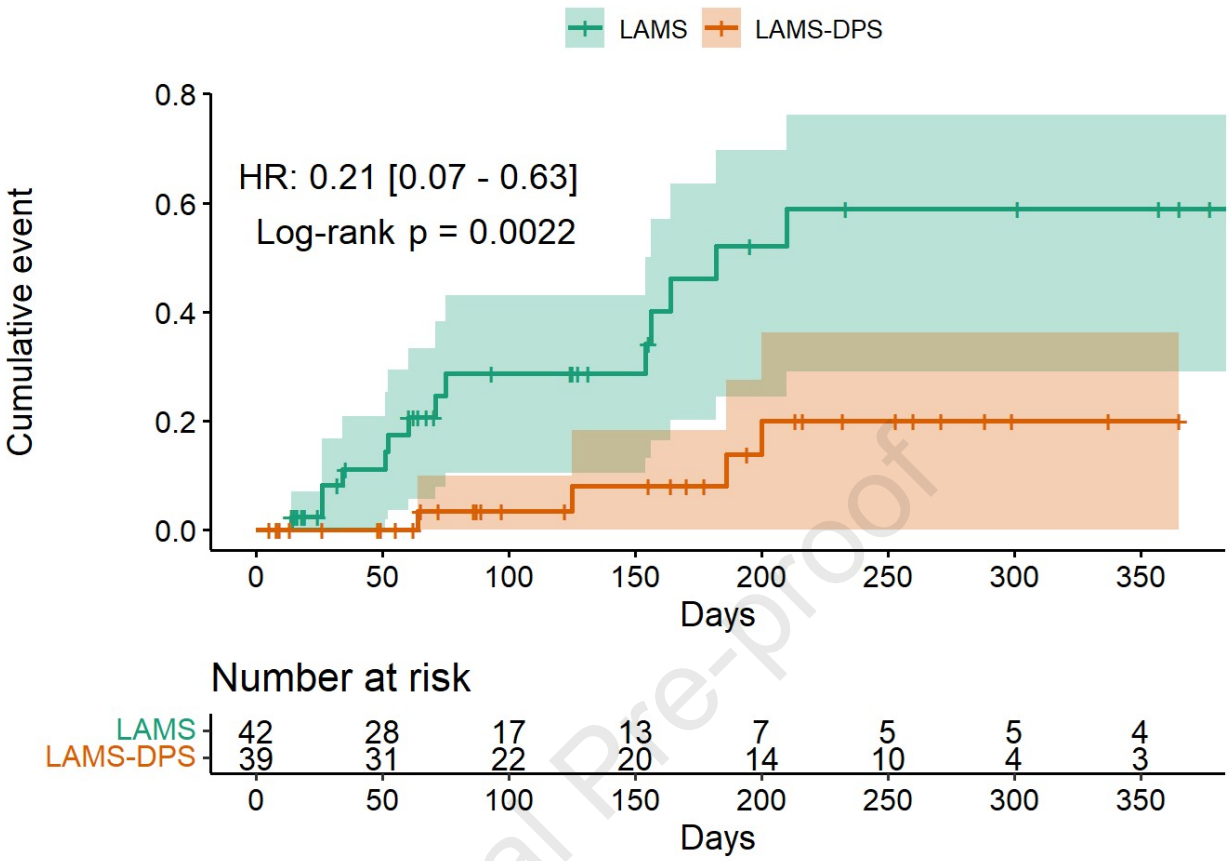
Data are n (%) or median (IQR). Effect includes different analyses: [1]Relative risk (95%CI); [2]median difference (95%CI). LAMS as reference group. Additional outcomes are provided in online supplement-2: Table S4 (per-protocol analysis), S5 (interventions), S9 (gastric outlet obstruction sub-analysis).

ɬ Data missing for 2 patients (in LAMS group). *Data missing for 3 patients (in the LAMS group).

SAEs, serious adverse events; DPS, double-pigtail plastic stent; LAMS, lumen-apposing metal stent.







WHAT YOU NEED TO KNOW

BACKGROUND

Although recent metanalyses have postulated that Endoscopic ultrasound-guided biliary drainage using lumen-apposing metal stents (LAMS), in malignant distal biliary obstruction, has high technical and clinical success rates, some concerns exist regarding recurrent biliary obstruction.

FINDINGS

This multicenter randomized trial provides valuable information in favor of the use of coaxial pigtail over LAMS alone, as it is associated with a lower rate of recurrent biliary obstruction and shorter hospitalization.

IMPLICATIONS FOR PATIENT CARE

If the insertion of a coaxial plastic pigtail within a LAMS improves the biliary stent patency, it might prevent delays in oncological management and improve survival rates.

Statistical Analysis Plan

Protocol Title:	Multicenter study of lumen-apposing metal stents with or without pigtail in endoscopic ultrasound-guided biliary drainage for malignant obstruction-BAMPI TRIAL: an open-label, randomized controlled trial protocol
Protocol:	BAMPI TRIAL 01-2021 version 1.3
Trial registration:	NCT 04595058
Compound:	Endoscopic ultrasound-guided biliary drainage
Phase:	N/A
Sponsor:	Hospital Universitari de Bellvitge
Coordinating Investigator	Joan B. Gornals Servei d'Aparell Digestiu. Endoscopia Digestiva Feixa Llarga s/n. L'Hospitalet Llobregat, 08907 Barcelona, España
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SAP Version:	FINAL Version 1.0
SAP Date:	February,15th 2022.

CONFIDENTIAL

DOCUMENT HISTORY

Version	Date	Author	Description
1.0	February,15th 2022.	Judith Peñafiel Muñoz	First final version

SIGNATURE

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PAGE AND APPROVALS

1. TABLE OF CONTENTS

2. ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
AE	Adverse Event
ASA	American Society of Anesthesiologists' classification
BD	Biliary drainage
BRI	Biliary reintervention
CBD	Common bile duct
CEIC	Clinical research ethics committees
CRF	Case Report Form
DPS	Double-pigtail plastic stent
eCRF	Electronic Case Report Form
EE	Electrocautery-enhanced
EDC	Electronic data capture
EUS	Endoscopic ultrasound
EUS-BD	Endoscopic ultrasound-guided biliarydrainage
FAS	Full Analysis Set
LAMS	Lumenapposing metal stent
FPFV	First Patient First Visit
ICF	Informed Consent Form
MRI	Magnetic resonance imaging
MBO	Malignant biliary obstruction
IMP	Investigational Medicinal Product
ITT	Intent-to-Treat
LPLV	Last patient completes the last visit
PI	Principal Investigator
PP	Per Protocol
PPAS	Per Protocol Analysis Set
SAE	Severe adverse events
PTBD	Percutaneous biliary drainage
t-RBO	time to RBO
RBO	Recurrent biliary obstruction
SAP	Statistical Analysis Plan
SAS	Security Analysis Set
SEED	Spanish Society of Digestive Endoscopy

SDV	Source data verification
TA	Tissue acquisition

1. OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for BAMPI TRIAL (An open label, multicenter, randomized, controlled trial of lumen-apposing metal stents (LAMS) with or without pigtail in endoscopic ultrasound-guided biliary drainage (EUS-BD) for malignant distal biliary obstruction).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analysis will be clearly identified as such in the final CSR.

In addition to the study protocol, the following documents were reviewed in preparation of this SAP:

- ICH Guidance on Statistical Principles for Clinical Trials (E9)

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

To assess the potential benefits in terms of reduction in the rate of recurrence of biliary obstruction (ROB) during the follow-up between the lumen apposing metal stent (LAMS) group and LAMS plus double-pigtail plastic stent (DPS) group.

2.1.2 Secondary Objectives

The secondary objectives are as follows:

The secondary outcomes include technical and clinical success (> 50% decrease in bilirubin at 14 days from stent placement), safety data, and other patient-relevant outcomes (time to RBO (t-RBO), number of biliary reinterventions (BRI), procedural time, and mortality rates).

Clinical

- Evaluate the efficacy in terms of clinical success (defined as a reduction of >50% in bilirubin at 14 days of EUS-BD) between the two proposed strategies.
- Evaluate the technical success of USE-DB using both strategies (LAMS vs. LAMS plus DPS)
- Evaluate the safety of EUS-BD: intra-procedural and post-procedural adverse events (AEs)
- Other patient-relevant outcomes: t-RBO, BRI, procedure time and survival/mortality rates.

Exploratory

Not planned.

Safety

Further to the primary objective of the study, the following safety objectives will be studied during ICU stay and hospital stay:

- **Nature, frequency, severity, and timing of all AES**. An AE is defined as any unwanted medical event, injury, or clinical abnormality (e.g., signs, symptoms, or abnormal laboratory results) experienced by patients during the study, whether related to the procedure or the medical device. All AEs reported by either medical staff or patients must be documented.
- **Serious Adverse Events (SAEs)** will be reported to the principal investigator within 3 days, and in case of death, notification must occur within 24 hours. AEs will be classified by severity as:
    - Mild: hospitalization for 1-3 days,
    - Moderate: hospitalization for 4-10 days, ICU admission for 1 night, or reuiring endoscopic/radiological intervention,
    - Severe: hospitalization for more than 10 days, ICU admission for more than 1 night, or necessitating surgery,
    - Fatal, following the nomenclature for AEs in endoscopy (ASGE Workshops 2010).
- **Procedure-related and device-related AEs**: Any adverse events associated with the use of the stent (e.g., pancreatitis, non-occlusion cholangitis, cholecystitis, bleeding, perforation, bile leakage) will be defined following the Tokyo criteria (2018). It is important to note that recurrent biliary obstruction (RBO) is not considered an AE but rather a result of stent occlusion or migration.Clinical laboratory test results.
- **Chronological classification of AEs**: AEs will be categorized as pre-procedure, intra-procedure, post-procedure, or as early AEs (up to 14 days from the procedure) and late AEs (after 14 days), as per ASGE guidelines. An additional follow-up phone call at 30 days will be conducted to detect any stent-related AEs, in line with the Tokyo criteria.
- **Determination of AEs**: The medical team, in consultation with the local investigator, will determine whether an AE is related to the procedure or the device, with the final approval from the principal investigator.

Safety assessments will involve reviewing patient diaries for AEs and concomitant medications, monitoring and documenting all AEs (including SAEs), performing protocol-specified safety lab assessments, measuring vital signs, and conducting other critical tests essential for safety evaluation, as specified by the protocol. The classification of AEs, their causal relationship, and severity will follow MEDDEV 2.12 guidelines (rev 8, July 2019) for medical devices.

2.2 Efficacy and Safety Endpoints (Target Variables)

2.2.1 Efficacy Variables

The primary outcome is the rate of RBO after the index procedure, detected during follow-up:
-Rate of recurrent biliary obstruction (RBO) between the two strategies (LAMS with and without coaxial DPS), detected during follow-up: RBO is associated with a stent dysfunction (an endpoint of either

occlusion or migration). Tokyo criteria
- Clinical recurrence (jaundice, fever, suspicious cholangitis, pruritus).
- Recurrence of cholestasis parameters (Any increase in GGT/ALP or bilirubin from its lowest level post-index procedure).
Both WITH evidence of biliary obstruction on imaging (dilation on US/ CT/MRI) or endoscopic findings suggesting it.

