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Plastic pigtail vs lumen-apposing metal stents for drainage of walled-off necrosis (PROMETHEUS study): an open-label, multicenter randomized trial

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Abstract

Background Lumen-apposing metal stents (LAMS) have displaced double-pigtail plastic stents (DPS) as the standard treatment for walled-off necrosis (WON),β but evidence for exclusively using LAMS is limited. We aimed to assess whether the theoretical benefit of LAMS was superior to DPS.

Joan B. Gornals and Julio G. Velasquez-Rodriguez have contributed equally to this work.

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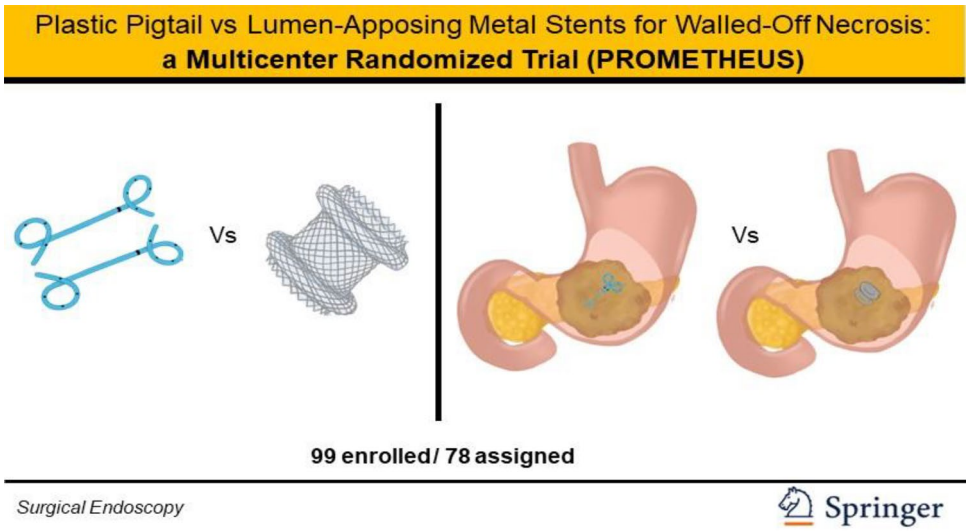
Methods This multicenter, open-label, randomized trial was carried out in 9 tertiary hospitals. Between June 2017, and Oct 2020, we screened 99 patients with symptomatic WON, of whom 64 were enrolled and randomly assigned to the DPS group ($n=31$) or the LAMS group ($n=33$). The primary outcome was short-term (4-weeks) clinical success determined by the reduction of collection. Secondary endpoints included long-term clinical success, hospitalization, procedure duration, recurrence, safety, and costs. Analyses were by intention-to-treat. ClinicalTrials.gov, NCT03100578.

Results A similar clinical success rate in the short term (RR, 1.41; 95% CI 0.88–2.25; $p=0.218$) and in the long term (RR, 1.2; 95% CI 0.92–1.58; $p=0.291$) was observed between both groups. Procedure duration was significantly shorter in the LAMS group (35 vs. 45-min, $p=0.003$). The hospital admission after the index procedure (median difference, − 10 [95% CI − 17.5, − 1]; $p=0.077$) and global hospitalization (median difference − 4 [95% CI − 33, 25.51]; $p=0.82$) were similar between both groups. Reported stent-related adverse events were similar for the two groups (36 vs.45% in LAMS vs. DPS), except for de novo fever, which was significantly 26% lower in LAMS (RR, 0.26 [0.08–0.83], $p=0.015$).

Conclusions The clinical superiority of LAMS over DPS for WON therapy was not proved, with similar clinical success, hospital stay and similar safety profile between both groups, yet a significant reduction in procedure time was observed.

Trial registration number ClinicalTrials.gov, NCT03100578.

Graphical abstract



Keywords Endoscopic ultrasound · Necrotizing pancreatitis · Randomized clinical trial · Therapeutic endoscopy · Transmural drainage

In recent years, endoscopic techniques such as the use of endoscopic ultrasound (EUS)-guided transmural drainage have been displacing surgery, as a preferable treatment for the management of walled-off pancreatic necrosis (WON) [1, 2].

Double-pigtail plastic stents (DPS) have become the standard treatment before the introduction of lumen-apposing metal stents (LAMS) [3, 4]. The potential benefits of using LAMS include the large diameter, offering better drainage or the possibility of direct endoscopic necrosectomy (DEN) [3–5]. In addition, the risk of leakage, stent occlusion, or migration is lower thanks to the design of LAMS. However, LAMS are more expensive, and their safety is controversial, with some reports suggesting a higher rate of adverse events (AEs) in comparison to plastic stents [5–7].

Although some systematic reviews or guidelines have recommended LAMS as the first-option for WON drainage, the quality of evidence is limited, and the benefits of LAMS are not yet proven [8–11].

Few studies have compared DPS with LAMS. To date, the high-level evidence comes from two single-center randomized trials and a multicenter prospective study [12–14]. A first single-center trial did not find significant differences in treatment outcomes between DPS and LAMS and raised a safety concern regarding LAMS, recommending stent

removal at 3 weeks if WON was resolved, with the aim of minimizing AEs [12]. These results were not confirmed in two more recent studies reporting comparable bleeding rate between both groups, hospitalization or costs [13, 14].

Because of this lack of clear evidence to support the routine use of LAMS, a multicenter randomized trial was designed to determine whether LAMS are superior to DPS in the endoscopic treatment of WON [15].

Material and methods

Study design

The PROMETHEUS trial was a multicenter (9 centers, Online Appendix 1, Table S1), industry-independent, open-label, parallel group, randomized, superiority trial designed to test two strategies (DPS vs. LAMS) for endoscopic transmural drainage (ETD) of symptomatic WON. The protocol was published previously, and approved by the research and ethics committees (Comité Étic d'Investigació Clínica, Bellvitge, ref.140/15) and the Spanish Agency of Medicines and Medical Devices (AEMPS), (ref.560/16/EC) [15].

This trial was registered at ClinicalTrials.gov on April 42017(NCT03100578). The recruitment study was initiated in June-2017 and ended in October-2020.

An independent data and safety monitoring board (DSMB); evaluated the progress and safety SAEs (Serious AEs) of the trial with two planned meetings (after consecutive enrolment of 10 patients in each group, and after enrolment of 25 in one of the groups). Serious AEs (SAEs) were reported by clinician' investigators to the coordinating team supervised by the Spanish Platform of Clinical Research Network and (SCReN), who reported all SAEs to the AEMPS, the DSMB, and the local ethics committee. The DSMB did not consider stopping recruitment or making changes to the protocol for safety reasons.

The study was conducted in accordance with CONSORT guidelines and with the principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice. Clinical monitoring was performed by an independent monitoring platform (SCReN).

Participants

Patients with a local complication in acute pancreatitis were eligible as candidates for EUS-guided transmural drainage of WON-type collection. The term WON (a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall) was used in accordance with the revised Atlanta classification [16]. At least two imaging tests (CTMD, MRI or EUS) were required prior to the transmural drainage, and the results needed to be in agreement with the classification of the collection as WON. Only in case of radiological doubts, two radiologists (SRO,DL) from the coordinator center, with expertise in pancreatic diseases, reviewed the imaging studies from other participating centers. Asymptomatic patients, without clinical indication of drainage, were excluded, except for those with vascular compression involvement. The inclusion and exclusion criteria are listed in Online Appendix 1 (Table S2).

Randomization and masking

Random assignment was displayed in our web-based (password-protected) program by the endoscopist before the procedure. Patients were randomized equally to receive DPS or LAMS with a random number table generated by an independent online platform. A code list was generated with a 1:1 randomization ratio, by blocks, stratified by centers and ASA, to keep numbers balanced. Patients and researchers were not masked to the treatment allocation, given the difference between the two stent types.

Procedures

Interventions were performed by endoscopists with previous experience in ETD with metal and plastic stents, and a minimum of 10 procedures per year, in addition to appropriate material at their disposal for carrying out an ETD with both types of stents.

General description of the technique

Prophylactic antibiotic was administered in accordance with the protocol of each center, and antibiotics were administered when infection was suspected or evidenced. 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. ETD was performed, as described in the published protocol [15].