The secondary efficacy variables are as follows:

- Clinical success defined as > 50% decrease in bilirubin at 14 days from stent placement. For cholangitis, clinical success is defined as cessation of antibiotics or normalization of levels of blood inflammatory markers within 14 days of stent placement.
- Technical success defined as successful stents (LAMS, DPS, or either) between the extrahepatic biliary duct and the upper gastrointestinal tract determined by endoscopy, endosonography, or fluoroscopy.
- t-RBO or stent patency is defined as the time from stent placement until the point when symptoms associated with occlusion or migration are observed.
- BRI is defined as the need to perform a new therapeutic maneuver on the bile duct due to RBO. A distinction must be made between:

  - Endoscopic biliary reintervention (e-BRI): endoscopic procedure with the aim of optimizing the transmural BD. It includes stent cleaning, stent change, additional stent insertion, or any other stent-related endoscopic maneuver. For specific information, see Rescue options below.

  - Radiological biliary reintervention (r-BRI): interventional radiological procedure with percutaneous access, with the aim of repermeabilizing the obstructed BD.

- Procedure time
- Survival/mortality rates.

2.2.2 Safety Variables

Safety, as defined per the ASGE lexicon/Tokyo criteria for endoscopic AEs and divided into early adverse events (within 14 days of index procedure) and delayed AE (> 14 days).

3. OVERALL STUDY DESIGN AND PLAN

For full details of the study design, please see the protocol.

This is a phase IV, open-label, multicenter, randomized, controlled trial study of lumen-apposing metal stents with or without pigtail (LAMS vs LAMS-DPS) in endoscopic ultrasound-guided biliary drainage for malignant distal biliary obstruction (MDBO). Enrolment of patients was carried out by gastroenterologists, surgeons, oncologists and endoscopists who will evaluate the cases in the inpatient wards or outpatient consultation areas. All patients admitted with MDBO and clinical criteria that justify EUS-BD will be considered for consent. The investigator at each center will assess the inclusion of the patient in the study, and eligibility either as a first-line BD method, or as a rescue method after failed ERCP. The patient will be correctly informed by personnel knowledgeable about the specifics of the study, who will help to resolve any questions that may arise. The informed consent form will be signed prior to the procedure and signed copy will be given to the patient. The patient has the right to opt-out of the study at any time.

Investigators of each center will be responsible of entering all necessary criteria to an online platform that will generate the randomization sequence and participants will be randomized with an arbitrary number .A code list will be generated using R software (v 3.6.3) by randomization with a 1:1 randomization ratio, by blocks, stratified by age (<65 years-old / >65 years-old) and by the presence of liver metastases. The assumption is made that liver metastasis may elevate bilirubin and cholestasis parameters without involving bile duct obstruction. Everyone will be assigned a randomization code along with the treatment that corresponds. Once the patient meets the eligibility criteria and has provided informed consent, we will proceed to the allocation of each participant centrally, ensuring allocation concealment, and based on the randomization list. To prevent different subject recruitment rates at the various hospitals from interfering in the development of the study, the entire population will be randomized in blocks of four between the two treatment possibilities.

All eligible patients who meet the study inclusion/exclusion criteria (see section 3.2) will be invited to participate in the study consecutively.

Based on recently published data, we estimate a recurrent biliary obstruction rate of 20% vs. 1% for the LAMS alone vs LAMS-DPS groups, respectively up during the follow-up period. Investigators estimated that a population size of 40 subjects per arm should be enrolled to be able to reject the null hypothesis

that RBO rates are equal by groups, with a power of 80% (α=5%). Considering a drop-out rate of approximately 10%, the final sample size is 88 patients (44 in each arm).

The collecting of clinical information of the patients will begin at the outset (baseline) and will continue with follow-up as established and defined in the study. Data will be collected at baseline visit, indexing procedure 24 hours later, and at days 14, 30, 90, 180, 270, and 1-year post-randomization. Collected data include primary, secondary, and additional endpoint data, demographics, comorbidities, oncological data, laboratory test findings, technical details, and clinical data during follow-up

4. ANALYSIS AND REPORTING

4.1 Interim Analysis

No interim analysis is planned given the short accrual time, relatively small sample size, and short follow-up period.

4.2 Final Analysis

All final, planned analyses identified in the protocol and in this SAP will be done after the last subject has completed 1-year post-randomization visit and all relevant study data have been processed and integrated into the analysis database, data have been reviewed at a blinded data review meeting, and the database has been locked. Any post-hoc, exploratory analysis that was not identified in this SAP to support planned study analyses will be documented and reported in appendices to the CSR. Any results from unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

5. ANALYSIS SETS

The following analysis sets are planned for this study:

- **Safety Set**: The safety set includes all subjects who were allocated in any group and started endoscopic treatment.
- **Per Protocol Analysis Set (PPAS):** The PPAS set includes all enrolled patients for whom the procedure was performed according to the assigned group and without major protocol violations.
- **Intention to Treat (ITT):** The ITT set includes all enrolled patients. Patients who lost to follow-up will be analyzed based on the available data.

  The following protocol deviations may be considered as major and will lead to an exclusion of subjects form the PPAS:

  - Pigtail insertion in LAMS group
  - Non pigtail insertion in LAMS plus pigtail group
  - No intervention due patient conditions
  - Lost to follow up.

Additional protocol deviations may be considered major at the blinded data review meeting and will be documented appropriately.

If a subject is randomized incorrectly, or is administered the incorrect study intervention, analyses of the primary endpoint by ITT will be based on the assigned treatment, whereas all other analyses will be based on the treatment received.

The primary analysis will be based on the Intent-to-Treat (ITT) population, defined as all enrolled patients. As a sensitivity analysis, the analysis will be repeated based on the Per Protocol (PP) population, defined as patients for whom the procedure was performed according to the assigned group and without major protocol violations.

All subjects who signed informed consent will be considered as study participants.

6. GENERAL ISSUES FOR STATISTICAL ANALYSIS

6.1 General Statistical Methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, tables will summarize data by treatment group.

Continuous, quantitative, variable summaries will include the number of subjects (N) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise specified.

Categorical, qualitative, variable summaries will include the frequency and percentage of subjects in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the analysis set for the treatment groups, unless otherwise specified.

The primary objective for this study is assess the potential benefits in terms of reduction in the rate of ROB during the follow-up between LAMS and LAMS-DPS groups. RBO is defined as a composite endpoint of stent dysfunction (either occlusion or migration). The cumulative incidence of RBO (as a stent dysfunction parameter) in the LAMS cohort versus LAMS-DPS cohort will be compared using a Chi-Square test. The magnitude of the effect will be estimated through an incidence ratio and relative risk with 95% confidence interval. The main analysis will be replicated in an adjusted way using a binomial regression model. Age, sex, oncological status, and comorbidities will be taken as adjustment variables. Adjusted relative risk with 95% interval will be reported. Applicability conditions of the log-binomial regression model will be evaluated.

Baseline characteristics of LAMS alone and LAMS-DPS subjects will be described and evaluated using mean and standard deviation for continuous symmetric variables, median and interquartile range (Q1-Q3) for non-symmetric variables and absolute and relative frequencies for categorical variables.

To evaluate the clinical and technical success between the two proposed strategies, the cumulative incidence of both endpoints will be compared using a Chi-Square test. The magnitude of the effect will be estimated through an incidence ratio and relative risk with 95% confidence interval.

To compare BRI between groups, the cumulative incidence will be compared using a Chi-Square test. The magnitude of the effect will be estimated through an incidence ratio and relative risk with 95% confidence interval.

The other patient-relevant outcomes: t-RBO, procedure time and survival time will be compared between groups using Wilcoxon rank sum test or Kruskal-Wallis test. The differences will be expressed by median accompanied by its 95% CI estimated by bootstrapping

To study time to ROB and time to mortality, survival curves will be drawn and compared between randomization groups by means of the log-rank test. Cox regression models will be used to explore the association between randomization group and time until event/censoring. Results will be reported as HR and 95% confidence intervals. The proportional hazards assumption will be tested.

All statistical tests will be based on a 2-sided test at the significance level of 0.05 and 95% confidence intervals, unless otherwise specified.

Graphical presentations will be employed to illustrate results from the statistical analyses.

R[4] version 3.3.1 or superior will be used for the analysis.

6.1.1 Handling of Missing Data

No imputation will be done for missing data on efficacy assessments.

6.1.2 Pooling of Centres

No pooling of centers is planned.

7. STUDY SUBJECTS AND DEMOGRAPHICS

7.1 Disposition of Subjects and Withdrawals

All subjects who provide informed consent will be accounted for in this study. Descriptive summaries of analysis set data will be presented for all subjects unless otherwise specified and will include the following:

- The frequency and percent of subjects in each analysis set, overall and by treatment group and centre
- The disposition of subjects (including number of study participants, screening failures, number of subjects randomized, number of subjects treated and number of completers), overall and by treatment group and centre
- Patients who discontinue study by reason for discontinuation, overall and by treatment group
- Study withdrawals by reason for withdrawal, overall and by treatment group

In addition, all study withdrawals will be listed.

7.2 Protocol Violations and Deviations

Protocol violations and deviations will be categorized as major or minor at the blinded data review meeting before defining the analysis sets as described in Section 5.

Major protocol violations (ie those leading to exclusion from the PPAS) will be summarized by type of violation, overall and by treatment group. Individual major and minor protocol violations will be listed by subject.

7.3 Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be presented for the safety set. All demographic and baseline characteristics will be presented both overall and by treatment group.

The following demographic and baseline data will be presented:

- Demographics: Age, Sex, Etiology of biliary obstruction Relevant medical history, ASA, Charlson comorbidity index, Oncological staging, Liver metastases, Reason for EUS-BD, GOO, Diameter of common bile duct
- Initial laboratory values: Total bilirubin, ALT, AST, White cell count, Platelet count
- EUS-CDS Indication: First line EUS-BD, Failed ERCP, Time Failed ERCP to EUS-CDS
- EUS-CDS findings and technical details: Orotracheal intubation, EUS findings, EUS-FNA, EUS-BD technique, Transducer tip direction, LAMS size, DPS diameter, LAMS dilatation, Global procedure time (min)

Demographic and other baseline data will be presented using descriptive statistics only; no hypotheses will be tested.

8. EFFICACY ANALYSIS

This study will evalute the potential benefits in terms of reduction in the rate of recurrence of biliary obstruction (ROB) during the follow-up between the lumen apposing metal stent (LAMS) and LAMS plus double-pigtail plastic stent (DPS) groups.

The analyses described here are intended as confirmatory analyses.

It may be necessary to complete additional exploratory analyses after the planned analyses are completed. Full details of additional analyses will be presented in the CSR, and any such analyses will be clearly identified as post-hoc.