After the interventional procedure, all inpatient cases were returned to the hospital ward and discharged after clinical improvement. Outpatients spent a minimum of 24 h under observation and were discharged the next day unless there was no improvement of symptoms or there was appearance of AEs.

Plastic stent group

DPS (5–10 cm length, diameter 7–10Fr, Advanix, Boston Scientific) were used in this study. After initial EUS-guided access using a 19-gage, a guidewire was coiled within the

collection. The ostomy was dilated first, using a cystotome, and secondly balloon dilations were made. DPSs were inserted and delivered. Number of plastic stent and size of the balloon used to dilate the ostomy depended on the WON size and content (see Table 3, in the published protocol) [15]. The time to plastic stent withdrawal was until total resolution was seen by imaging. If there was pancreatic duct involvement, non-withdrawal of stent was considered.

LAMS group

LAMS (10, 15, or 20-mm in diameter, and 10-mm in length, HotAXIOS stent with electrocautery-enhanced delivery system, BostonScientific) were used in this study. LAMS size depended on the WON size and content (Table 3, published protocol) [15]. After the EUS-guided access into the WON using first a 19G or directly with the electrocautery tip, the delivery system was advanced into the cavity and the distal flange was deployed under EUS guidance. The proximal flange was released under EUS or endoscopic guidance. The time to stent withdrawal depended on the clinical success, however, the intention to remove a LAMS was no later than 4–6 weeks. LAMS were not exchanged for DPS.

Additional interventions

Necrosectomy was considered in WON with predominantly solid debris. In cases that required sessions of DEN, after tract dilation up to 15-mm, the different technical variants described in the literature were used (irrigation technique with normal saline; mechanical technique; or combination with nasocystic catheters). The periodicity was every 2–5 days depending on the decision of the expert endoscopist and not clinical improvement after ETD.

Additional comments

In the case of collections of significant size with clinical-radiological success but without total disappearance of the collection, precluding the removal of the stent, a new CTMD was performed after 4 weeks to assess removal of the stent. In this case, the removal of a stent was contemplated when there was disappearance of the collection or a decrease < 5 cm.

A cross-over rescue treatment was considered when the initial protocol treatment failed. Another accepted rescue technique for LAMS cohort was the insertion of a coaxial DPS.

Alternatively, if a cross-over treatment or technical variant was not possible, percutaneous surgical or radiological treatment was offered.

Follow-up

This study data was introduced into an electronic database by the participating investigator. Remote supervised monitoring was done by two research coordinators (JGV,FBC) and an independent data manager.

Patients were assessed (visit and telephone call) on days 1 and 7, at 4, 8, and 16 weeks, and at 6, 8, and 12 months. More details, Online Appendix 1 (supplementary text) and protocol [15].

Outcomes

The primary outcome was short-term (4 weeks) clinical success (DPS vs. LAMS) determined by the reduction of the collection (> 50% from its initial size), along with clinical improvement.

The secondary outcomes were long-term (4 months) clinical success (DPS vs. LAMS) determined by total resolution, along with clinical improvement; technical issues such as procedure duration and difficulty level; safety; hospitalization; and recurrences and costs.

Technical success was defined as the correct release of the stent at both ends, with observed drainage of the liquid. Clinical success was defined as significant reduction of the collection along with clinical resolution. Recurrence was defined as a collection diagnosed with imaging test during the follow-up of prior procedure with initial clinical success.

AEs were defined as undesirable situations suffered by patients during the study, whether related or not to the ETD with a stent. AEs were classified as mild, moderate, serious, or fatal, in accordance with the ASGE lexicon. 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. 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. More details, at the published protocol [15].

Statistical analysis

Prior data indicated that the clinical success rate at 4 weeks among the plastic group was 50% [17, 18]. If the clinical success rate in the LAMS group was 75%, 114 subjects were required to be able to reject the null hypothesis that the clinical success rate for LAMS and the plastic group were equal with power 80%. The type I error probability associated with this test was 5%.

Because recruitment was slower than hoped for (in part, because of AEMPS authorization pending for some centers, and finally the COVID-19 pandemic), the steering

committee considered the need for an extension of 1 year for the recruitment period. Finally, after this year of recruitment extension, because of financial limitations (insurance cost for all centers; and derived costs for the clinical monitoring by an independent monitoring platform -SCReN) we could not guarantee the rigorous external monitoring. The steering committee (after Data Monitoring Committee advise) ruled out another extension for the inclusion period and finalized follow-up of the 99 patients who had been selected.

Demographic and clinical characteristics were described by each group. Categorical variables were presented as the number of cases and percentages, and continuous variables were presented as the mean and standard deviation or median and 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-square test. Relative risk (RR) and its 95% confidence interval (CI) were estimated to quantify the magnitude of the observed differences in the clinical success rate at 4 weeks. Statistical analyses were performed using R (version4.1.2). More details, in Online Appendix 1.

Cost analysis

The financial study was based on data provided by the finance department of the PI's center. The analysis of direct cost included professional fees, cost of the material used, type of procedure, and expected costs of hospital stay. The average procedure duration and hospitalization days for all procedures were calculated in order to estimate the costs of hospital stay for each group. More details, Online Appendix 1.

Results

Study enrolment

Between June-2017 and October-2020, 99 patients with WON were assessed for eligibility, of whom 21 were ineligible. 78 patients were randomly assigned to treatment—40 to the LAMS group and 38 to the DPS group—and 7 patients were excluded from each group, mainly due to in situ EUS findings (pseudocyst or unidentified WON) on the index procedure. In each treatment group, two patients discontinued treatment because of death (unrelated to the procedures). Two other patients in the LAMS group discontinued due to surgery in one case and follow-up loss in the other (Fig. 1).

A sensitivity analysis by center was performed on the primary outcome. The results showed a wider confidence interval due to the number of subjects available by center, but no changes in the direction of the effects were observed.

Baseline characteristics

Mean WON size was 112 mm (±47.2) in the LAMS, and 115 mm (±35.5) in the DPS group, with suspected infection in 40% (LAMS) and 42% (DPS), respectively. The most frequently used LAMS bore sizes were 15 mm (63%) and 20 mm (21%), and average number of DPS number per patient was 2. The two groups were comparable in all background variables and the differences observed did not seem to be clinically relevant, except for the difference in WON content between the two groups (Table 1).

Outcomes

The short-term clinical success rate, as primary outcome, is presented in Table 2 and was similar between both groups (RR 1.41 [95% CI 0.88–2.25]; $p=0.218$). Similarly, the long-term clinical success, (RR1.2 [95% CI 0.92–1.58]; $p=0.291$) (Online Appendix 1, p10, Fig. S2) was alike. Similar results were noted at the *per-protocol* analysis (Online Appendix 1, Table S3).

There were 3 cases of technical failure in the DPS group, but no differences were encountered in technical success of index procedure between the two groups. Technical difficulty was undetected in LAMS but noted in three cases (9%) in the DPS group (Table 2).

Procedure time was significantly lower in LAMS (35 min [IQR, 24–50]) than in DPS (45 min [IQR, 38–63]), Table 2, Online Appendix 1 (Fig. S3). In the same line, fluoroscopy use was significantly lower in LAMS (RR, 0.72 [95% CI 0.57–0.91], $p=0.006$).

The hospital admission after the index procedure (median difference, − 10 [95% CI − 17.5, − 1]; $p=0.077$) and global hospitalization (median difference − 4 [95% CI − 33, 25.51]; $p=0.82$) were similar between both groups and are shown in Fig. 2.

Similar therapeutic endoscopic procedures (58 vs 65 sessions) and DEN sessions (25 vs 33 sessions) were performed in DPS. In 7 cases, DEN was performed in the index procedure in the LAMS group. No differences were detected in the median number of overall interventions (Table 2; Online Appendix 1, Table S4). Total cross-over between the two groups was higher in DPS. No LAMS case had a cross-over to DPS, only to coaxial DPS.