All statistical tests will be based on a 2-sided test at the significance level of 0.05, unless otherwise specified.

All efficacy variables will be presented with descriptive statistics, broken down by treatment group. In addition, statistical analyses will be presented as described below.

8.1 Primary Efficacy Variable Analysis

In the primary efficacy analysis, to assess the potential benefits in terms of reduction in the rate of recurrence of biliary obstruction (ROB) during the follow-up between the lumen apposing metal stent (LAMS) and LAMS plus double-pigtail plastic stent (DPS) groups. The hypotheses will be tested:

- Null hypothesis (H0): $\pi LAMS = \pi LAMS\text{-}DPS$
- Alternative hypothesis (H1): $\pi LAMS \neq \pi LAMS\text{-}DPS$

The primary efficacy analysis will compare cumulative incidence of RBO (as a stent dysfunction parameter) in the LAMS cohort versus LAMS-DPS cohort will be compared using a Chi-Square test test with a two-sided significance level $\alpha = 0.05$. The magnitude of the effect will be estimated through an incidence ratio and relative risk with 95% confidence interval. Relative risk will be performed by log-binomial regression model, using the presence (or not) of RBO as the dependent variable and group as independent variable. The main analysis will be replicated in an adjusted way using a binomial regression model. Age, sex, oncological status, and comorbidities will be taken as adjustment variables. Adjusted relative risk with 95% interval will be reported.

The primary efficacy analysis will be done in the ITT population.

8.2 Secondary Efficacy Variable Analysis

No formal statistical inferences will be drawn from secondary efficacy analyses. Any P values presented from secondary efficacy analyses will be interpreted in an exploratory sense only.

The following efficacy variables will be analyzed in the same manner as the primary analysis, but without any sensitivity analyses:

- Evaluate the efficacy in terms of clinical success (defined as a reduction of >50% in bilirubin at 14 days of EUS-BD) between the two proposed strategies.
- Evaluate the technical success of USE-DB using both strategies (LAMS vs. LAMS plus DPS)
- Evaluate the safety of EUS-BD: intra-procedural and post-procedural adverse events (AEs)
- Other patient-relevant outcomes: t-RBO, BRI, procedure time and survival/mortality rates.

To evaluate the clinical and technical success between the two proposed strategies, the cumulative incidence of both endpoints will be compared using a Chi-Square test. The magnitude of the effect will be estimated through an incidence ratio and relative risk with 95% confidence interval.

To compare BRI between groups, the cumulative incidence will be compared using a Chi-Square test. The magnitude of the effect will be estimated through an incidence ratio and relative risk with 95% confidence interval.

Relative risk will be performed by independent log-binomial regression models, using the clinical ,technical success or the BRI as the dependent variable and the group as the independent variable.

The other patient-relevant outcomes: t-RBO, procedure time and survival time will be compared between groups using Wilcoxon rank sum test or Kruskal-Wallis test. The differences will be expressed by median accompanied by its 95% CI estimated by bootstrapping

To study time to ROB and mortality , survival curves will be drawn and compared between randomization groups by means of the log-rank test. Cox regression models will be used to explore the association between randomization group and time until event/censoring, with group as the independent variable and time until event/censoring as the dependent variables. Results will be reported as HR and 95% confidence intervals.

8.3 Subgroup Analysis of Efficacy Variables

The main analysis will also be carried out in the following subgroups:

- Age <65 vs. Age >65.
- Presence of liver metastasis vs. Absence of liver metastasis.

9. SAFETY AND TOLERABILITY ANALYSIS

The analysis of safety assessments in this study will include summaries of the following categories of safety data collected for each subject:

- Adverse events
    - Adverse events (AEs), Device Deficiency, Adverse Device Effect (ADE), Serious Adverse Device Effect (SADE), Serious Unexpected Adverse Device Effect (SUADE) and serious adverse events (SAEs)
    - AEs o ADEs leading to withdrawal
    - Any deaths

All safety analyses will use the safety analysis set.

9.1 Adverse Events

All AEs, ADEs, SADEs, SUADEs and serious adverse events (SAEs) will be coded using the MedDRA , ASGE lexicon, Tokyo guidelines, and their causal relationship, and severity will follow MEDDEV 2.12 guidelines for medical devices (the most recent version before starting the trial will be used).

AE is any unwanted medical event, injury or clinical (e.g., signs, symptoms, or abnormal laboratory results) suffered by patients during the study, whether related to the endoscopic procedure or stent. All AEs (reported by medical staff or patients) must be documented.

All AEs will be summarized in a table whose rows give the number and percentage of subjects reporting at least one AE and the number of reported AEs for each of the following:

- Any AE
- Any ADE
- Any serious ADE
- Any related serious ADE
- Any serious ADE leading to death
- Any drug-related ADE
- Any severe ADE
- Any ADE requiring additional therapy
- Any ADE leading to discontinuation of study medication
- Any ADE of special interest

Summaries of incidence rates (frequencies and percentages of subjects reporting at least one AE) and the number of reported AEs of individual ADE s by MedDRA SOC and preferred term will be prepared. Such summaries will be displayed for all SUARs, ADE s by maximum intensity, and ADE s by strongest relationship to study medication.

Each subject will be counted only once within each preferred term. If a subject experiences more than 1 ADE within a preferred term, only the ADE with the strongest relationship or the maximum intensity, as appropriate, will be included in the summaries of relationship and intensity.

The most frequent ADE, defined as PTs reported in more than 5% of subjects in any treatment group will also be summarised.

Absolute and percentage differences of all declared adverse events will be describe by diet group and causal relationship between adverse event and investigational medicinal product.

In the AE data listings, all AEs will be displayed. Adverse events that are not treatment-emergent will be flagged.

9.1.1 Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages of subjects) and number of episodes of ADE s leading to withdrawal, by treatment group, SOC, and preferred term, will be prepared.

A data listing of AEs leading to withdrawal of study medication will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2 Serious Adverse Events

A summary of incidence rates (frequencies and percentages of subjects) and number of episodes of SAEs by treatment group, SOC, and preferred term will be prepared.

A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF system, with Lowest Level Terms (LLT) such as “feeling queasy” being most specific

9.2 Clinical Laboratory Test Results

Descriptive summaries of clinical laboratory test will be not planned.

9.3 Exposure and Compliance

Not planned.

10. CHANGES FROM PLANNED ANALYSIS

No changes from the analyses specified in the protocol are planned.

11. OTHER PLANNED ANALYSIS

No other analyses are planned for this study.

12. REFERENCES

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

2.ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm

3.RSS. (1993) The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.

4.**R Core Team** (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/

13. TABLES, LISTINGS, AND FIGURES

The description of the planned tables, listings and figures will be provided in this section in the next version of this SAP

13.1 Planned Table Descriptions

The following are planned summary tables for the study. The numbering is intended to be compatible with the format of clinical study reports as per ICH E3 (ICH, 1995), so tables are included in section 14 of the report.

Table Number	Population(s)	Table Title / Summary
14.1 Demographic and baseline tables		
14.1.1	ALL	Analysis populations
14.1.2	SAS	Summary of Baseline characteristics
14.1.3	SAS	Summary of EUS-CDS Indication
14.1.4	SAS	Summary of EUS-CDS findings and technical details
14.1.5	SAS	Summary of Initial laboratory values
14.2 Efficacy tables		
14.2.1	ITT	Primary outcome
14.2.2	ITT	Multivariate analysis RBO
14.2.3	ITT	t-ROB
14.2.4	ITT	Secondary outcomes
14.2.5	ITT	Time to mortality
14.3 Safety and tolerability tables		
14.3.1 Displays of adverse events		
14.3.1.1	ITT	AEs by study group and causal relationship between adverse event and investigational medicinal product: summary
14.3.1.2	SAS	Clinical adverse events during study by SOC and preferred term
14.3.1.2	SAS	
14.3.1.3	SAS	

13.2 Planned Figure Descriptions

The following are planned summary figures for the study. Figures will numbered according to the ICH E3 guidelines CSRs (ICH, 1993), and so will be included in section 14, after the tables.

Figure Number	Population	Figure Title / Summary
14.4 Efficacy figures		
14.4.1	ITT	Primary outcome
14.4.2	ITT	t-ROB
14.4.3	ITT	Secondary outcomes

14. TABLE SHELLS

Table shells will be provided in a separate document.

SUPPLEMENTARY_2 to manuscript (Suppl. Tables and Figures):

Title: Lumen-apposing Metal Stents with or without Plastic Pigtail in Endoscopic Ultrasound-Guided Biliary Drainage for Malignant Obstruction (BAMPI study): a Multicenter Randomized Controlled Trial.

Table of contents:

Table S1: Number of included patients and name of the principal investigator per hospital. Page 2.

Hospital	Principal Investigator	Selected patients (n)	Included patients (n)	LAMS group (n)	LAMS-DPS group (n)
Hospital Universitari de Bellvitge, Barcelona*	Joan B Gornals	+11	28	11	17
Hospital Universitario de Alicante, Valencia	Jose R Aparicio-Tormo	+2	18	9	9
Hospital Universitario de Castellon, Valencia	Rafael Pedraza	+10	17	12	5
Hospital Clínico de Valencia, Valencia	Vicente Sanchiz	+2	11	6	5
Hospital Universitario Rio Hortega, Valladolid	Carlos De-la-Serna	+3	8	4	4
Hospital Universitario Mutua Terrassa, Barcelona	Carme Loras	+3	7	4	3
Hospital Universitario Ramón y Cajal, Madrid	Enrique Vazquez-Sequeiros	0	2	1	1
Total	..	123	91	47	44

*****Coordinating centre. All centers are member of the Spanish Society of Gastrointestinal Endoscopy (SEED), Spain, Europe.

Table S2: Inclusion and exclusion criteria. Page 3.

Inclusion criteria: **Patients eligible for the trial must fulfil all the following at randomization** - Age 18 years or more - Malignant distal biliary obstruction* with clinical criteria that justify EUS-guided biliary drainage. - Capable of understanding and signing informed consent form. - Understanding the type of study and complying with the follow-up of complementary tests during the study's duration.
Exclusion criteria: **Patients with any of the following will be excluded** - Pregnancy or breast-feeding. - Severe coagulation disorder: INR > 1.5 not correctible with administration of plasma and/or platelets < 50,000/mm3. - Maximum cross diameter of the CBD <10mm. - Another type of biliary drainage at the time of the procedure (cholecystostomy, percutaneous drainage, etc.). - Failure to sign informed consent form. - Intellectual handicap or unable to understand the nature and possible consequences of the study, unless there is a competent legal representative. - Unable to adhere to subsequent follow-up requirements.

Published in Trials 2022. Supplementary appendix_1.
*Secondary to resectable, locally advanced, or unresectable cancers.
CBD common bile duct; EUS endoscopic ultrasound; INR international normalized ratio.

Table S3: Other baseline characteristics of patients and procedural data according to group. Page 4.