Similar rates of stent-related SAEs were detected (36 vs 45%, RR 0.81 [95% CI 0.44–1.46], $p=0.61$) for the LAMS vs DPS, but de novo fever episodes were significantly (26%) lower in LAMS (RR, 0.26[0.08–0.83]), $p=0.015$) (Table 2; Online Appendix 1, Table S5, Fig. S4). Bleeding rates were similar, including five patients (15%) in LAMS and three patients (10%) in DPS. All related bleeding episodes occurred within the first two weeks from the index procedure (intra-procedure to 14 days). Pseudoaneurysms were present

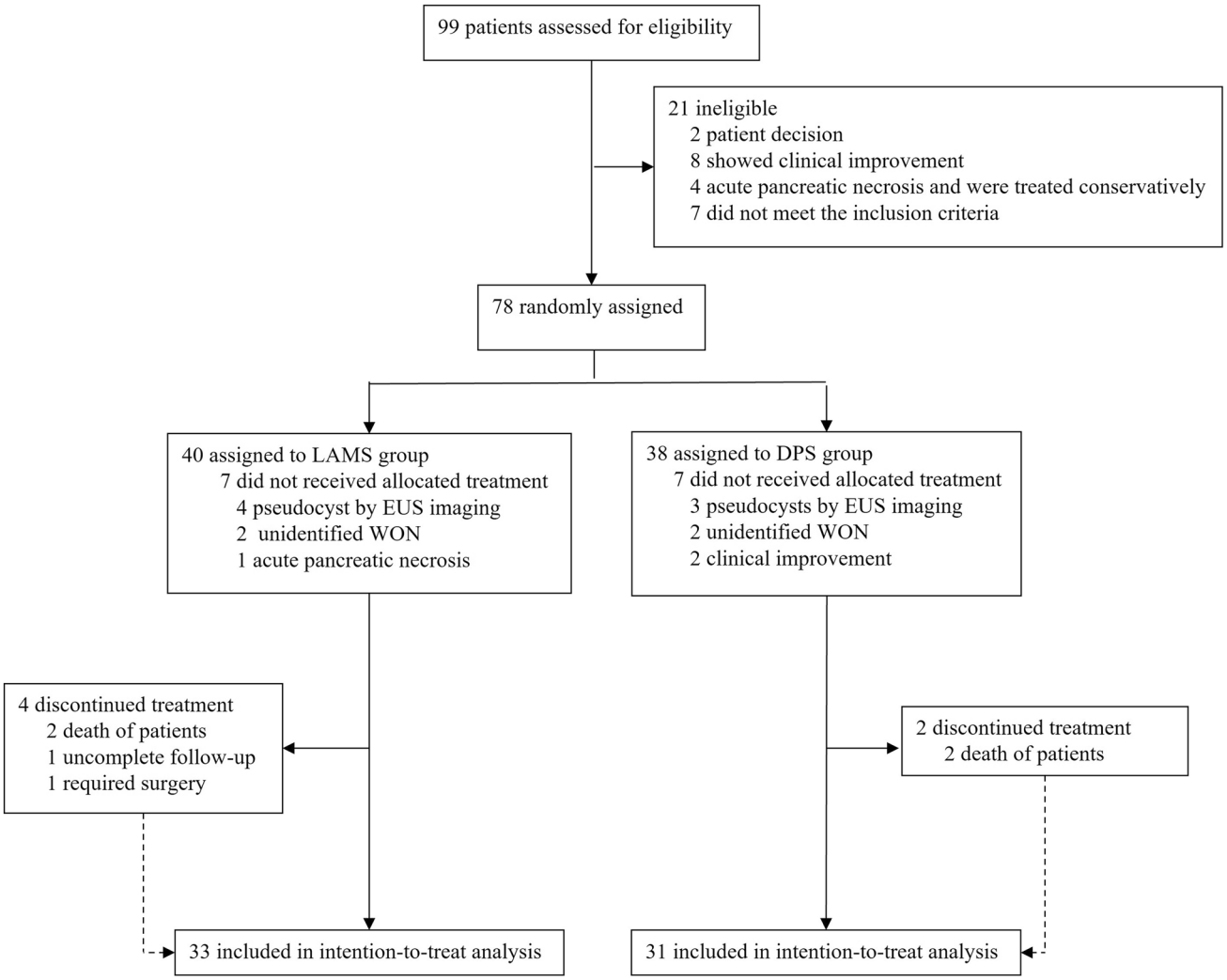


Fig. 1 Trial profile. *DPS* double-pigtail plastic stent, *LAMS* lumen-apposing metal stent, *WON* walled-off necrosis

in 2 of 7 episodes (28%) in LAMS, and in one of three cases (33%) in the DPS group, all of them detected after the ETD. All patients had indwelling stents (LAMS or DPS) at the time of bleeding, except for one patient in the DPS group. A detailed bleeding analysis case by case is shown in Online Appendix 1 (Table S7, Fig. S5).