	LAMS group (N=47)	LAMS-DPS group (N=44)
Patient characteristics and clinical details		
Medication -n (%) *		
Anti-platelet/anti-thrombotic agent	40 (95)	31 (78)
Anti-coagulation agent	2 (5)	9 (22)
Initial laboratory values - mean (SD)		
AST, U/L ł	238 (184)	189 (138)
GGT, U/L ǂ	1058 (885)	1067 (864)
Albumin ¶	32 (6)	30 (8)
PT - median (IQR) ‖	1.23 (1.1-1.42)	1.20 (1.0-1.3)
Biliary drainage indication – n (%)		
Obstructive jaundice	43 (92)	42 (96)
Acute cholangitis	4 (8)	2 (4)
Procedure details		
Sedation – n (%)		
General anesthesia	8 (17)	8 (19)
Conscious sedation	38 (83)	35 (81)
Reasons for ERCP failure - n (%)		
Failure in biliary cannulation	15 (60)	22 (71)
Duodenal stenosis	10 (40)	9 (29)
ERCP duration. min - median (IQR) ǂǂ	18 (6-43)	15 (8-40)
Distance from CBD and EUS-scope tip, mm - mean (SD) ł ł	4 (3)	4 (2)
EUS-TA, n (%)	28 (61)	27 (63)
EUS-CDS access technique – n (%)		
Free-hand with preloaded guidewire	26 (58)	27 (68)
Free-hand without preloaded guidewire	15 (33)	8 (20)
Classic technique (needle-guidewire first)	4 (9)	5 (12)
Dilation after CDS, yes / no – n (%) ¶¶	4 (9) / 40 (91)	2 (5) / 38 (95)

Data are median (IQR), mean (SD), n (%), or n/N (%). *Data missing for one patient 9 patients ł Data missing for 25 patients ǂ Data missing for 16 patients. ¶ Data missing for 28 patients. ‖ Data missing for 28 patients. ** Data missing for patients. ł ł Data missing for 10 patients. ¶¶ Data missing for one patient. AST, aspartate transaminase; DPS, double-pigtail plastic stents; EUS-CDS, endoscopic ultrasound-guided biliary choledochoduodenostomy; EUS-TA endoscopic ultrasound-guided tissue acquisition; GGT gamma-glutamyl transferease; GOO, gastric outlet obstruction; LAMS, lumen-apposing metal stents; PT, prothrombin time.

Table S4: Primary and secondary outcomes according to the per-protocol analysis. Page 5.

	LAMS group (N=44)	LAMS-DPS group (N=40)	Effect [1,2]	P value
Primary outcome				
Recurrent biliary obstruction (IQR) - n (%)	14 (32)	4 (10)	0.31 (0.09-0.77) [1]	0.02
Secondary outcomes				
Time-to RBO	68 (28-156)	155 (63-242)	-86.5 (-146.5,-1) [2]	0.07
Biliary re-interventions - n (%)	12 (27)	5 (12)	0.45 (0.15-1.09) [1]	0.09
Technical success – n (%)	39 (89)	37 (92)	1.04 (0.91-1.2) [1]	0.54
Clinical success – n (%)	37/44 (84)	34/40 (85)	1.01 (0.83-1.23) [1]	0.90
Procedure time, mins ɬ				
Median (IQR)	21 (16-37)	32 (20-60)	-11 (-29, -2) [2]	0.01
Overall length of hospital stay, days *				
Median (IQR)	9 (4-18)	5 (3-10)	4.5 (0, 9) [2]	0.01
Safety, global SAEs – n (%)	9 (20)	12 (30)	1.47 (0.7-3.25) [1]	0.31
Other outcomes				
Fluoroscopy assistance – n (%)	31 (70)	36 (90)	1.28 (1.03-1.59) [1]	0.10
Rate of pancreaticoduodenostomy - n (%)	4 (8)	3 (7)	..	..
Mortality rate – n (%)	1 (2)	5 (12)	5.5 (0.94-103) [1]	0.09
Mean survival time, days - median (IQR)	129 (54-230)	164 (63-260)	-35 (-141, 62) [2]	0.66

Data are n (%) or median (IQR). Effect includes different analyses: [1]Relative risk (95%CI); [2]median difference (95%CI). LAMS as reference group. ɬ Data missing for 2 patients (in LAMS group). *Data missing for 3 patients (in the LAMS group).
SAEs, serious adverse events; DPS, double-pigtail plastic stent; LAMS, lumen-apposing metal stent; RBO, recurrent biliary obstruction.

Table S5: Procedural interventions other than secondary outcomes. Intention-to-treat. Page 6.

n (%)	LAMS group (N=47)	LAMS-DPS group (N=44)
Technical failure, (n = 14) – n (%)	7 (15)	7 (16)
Causes for technical failure *		
Procedural -related, n= 8	5	3
Failure inserting DPS within LAMS [a,b]	0	2
LAMS mis-deployment [c,d,e,f,g]	4	1
Bleeding post-puncture [h]	1	0
Non-procedure-related, n=6	2	4
Inaccessible bile duct from bulb [i, j]	1	1
Patient fragility [k]	1	3
Salvage drainage for technical failure	5	2
SEMS within previous failed CDS/LAMS [c,d,e,f]	4	0
Transpapillary stent- ERCP [g]	0	1
HGS + antegrade + (GE) [j]	1	0
HGS + (GE) [i]	0	1
Other additional endoscopic procedures (same intervention), n	x	y
EUS-Celic plexus neurolysis	1	0
Esophageal stent	1	0
Enteral stent	1	0
EUS-gastroenterostomy, n ǁ	4	5
Prior/same time/after to the EUS-CDS	0 / 1/ 3	1 / 1/ 2

*Explanations for each case:
a,b Failure advancing DPS (7F x 5cm, 7F x 3cm).
c LAMS mis-deployment (or doubt); LAMS removal and salvage with biliary SEMS.
d,e,f LAMS mis-deployment (or doubts); salvage with coaxial biliary SEMS.
g Transpapillary biliary SEMS via ERCP.
h Bleeding after puncture forced stop of procedure.
i no optimal EUS window.
j multiple interposal vessels in EUS window drained by EUS-HGS and antegrade drainage.
k Excluded cases where endoscopic biliary drainage was not performed due to unfitness of patient for interventional procedure (anesthesiologist decision).

CDS, choledochoduodenostomy; DPS, double-pigtail plastic stent; EUS, endoscopic ultrasound; GE, gastroenterostomy; HGS, hepaticogastrostomy; LAMS, lumen-apposing metal stent; SEMS, self-expandable metal stent.

Table S6: **Case by case of 'recurrent biliary obstruction' description.** Page 7-8.

No	Age (y)	Group	SAEs	Time to RBO (d) ǁǁ	Con. GOO	BRI	Findings (Imaging or/and endoscopy)	Type ¶	Therapy interventions (including BRI)	Type¶	Comments	Outcome
1	53	LAMS-DPS	Cholangitis	186	No	Yes	Food impaction + DPS migration	2b	Coaxial DPS	A	None	Favorable
2	70	LAMS	Jaundice	182	No	Yes	Food impaction	2b	Coaxial DPS + Balloon	B	None	Favorable
3	74	LAMS	Cholangitis	75	No	Yes	Food impaction	2b	Coaxial DPS	A	None	Favorable
4*ǁ	72	LAMS-DPS	Jaundice	64	Yes	Yes	Food impaction	2b	Coaxial DPS	A	Clinical persistence	Persistence
4*ǁ	72	LAMS-DPS	Jaundice	68	Yes	Yes	Food impaction	2b	SEMS through LAMS	C	After 4 days → DPS exchange for SEMS through LAMS	Favorable
5	79	LAMS-DPS	Cholangitis	200	No	Yes	Food impaction + DPS migration	2b	Balloon + SEMS through LAMS	B, C	None	Favorable
6	92	LAMS	Jaundice	52	No	No	Signs of stent dysfunction **	NA	Non endoscopic. Adjusted antibiotics	-	Dilated intra/extrahepatic ducts. Fragility. Medical team and family agreed on conservative measures	Death
7	70	LAMS-DPS	Cholangitis	125	No	Yes	Stone/Sludge impaction	2a	Coaxial DPS + Balloon	A	DPS wrapped within food debris, CBD cleaning, and DPS replacement	Favorable
8 †	77	LAMS	Cholangitis	51	Yes	Yes	Food impaction	2b	Coaxial DPS + Balloon	A, B	First RBO treated by endoscopy	Favorable
8 †	77	LAMS	Cholangitis	151	Yes	Yes	Food impaction	2b	PTBD	NA	Second RBO with HD instability, treated by radiology	Favorable
9	78	LAMS	Cholangitis	154	No	Yes	LAMS compression on biliary side	3a	Coaxial DPS + Balloon	A, B	None	Favorable
10	75	LAMS	Cholangitis	156	No	No	Signs of stent dysfunction **	NA	Non endoscopic. Adjusted antibiotics	-	Dilated intra/extrahepatic ducts.Fragility.	Favorable
11	74	LAMS	Cholangitis	71	No	Yes	Food impaction	2b	Coaxial DPS + Balloon	A, B	None	Favorable
12	71	LAMS	Cholangitis	210	Yes	Yes	LAMS migration	4	Transpapillary USEMS / ERCP	D1	Significant tumoral reduction after chemotherapy allowing access to the papilla with duodenoscope	Favorable
13	68	LAMS	Cholangitis	34	No	No	Signs of stent dysfunction **	NA	Non endoscopic. Adjusted antibiotics.	-	Dilated intra/extrahepatic ducts. Fragility. Medical team and family agreed on conservative measures	Favorable
14 ł	77	LAMS	Cholangitis	26	Yes	Yes	LAMS migration	4	SEMS + DPS through CDS fistula	NA	Clinical persistence	Persistence
14 ł	77	LAMS	Cholangitis	31	Yes	Yes	LAMS migration	5	EUS-GB + EUS-GE	NA	Biliary drainage optimized with EUS-GB. Last, EUS-GE for GOO	Favorable
15ǂ	68	LAMS	Cholangitis	15	Yes	Yes	Food impactation and Sump syndrome	1	Coaxial DPS + Balloon	A, B	Initial improvement, with resolution of clinical symptoms. Clinical relapse after 10 d	Relapse
15ǂ	68	LAMS	Cholangitis	25	Yes	Yes	GOO	5	EUS-GE	NA	After 10 days, EUS-GE was performed	Relapse
15ǂ	68	LAMS	Cholangitis	85	Yes	Yes	GOO	1	EUS-GB	NA	After 2 months, another cholangitis episode. DPS removal. EUS-GB performed due to suspicion of sump syndrome	Favorable

16	54	LAMS	Cholangitis	60	No	Yes	Food impaction	2b	Balloon	B	None	Favorable
17	87	LAMS	Jaundice	26	No	Yes	Food impaction	2b	Coaxial DPS + Balloon	A, B	None	Favorable
18	77	LAMS	Cholangitis	201	No	No	Signs of stent dysfunction **	NA	Non endoscopic. Adjusted antibiotics.	-	Dilated intra/extrahepatic ducts. Fragility. Biliary sepsis leading to exitus after 48 hours.	Death

***** Patient randomly assigned to the LAMS-DPS group, but DPS could not be placed due to technical failure. ‖ † ǂ ǂ Same patient (presented >one RBO episode).
¶ Recently published specific classification (Multicenter evaluation from the Leuven-Amsterdam-Milan Study Group) [20].
‖‖ RBO defined as a composite endpoint of stent dysfunction (either occlusion or migration).
** Fragile patients with signs of stent dysfunction/occlusion (RBO) only by imaging studies. Endoscopy not performed. More details in published protocol [22].
BRI, biliary reintervention; CDS, choledochoduodenostomy; CT, computed tomography; Con, concomitant; DPS, double-pigtail plastic stent; EUS, endoscopic ultrasound; EUS-GB, guided gallbladder drainage; EUS-GE, guided gastroenterostomy; GOO, gastric outlet obstruction; LAMS, lumen-apposing metal stent; PTBD, percutaneous transhepatic biliary drainage; RBO, recurrent biliary obstruction; SAEs, serious adverse events; SEMS, self-expandable metal stent; US, ultrasound.