A deeply buried stent occurred in one case. The LAMS was successfully removed, but two sessions were required [19].

No global SAEs and related stent SAEs differed between groups; this is listed in Online Appendix 1 (Table S5, Table S6, Fig. S4). No patient died of complications related to the endoscopy intervention (mesenteric ischemia, COVID-19 and sudden unexpected death).

Stent removal was significantly earlier in LAMS, at almost 4 weeks (median difference − 3.43[95% CI − 7.7, − 0.5], $p = 0.001$). Only one patient required surgery (debridement of necrotic tissue) in LAMS related to the WON; and other patient required surgery for a suspicious of perforation. Recurrences were similar between groups, six vs four (LAMS vs DPS), but none of them required intervention. Overall mortality was similar in both groups (6%) (Table 2).

The mean cost of treatment in LAMS was 41,565$ per patient compared with 41,971$ per patient in the DPS group (cost difference-406$). (Table 3; Online Appendix 1, Table S9).

Table 1 Baseline characteristics of patients according to each group

	LAMS group ($n=33$)	DPS group ($n=31$)
Patient characteristics and clinical details		
Age (years), mean (SD)	60 (13.5)	62 (15.4)
Sex—*n* (%)		
Male	25 (76)	20 (64)
Female	8 (24)	11 (35)
Aetiology of pancreatitis[a]—*n* (%)		
Biliar	19 (59)	18 (58)
Alcohol	9 (28)	8 (25)
Other[b]	4 (13)	5 (16)
Severity of pancreatitis		
White cell count $\times 10^9$ cells/L[c]—mean (SD)	9.17 (4.1)	8.43 (3)
C-reactive protein mg/L[d]—mean (SD)	129.83 (79.9)	101.44 (69.7)
Organ failure pre-procedure—*n* (%) (Respiratory, cardiovascular, or renal)	7 (25)	7 (26.9)
Admitted to ICU/high unit care—*n* (%)	6 (18)	6 (19)
ASA—*n* (%)		
I	0	1 (3)
II	16 (53)	15 (48)
III	14 (46)	14 (45)
IV	0	1 (3)
Charlson comorbidity score—median (IQR)[e]	3 (1–4)	3 (2–5)
WON characteristics		
Location[f]—*n* (%)		
Head/uncinate	11 (36)	10 (32)
Body/tail	19 (63)	21 (67)
WON content[g]—*n* (% of necrosis solid)		
$<50\%$	22 (66)	11 (36)
$\geq 50\%$	11 (33)	19 (63)
WON size (transverse axis diameter, mm)—mean (SD)	112 (47)	115 (35)
WON size (transverse axis diameter, mm)—median (IQR)	110 (80–140)	118 (86–140)
Suspected infection[h]—*n* (%)	13 (40)	13 (42)

Data are median (IQR), mean (SD), *n* (%), or *n*/N (%)

ASA American Society of Anesthesiologists, *DPS* double-pigtail plastic stents, *ICU* intensive care unit. *LAMS* lumen apposing metal stents, *WON* walled-off pancreatic necrosis

[a]Data missing for one patient

[b]Others includes medication, trauma, and unknown etiology

[c]Missing for four patients

[d]Data missing for 17 patients

[e]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 higher burden of coexisting conditions

[f]Data missing for one patient

[g]Data basically derived from EUS and/or MRI. Data missing for one patient

[h]Based on a positive culture of aspirated contents, presence of gas in WON on contrast-enhanced CT, or clinical deterioration without other explanation. Data missing for one patient

Discussion

This multicenter, randomized trial provides more evidence between plastic and LAMS in the treatment of WON-type collections. This trial did not show the expected significant superiority of LAMS in terms of short-term clinical success, long-term clinical success rates and hospital stay. Furthermore, shorter procedure time, less fluoroscopy needed, and fewer de novo fever episodes were significantly favor LAMS.