Table 3. Safety outcomes. Number of global serious adverse events.

	LAMS group (n/N=9/47)	LAMS-DPS group (n/N=12/44)	Effect [1,2]	P value
SAEs <14 d - n (%)	5 (10)	6 (13)	1.28 (0.41-4.17) [1]	0.66
Intra-procedural	1 (2)	3 (7)	..	..
- Cholecystitis	0	1 (16)	..	..
- Bleeding	1 (20)	2 (33)	..	..
- Abdominal sepsis	1 (20)	1 (16)	..	..
- Non-obstructive cholangitis*	2 (40)	1 (16)	..	..
- Perforation	0	1 (16)	..	..
- COVID-19 pneumonia	1 (20)	0	..	..
Time to SAEs, d - median (IQR)	4 (3-7)	3 (3-4)	0.5 (-4,9.5) [2]	0.78
SAEs >14 d – n (%)	4 (8.5)	6 (13)	1.6 (0.49,5.92) [1]	0.44
- Cholecystitis	1 (25)	3 (50)	..	..
- Bleeding	1 (25)	0	..	..
- Abdominal sepsis	1 (25)	0	..	..
- Non-obstructive cholangitis ł	0	1 (16)	..	..
- Pulmonary embolism	0	1 (16)	..	..
- COVID-19 pneumonia	1 (25)	1 (16)	..	..
Time to SAEs, d - median (IQR)	60 (44-94)	48 (29-73)	..	..
Severity (ASGE) *, n=17	7	10		
- Mild	2 (28)	0		
- Moderate	3 (43)	5 (50)		
- Severe	1 (14)	0		
- Fatal	1 (14)	5 (50)	..	..
Severity (AGREE) ǂ, n=17	7	10	..	
- I	0	0	..	..
- II	3 (43)	0	..	..
- III a/b	3 (43) / 0	5 (50) / 0	..	..
- IV a/b	0	0	..	..
- V	1 (14)	5 (50)	..	..

Data are n (%) or median (IQR). Effect includes different analyses: [1]Relative risk (95%CI); [2]median difference (95%CI).

ł Non-obstructive cholangitis defined as clinical symptoms or signs, without dilation of the drained duct or suspicion of stent occlusion/migration (details on published protocol [22]. *ǂ specific endoscopic classifications [23,24].

DPS, double-pigtail plastic stent. LAMS, lumen-apposing metal stent; SAEs, serious adverse events; RR, relative risk.

Table S8: Global number of related-adverse events. Case-by-case description. Page 10-11.

No	Age (years)	Group	SAEs	Time to AE (days)	Severity (AGREE)	Diagnostic intervention	Findings	Therapy interventions	Outcome
1	53	LAMS-DPS	Bleeding	24h	IIIa	Upper endoscopy	Blood clots. Pyloric laceration with a visible vessel. No detection of active bleeding	Endoscopic therapy (clips and sclerosis)	Favorable
2	79	LAMS-DPS	Sepsis after EUS-CDS and EUS-GE	3	V	CT-scan	No identification of local complications (no suspicious of perforation)	Adjusted antibiotics. Vasoactive drugs after intensive-care unit admission	Death after ICU admission
3	75	LAMS-DPS	Cholecystitis	5	IIIa	US/CT-scan, upper endoscopy/ERCP	Early cholecystitis. No suspicion of perforation, or stent dislodgement/migration	Adjusted antibiotics. Precut. Cholecystostomy, no significant improvement. LAMS removal after 27 days. Transpapillary SEMS by rendezvous technique	Favorable
4	79	LAMS	Non-obstructive colangitis*	4	IIIa	CT scan, upper endoscopy/ERCP	Cholangiogram. No detection of obstruction signs or stent dislodgement/migration	Adjusted antibiotics	Favorable
5	83	LAMS	Bleeding	0 (intrapr)	IIIa	Upper endoscopy	Duodenal active bleeding during puncture using enhanced-electrocautery-tip of LAMS catheter	Endoscopic therapy. LAMS not released. Optimal biliary drainage through CDS fistula without stent. Multidisciplinary committee decided conservative management	Favorable
6	84	LAMS-DPS	Cholecystitis	18	IIIa	US/CT-scan	Signs of acute cholecystitis	Percutaneous cholecystostomy.	Favorable
7	79	LAMS-DPS	Cholecystitis	48	V	CT-scan	Signs of acute cholecystitis. Progressive poor clinical course leading to biliary sepsis	Adjusted antibiotics	Death
8	81	LAMS-DPS	Cholecystitis	81	V	CT scan	Signs of acute cholecystitis. Progressive poor clinical course leading to biliary sepsis	Adjusted antibiotics	Death
9	71	LAMS	Abdominal sepsis	174	II	CT-scan	No significant abdominal findings. Septic shock due to polymicrobial bacteremia	Adjusted antibiotics	Favorable
10	58	LAMS-DPS	CBD perforation	4	V	CT-scan	Poor placement of distal flange LAMS. CBD perforation signs.	Adjusted antibiotics. Surgery ruled out due to advanced oncologic state.	Death

11	77	LAMS	Non-obstructive cholangitis*	3	II	CT-scan	No biliary obstruction signs, stent dislodgement/migration, or significant abdominal findings	Adjusted antibiotics	Favorable
12	68	LAMS-DPS	Bleeding	3	IIIa	Upper endoscopy	No HD instability. No detection of active bleeding	No endoscopic therapy.	Favorable
13	72	LAMS	Abdominal sepsis	13	IIIa	CT-scan	Over-infected liver cysts and liver abscesses.	Adjusted antibiotics. Percutaneous drainage of liver abscess	Favorable
14	72	LAMS	Cholecystitis	67	II	US/CT-scan	Signs of acute cholecystitis	Adjusted antibiotics	Favorable
15	70	LAMS-DPS	Non-obstructive cholangitis*	23	IIIa	CT-scan, upper endoscopy /ERCP	Febrile episode and altered liver enzyme parameters. Cholangiogram. No detection of obstruction signs or stent dislodgement/migration.	Adjusted antibiotics	Favorable
16	60	LAMS	Bleeding	53	V	Upper endoscopy	HD instability. Duodenal ulcer at posterior wall with an adherent clot.	Endoscopic therapy (sclerosis)	Death
17	87	LAMS-DPS	Non-obstructive cholangitis*	8	V	CT-scan	No biliary obstruction signs, stent dislodgement/migration. or significant abdominal findings. Septic shock	Adjusted antibiotics. Vasoactive drugs	Death

Adverse events associated with biliary stents are defined by the standardized reporting system for endoscopic biliary stent placement (details on published protocol) [22-24,31].
*Non-occlusion cholangitis defined as clinical symptoms or signs, without dilation of the drained duct or suspicion of stent occlusion/migration (details on published protocol [22].
CBD, common bile duct; CDS, choledochoduodenostomy; CT, computed tomography; DPS, double-pigtail plastic stent; ERCP, endoscopic retrograde cholangiopancreatography; HD, hemodynamic; LAMS, lumen-apposing metal stent; SAEs, serious adverse events; US ultrasound.

Table S9: Case-by-case 'gastric outlet obstruction' description. Page 12.

No	Age (y)	Group	Obstruction site	Time from EUS-CDS to GOO therapy (d)	Conc. ROB	Therapy interventions	Comments	Outcome
1	70	LAMS	DI-DII	NA	No	Conservative measures	None	Favorable
2	72	**LAMS-DPS**	DI-DII	NA	**Yes**	Conservative measures	None	Favorable
3	79	LAMS-DPS	DI-DII	Same endoscopic procedure	No	EUS-GE	Septic shock at 72 hours after double endoscopic by-pass. CT-scan without significant findings. No response to medical treatment (antibiotics, vasoactive drugs). Patient passed away after 5 days in ICU	Death
4	75	LAMS	DI-DII	NA	No	Conservative measures	None	Favorable
5	92	LAMS	DI-DII	Same endoscopic procedure	No	Enteral stent	Excellent oral tolerance (GOOSS 3). Survival > 12 months	Favorable
6	67	LAMS	DI-DII	NA	NA	Conservative measures	None	Favorable
7	79	LAMS	DI-DII	Prior to EUS-CDS	No	Surgical gastroenterostomy	At the time of EUS-CDS, the patient already had a surgical gastrointestinal by-pass, with complete tolerance to oral diet	Favorable
8	80	LAMS-DPS	DI-DII	Prior to EUS-CDS	No	EUS-GE	Initial GOO initial, leading to a duodenal cancer diagnosis, and treated by EUS-GE After 8 months, obstructive jaundice and EUS-CDS	Favorable
9	77	**LAMS**	DI-DII	NA	**Yes**	Conservative measures	None	Favorable
10	84	LAMS-DPS	DII	NA	No	Conservative measures	None	Favorable
11	72	LAMS-DPS	DI-DII	NA	No	Conservative measures	None	Favorable
12	71	LAMS-DPS	DI-DII	17	No	EUS-GE	Resolution of obstructive jaundice and GOO.	Favorable
13	73	LAMS	DI-DII	NA	No	Conservative measures	None	Favorable
14	71	**LAMS**	DI-DII	NA	**Yes**	Conservative measures	Significant tumoral reduction after chemotherapy allowing access to the papilla with duodenoscope	Favorable
15	58	LAMS-DPS	DII	28	No	EUS-GE	CBD perforation during EUS-CDS with fatal evolution	Death
16	77	LAMS	DII	NA	No	Conservative measures	None	Favorable
17	85	LAMS-DPS	DI-DII	NA	No	Conservative measures	None	Favorable
18	77	**LAMS**	DII	19	**Yes**	EUS-GE	LAMS migration. SEMS+DPS placed through the CDS fistula. Biliary drainage optimized with EUS-GB. Last, EUS-GE for GOO	Favorable
19	72	LAMS-DPS	DI-DII	NA	No	Conservative measures	None	Favorable
20	68	**LAMS**	DI-DII	21	**Yes**	EUS-GE	EUS-GE for resolving GOO and RBO episodes	
21	60	LAMS	DIII –DIV	236	No	EUS-GE	Resolution of obstructive jaundice and GOO.	
22	83	LAMS-DPS	DII	NA	No	Conservative measures	None	Favorable
23*	79	LAMS	DII	Same endoscopic procedure	NA	EUS-GE	Failed EUS-CDS (Multiple interposal vessels in EUS window). Drained by EUS-HGS and antegrade drainage[113]	Favorable
24*	79	LAMS-DPS	DII	Same procedure	NA	EUS-GE	Failed EUS-CDS. Drained by EUS-GE[96]	Favorable

DIIV, duodenal portion; CDS, choledochoduodenostomy; DPS, double-pigtail plastic stent; EUS-GB, endoscopic ultrasound-guided gallbladder drainage; GE, gastroenterostomy; GOO, gastric outlet obstruction; HGS, hepaticogastrostomy; ICU, intensive care unit; LAMS, lumen-apposing metal stent; RBO, recurrent biliary obstruction. * EUS-CDS was not performed.

Table S10: Sub analysis for gastric outlet obstruction (GOO) subgroup. Outcomes. Page 13.

	LAMS group (N=12)	LAMS-DPS group (N=10)	Effect [1]	P value
Primary outcome				
Recurrent biliary obstruction (RBO) - n (%)	4 (36)	1 (10)	0.28 (0.02 – 1.50)[1]	0.21
Secondary outcomes				
Biliary re-interventions - n (%)	5 (45)	1 (10)	0.22 (0.15 - 1.09)[1]	0.13
Technical success – n (%)	9 (75)	9 (90)	1.2 (0.91 - 1.2)[1]	0.35
Clinical success – n (%)	9 (82)	7 (70)	0.84 (0.91 - 1.2)[1]	0.47
Overall length of hospital stay, days				
Median (IQR)	18 (8-24)	7 (4-10)	..	0.02
Safety – n (%)	9 (20)	12 (30)	..	
Other outcomes				
Mortality rate – n (%)	1 (8)	2 (20)	..	0.57

Data are n (%) or median (IQR). Effect analyses expressed as [1] relative risk (95%CI).
DPS, double-pigtail plastic stent; LAMS, lumen-apposing metal stent; RBO, recurrent biliary obstruction.

Table S11: Case-by-case cephalic duodenopancreatectomy description. Page 14.

No	# red Cap	Sex	Age (y)	Group	Etiology/ Status	LAMS size	EUS-CDS first-line	AEs (endoscopy)	ROB	BRI	GOO	EUS-GE	Surgeon's comments	Outcome post-CDP
1	5	M	74	LAMS	Pancreatic cancer/borcderline	6 x 8 mm	Yes	No	Yes	Yes	No	-	No incidents	No AEs
2	11	F	75	LAMS	Pancreatic cancer/borderline	6 x 8 mm	No	No	No	No	Yes	No	No incidents	No AEs
3	30	M	63	LAMS	Pancreatic cancer/resectable	6 x 8 mm	No	No	No	No	No	-	No incidents	No AEs
4	35	F	57	LAMS-DPS	Pancreatic cancer/borderline	6 x 8 mm	No	No	No	No	No	-	No incidents	Pleural effusion, intrabdominal abscess
5	56	F	72	LAMS-DPS	Pancreatic cancer/borderline	8 x 8 mm	No	No	No	No	Yes	No	No incidents	No AEs
6	92	M	68	LAMS-DPS	Pancreatic cancer/borderline	8 x 8 mm	No	Bleeding	No	No	No	-	Severe retroperitoneal fibrosis (tumoral vs inflammatory). Impossible to complete resection	Unfit for complete CDP. Doubts of EUS-CDS (LAMS) role.
7	97	F	72	LAMS	Pancreatic cancer/borderline	10 x 10 mm	Yes	Cholecystitis	No	No	No	-	No incidents	No AEs

AE, adverse events; BRI, biliary reinterventions; CDP, cephalic duodenopancreatectomy; DPS, double-pigtail plastic stent; EUS-CDS, endoscopic ultrasound-guided choledochoduodenostomy; GE, gastroenterostomy; GOO, gastric outlet obstruction; LAMS, lumen-apposing metal stent; RBO, recurrent biliary obstruction.

Figure S1: Flowchart of the BAMPI trial protocol. DPS double-pigtail plastic stent, ERCP endoscopic retrograde cholangio-pancreatography, EUS-BD endoscopic ultrasound guided biliary drainage, EE-LAMS, electrocautery-enhanced, lumen-apposing metal stent. Page 15.

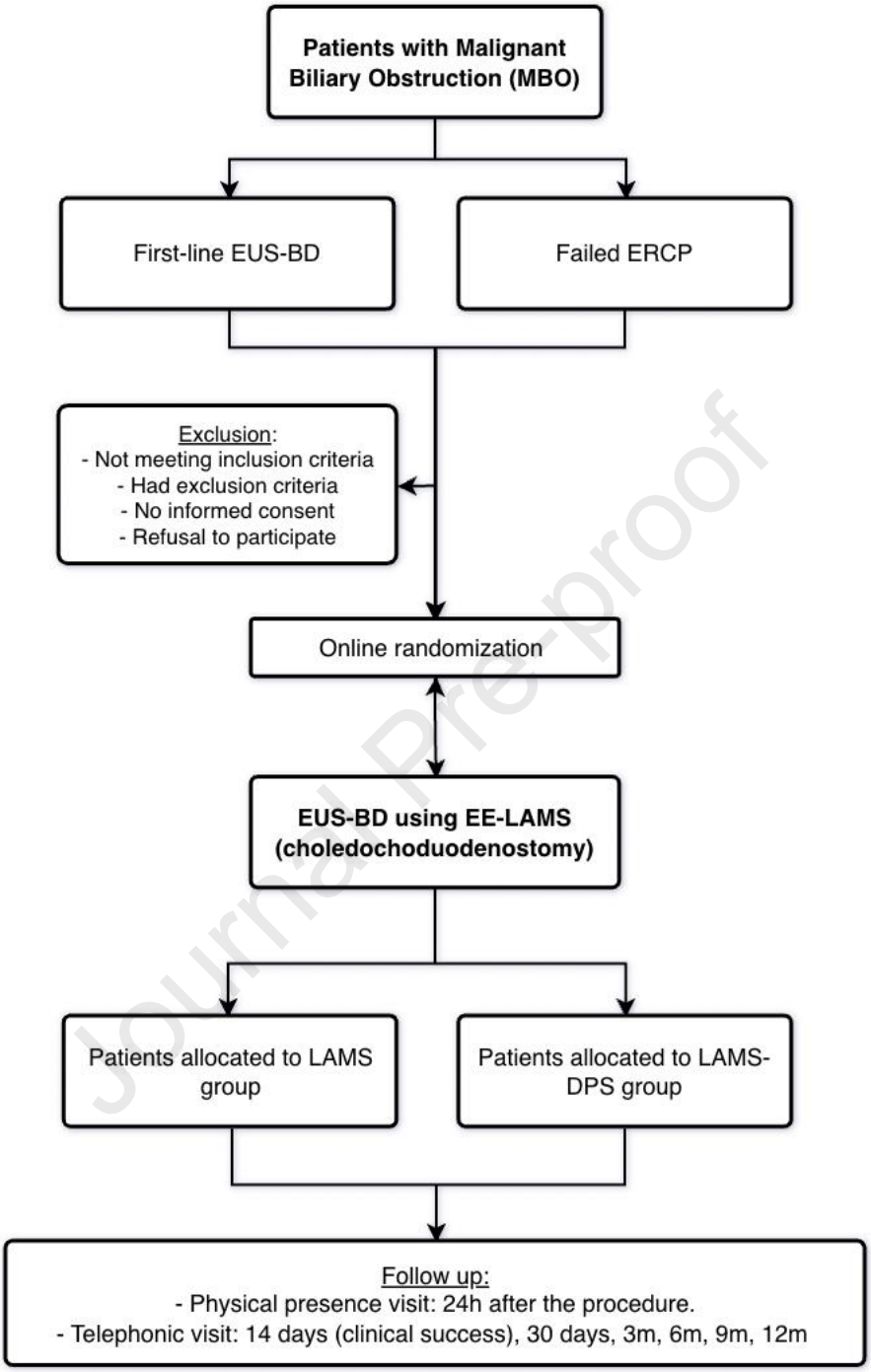
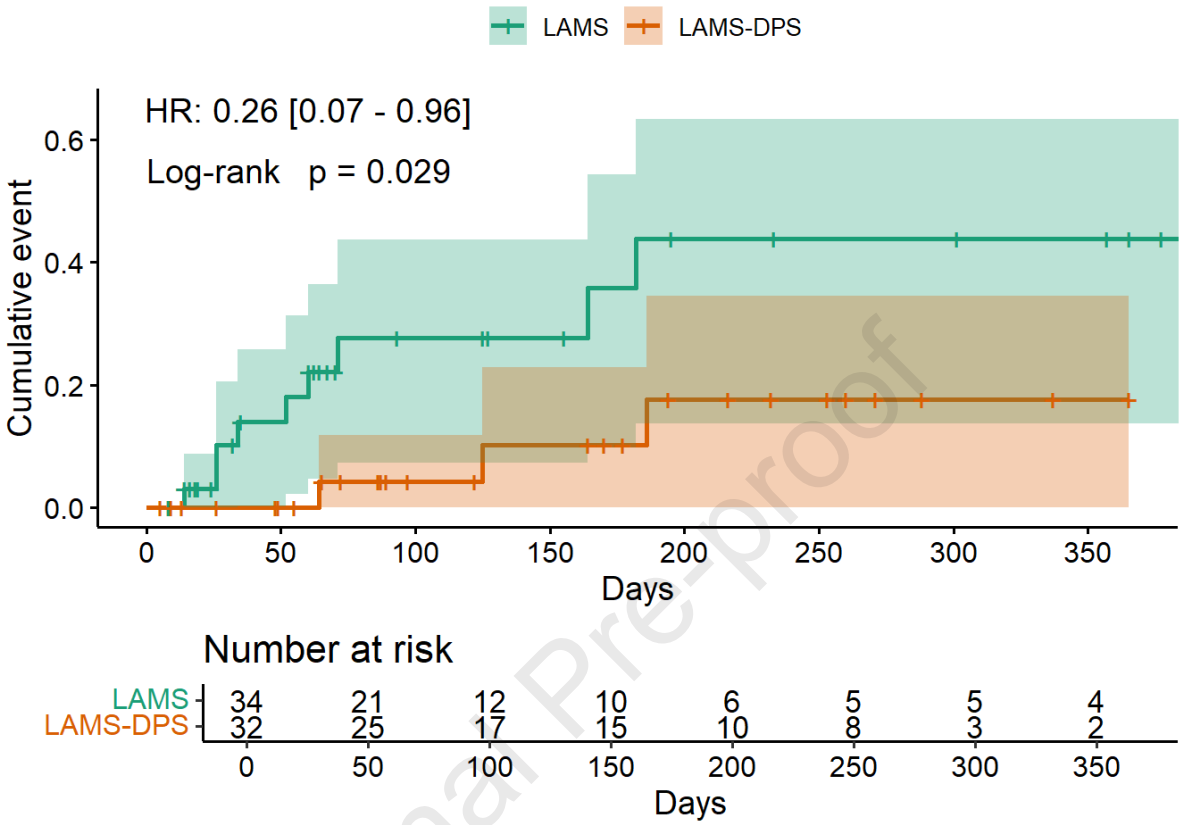


Figure S2: Kaplan-Meier. Time to RBO; (A) Palliative vs (B) non-palliative groups. DPS, double-pigtail plastic stent. LAMS, lumen-apposing metal stent. p-value of log-rank test. Page 16.

A- Palliative group



B- Non-Palliative group

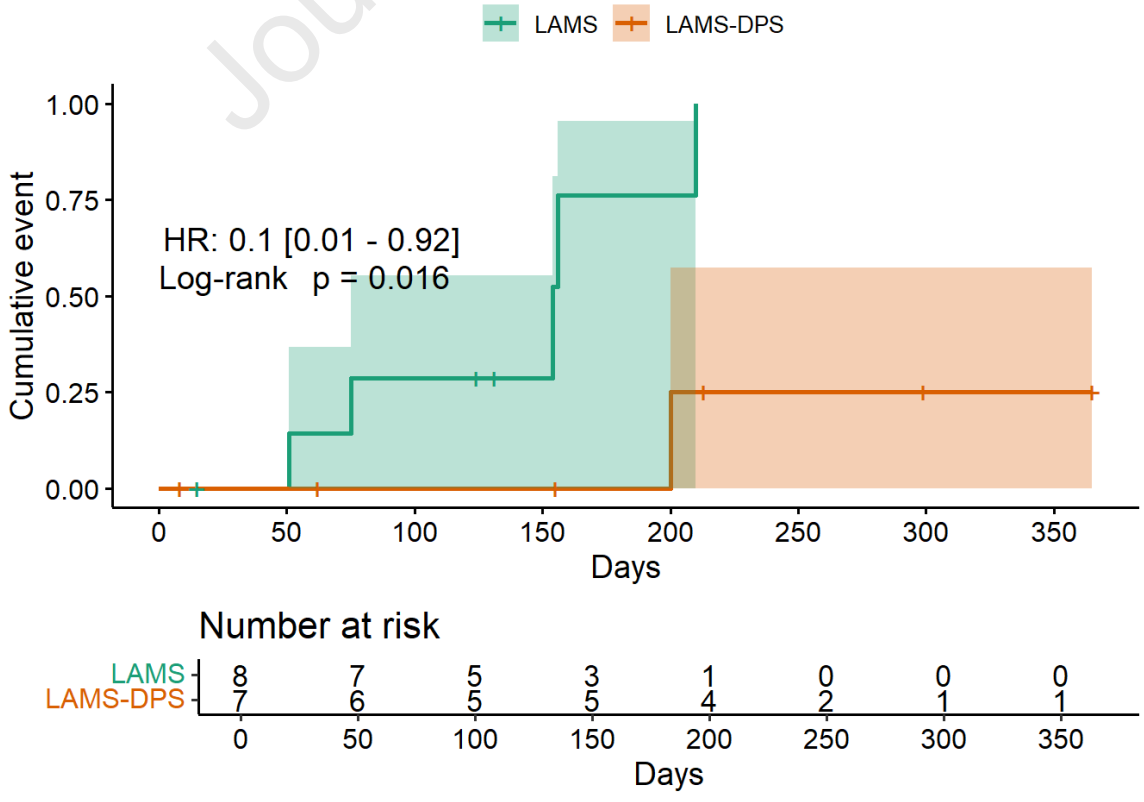


Figure S3: Kaplan-Meier. Difference between hospitalization days between the two groups. DPS, double-pigtail plastic stent. LAMS, lumen-apposing metal stent. p-value of log-rank test. Page 17.

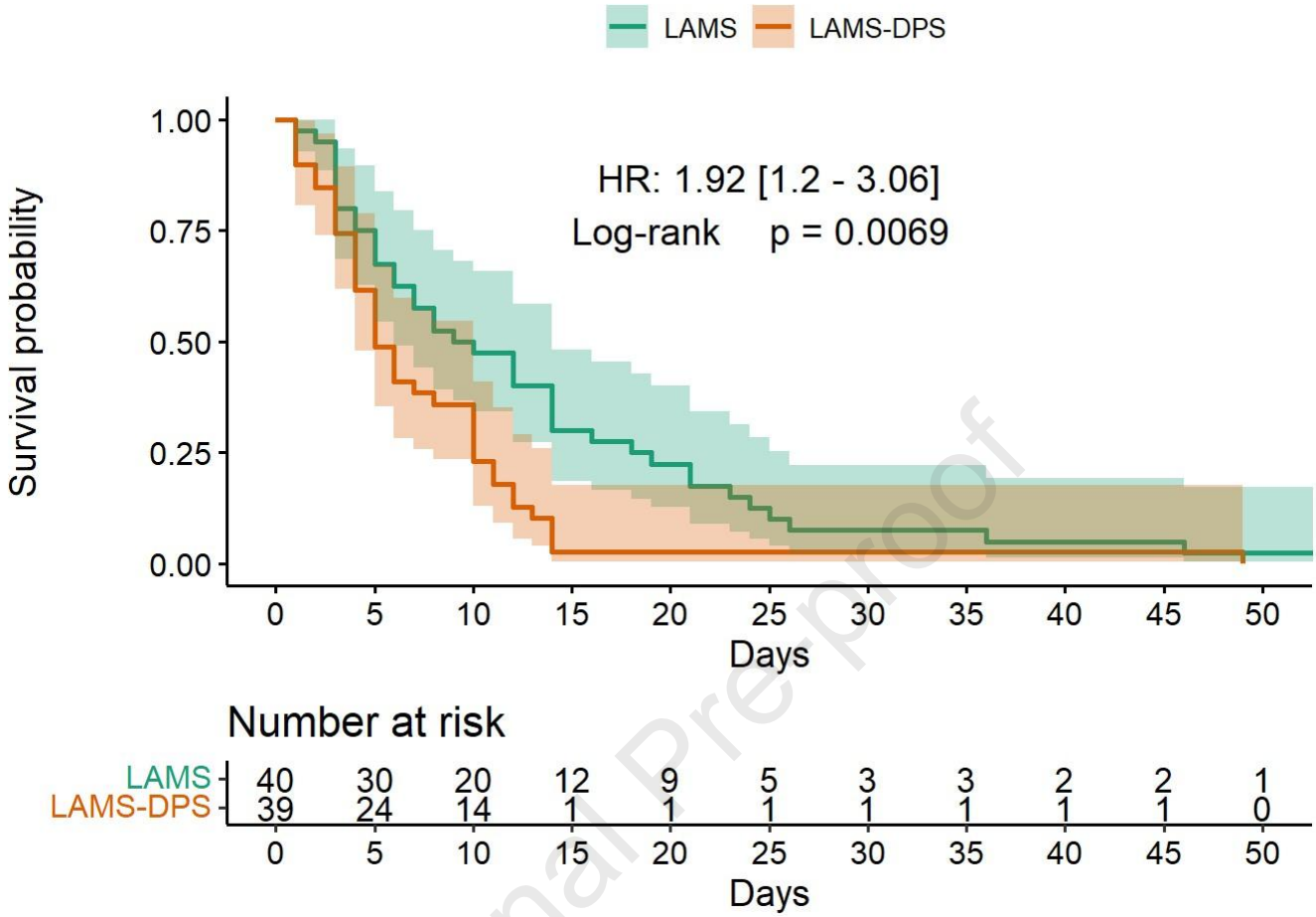


Figure S4: Global serious adverse events between groups. DPS, double-pigtail plastic stent. LAMS, Lumen-apposing metal stent. PE, pulmonary embolism. SAE, serious adverse event. Page 18.

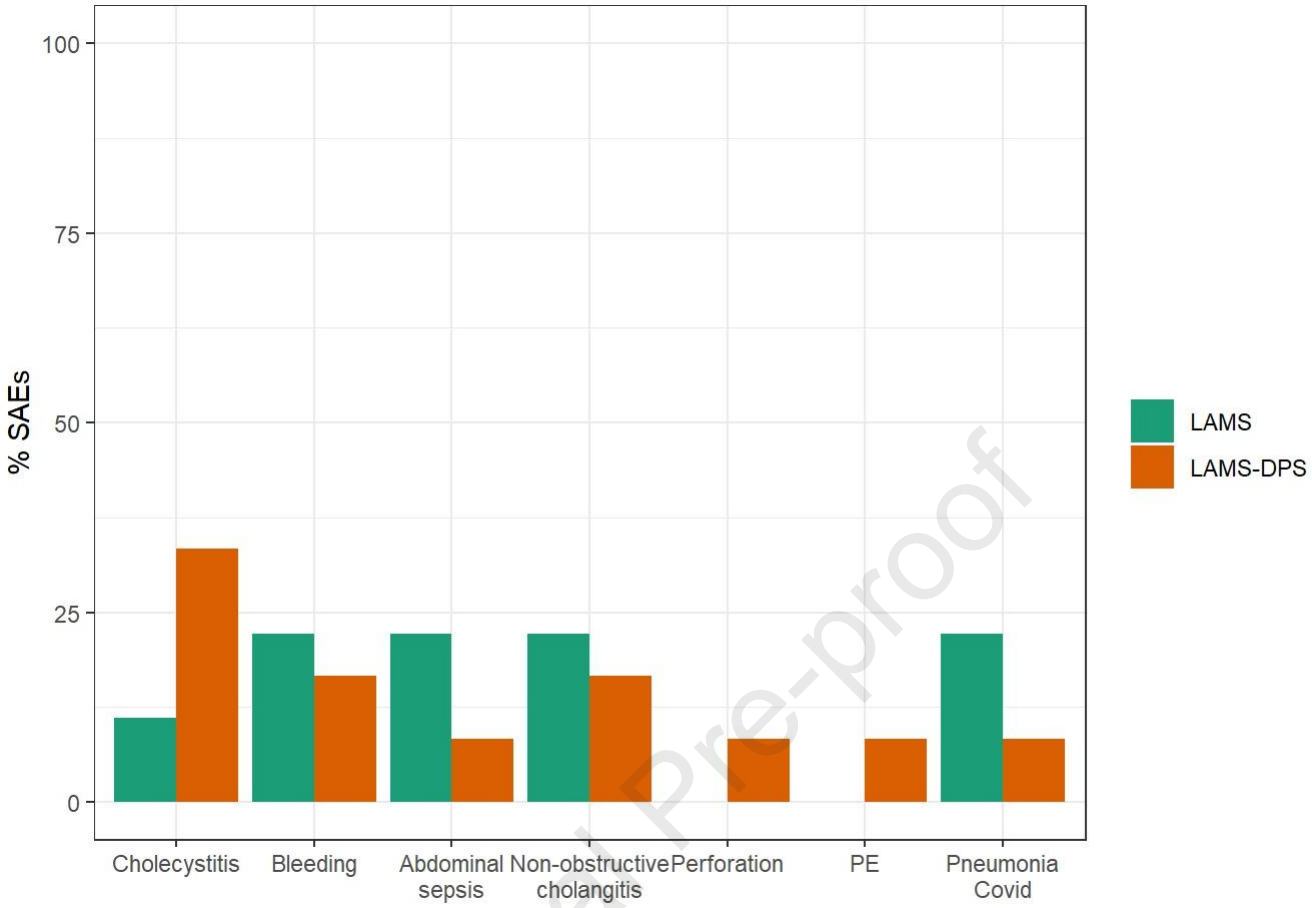
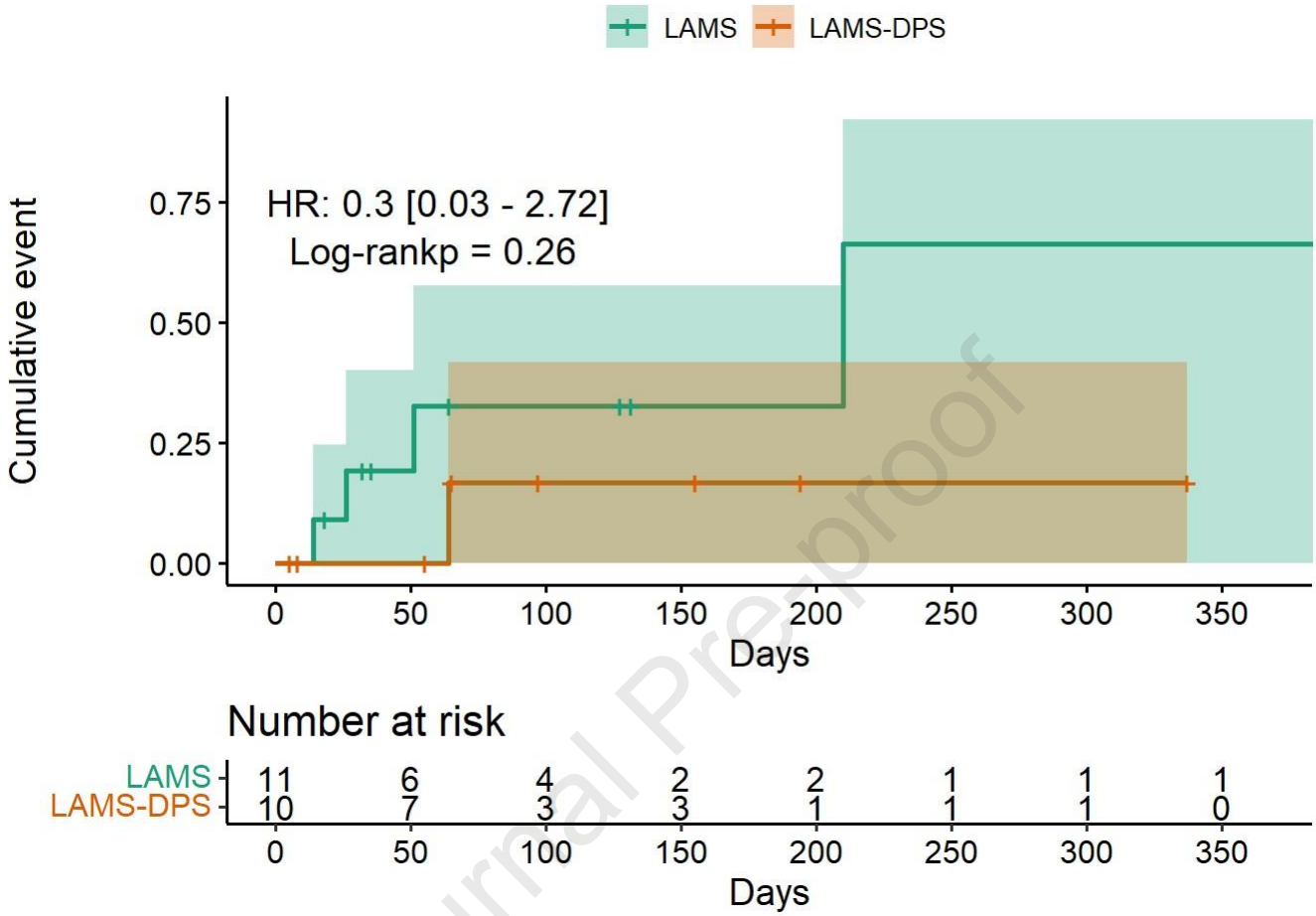


Figure S5: Kaplan-Meier. Gastric outlet obstruction sub-analysis between groups. DPS, double-pigtail plastic stent. LAMS, lumen-apposing metal stent. p-value of log-rank test. Page 19.



SUPPLEMENT_2 to manuscript (eMethods, eResults):

Title: Lumen-apposing Metal Stents with or without Plastic Pigtail in Endoscopic Ultrasound-Guided Biliary Drainage for Malignant Obstruction (BAMPI study): a Multicenter Randomized Controlled Trial.

eMethods

Study design:

Serious AEs (SAEs) were reported by clinician investigators to the coordinating team, who reported all SAEs to the DMC. The DMC did not consider stopping recruitment or making changes to the protocol for safety reasons.

Participants:

Study population. Patient identification.

The investigator at each participating center identified potential patients and assessed the inclusion of the patient in the study, and eligibility either as a first-line BD method, or as a rescue method after failed ERCP.

Randomization and masking:

Potential candidates were assessed for eligibility by study personal (gastroenterologists, surgeons, oncologists, and endoscopists) at each participating site.

Procedures:

General description of the technique

Prophylactic antibiotic was administered in accordance with the protocol of each center. All interventions were done using a linear echoendoscope, under deep sedation or general anesthesia in accordance with the directives of each center. CO_2 insufflation was used in all endoscopic procedures. EUS-CDS was performed as described in the published protocol.[22] The long-scope position was preferred to maintain stability and, if necessary, to ease advance of a guidewire in an intrahepatic direction. A small-medium sized EE-LAMS (6,8 or 10-mmm in diameter, and 8 or 10-mm in length, Hot-AXIOS stent, BostonScientific, Marlborough, USA) was used. In all cases the LAMS was deployed under EUS-guidance without tract dilation, and the use of fluoroscopy was decided upon on technical grounds and the endoscopist's criteria.

After the interventional procedure, all inpatient cases were returned to the hospital ward and discharged after clinical improvement. Outpatients spent a minimum of 24hours under clinical supervision.

If necessary EUS-guided tissue acquisition (TA) was performed prior to or immediately after the transmural drainage, with the TA technique being chosen at the endoscopists' discretion.

LAMS plus DPS group

A DPS (7-Fr x 3, 5 or 7-cm, Advanix, BostonScientific) was placed coaxially within the biliary LAMS, preferably with upward orientation (toward the liver).

Additional comments:

No removal of the stents was considered due to the malignant disease of the included cases. In case of technical failure, alternative strategies were used with the aim of offering the best possible treatment to the patient.

Outcomes:

-Technical success was defined as the successful placement of a stent (LAMS and/or DPS).

-Clinical success was defined as a 50% decrease in or normalization of total serum bilirubin level within 14 days of index procedure (stent placement). For cholangitis without obstructive jaundice, success was defined as cessation of antibiotics or a 50% decrease in or normalization of levels of blood inflammatory markers within 14 days of stent placement.

-AEs were defined as undesirable situations suffered by patients during the study, whether related or not to the procedure or stent. All AEs from the time of the signing of informed consent until 30 days after the final visit in the study calendar were recorded using the appropriate medical terminology. AEs were classified as mild, moderate, serious, or fatal, in accordance with both ASGE lexicon and last AGREE classifications. AEs were considered associated with the endoscopy procedure (or stent-related) when a causal association was possible, probable, or definite. This determination was made by the patient's medical team, the local investigator, and the PI of the study (more details, on MEDDEV_guidelines.[22]

-Time to-RBO was defined as the time from stent placement until the point when symptoms associated with occlusion or migration were observed. BRI was defined as the need to perform a new interventional maneuver in the bile duct due to RBO (including endoscopic or radiological BRI).

Depending on the oncological status, patients received oncological concomitant treatment at the discretion of the oncologist.

Statistical analysis:

We performed additional prespecified analyses to assess secondary objectives. Procedure time and length of hospitalization were compared using the Wilcoxon rank sum test or

Kruskal-Wallis test, and differences were expressed by median accompanied by its 95% CI estimated by bootstrapping.

eResults

Demographics:

In most cases, EUS-CDS was performed immediately after failed ERCP, during the same procedure; but in 13 cases it was deferred, with a mean (SD) of 5(3) days.

Mean diameter of CBD size and mean (SD) distance from transductor were 17(3) and 4(2)-mm, respectively. Freehand technique was generally preferred (90%) to the classic technique (10%). Dilation post-LAMS deployment was only performed in 7% of cases, and the median procedure time was 28 (IQR, 20-49min). The most frequently used LAMS bore sizes were 8x8-mm (56%) and 6x8-mm (39%); and the most frequently used DPS were 7-Fr x3-cm (46%).

Procedures:

Technical failures in the LAMS group (seven patients) were due to LAMS misdeployment in four, bleeding post-puncture in one, inaccessible CBD in one, and patient condition in one. Technical failures in the LAMS-DPS group (seven patients) were due to severe fragility in three, failure in inserting DPS within LAMS in two, LAMS misdeployment in one, and inaccessible CBD in one.

Salvage drainage for LAMS misdeployment (as pure technical failure) was applied in 5 patients: four SEMS through previously misplaced LAMS in the LAMS group; one transpapillary stent in the LAMS-DPS group.

In fifteen patients, dilation plus endoscopic obstruction evidence was identified: food impaction was most common in ten, followed by LAMS invasion on the biliary side in two; LAMS migration in two, and stone and sludge in one. In four fragile patients, signs of RBO were detected only by imaging studies (i.e., biliary dilation) when no BRI was performed, and only when the patient received adjusted antibiotics. Three patients with early-RBO (<30d) were relieved of initial symptoms after EUS-CDS and then developed RBO.

Additional EUS-guided TA was performed in similar proportions of the two groups (61% vs. 62%). Other types of intervention were performed in the same procedure: EUS-guided neurolysis of celiac plexus(one patient); esophageal stent(one); enteral stent(one); combined EUS-HGS+/-EUS-antegrade stenting / EUS-GE(two).

COVID-19 pandemic:

The SARS-CoV2 (COVID-19) pandemic delayed some patient follow-up windows. The extent of these delays did not negatively impact on the assessment of RBO. Somehow, all RBO cases were able to be well documented case-by-case (**Supplement-2,TableS6**).