Table 2 Primary and secondary outcomes according to the intention-to-treat analysis

	LAMS group ($n=33$)	DPS group ($n=31$)	Effect[1,2]	p value
Primary outcome				
Short-term clinical success—*n* (%) (4 weeks)	21 (63)	14 (45)	1.41 (0.88–2.25)[1]	0.218
Secondary outcomes				
Long-term clinical success—n (%) (4 months)	22 (88)	19 (73)	1.2 (0.92–1.58)	0.291
Procedure time (mins)				
Median (IQR)	35 (24–50)	45 (38–63)	− 10 (− 23, 7)[2]	0.003
Range	15–89	24–134		
Technical difficulty -*n* (%)				0.11
Easy	33 (100)	28 (90)		
Difficult	0	3 (9.7)		
Length of global hospital stay (days)[a]				
Median (IQR)	34 (3.7–83.2)	38 (14–54)	− 4 (− 33, 25.5)[2]	0.82
Length of stay after index procedure[b]				
Median (IQR)	5 (3–15.5)	15 (5–24)	− 10 (− 17.5, − 1)[2]	0.077
Length of ICU stay (days)				
Median (IQR)	16 (11.5–17.5)	17.00 (7.5–20.5)	− 1 (− 11, 21)[2]	> 0.99
Safety—*n* (%)				
Stent-related SAEs	12 (36)	14 (45)	0.81 (0.44–1.46)[1]	0.61
Bleeding (requiring treatment)	5 (15)	3 (10)	1.57 (0.41–6.01)[1]	0.71
De novo fever	3 (9)	11 (35)	0.26 (0.08–0.83)[1]	0.015
Recurrence, 12 months—*n* (%)[c]	6 (24)	4 (15)	1.56 (0.5–4.88)[1]	0.50
Recurrence requiring interventions	0	0		
Other outcomes				
Technical success for index procedure—*n* (%)	33 (100)	30 (96.7)	1.03 (0.97–1.1)[1]	0.48
Fluoroscopy assistance—*n* (%)	23 (70)	31 (100)	0.72 (0.57–0.91)[1]	0.006
Median number of endoscopic interventions—median (IQR)	3 (2–3)	3 (2–4)	0 (− 2, 1)[2]	0.84
Total number—*n*	100	97		
ETD procedures—median (IQR)	1 (1–1)	1 (1–1.5)		0.32
DEN procedures—median (IQR)	2 (1–3)	2 (1–3)	0 (− 2, 2)[2]	0.97
Global endoscopy—median (IQR)	1 (1–2)	1 (1–3)	0 (− 2, 0)[2]	0.28
Need for surgery—*n* (%)	2 (6)	0		0.49
Death—*n* (%)	2 (6)	2 (6)	0.94 (0.14, 6.27)	> 0.99
Stent removal, weeks, median (IQR)[d]	6 (5–11]	10 (7–17)	− 3.43 (− 7.71, − 0.5)[2]	0.001

Data are *n* (%) or median (IQR). Effect includes three different analyses:

[1]Relative risk

[2]median difference (95% CI). LAMS as reference group. Additional outcomes are provided in online supplemental table S3 (per-protocol analysis), S4 (interventions), S5 (safety), and S6 (costs).

[a]Data missing for seven patients (five in the LAMS group, two in the DPS group)

[b]Index procedure refers to the first ETD performed. Data missing for one patient in the LAMS group

[c]Data missing for 13 patients (8 in the LAMS group, five in the DPS group)

[d]Data missing for four patients (one in the LAMS group, three in the DPS group). *DEN* direct endoscopic necrosectomy. *DPS* double-pigtail plastic stent. *ETD* endoscopic transmural drainage. *ICU* intensive care unit. *LAMS* lumen-apposing metal stent

To date, the highest evidence comparisons of LAMS vs. DPS in WON-type were two single-center randomized trials (USA, Denmark), and a Dutch study [12–14].

This both single-center trials concluded that there were no differences in clinical outcomes between the two, except for procedure time. In order to minimize LAMS-related AEs, the American study recommended follow-up imaging and LAMS removal at 3 weeks [12].

The AXIOMA study was a multicenter prospective cohort study which only included patients with infected

Table 3 Cost analysis

	LAMS group ($n=33$)	DPS group ($n=31$)	Total	Dif. LAMS vs DPS
Total cost per patient, € / $	35 145/41 565	35 488/41 971	70 633/83 536	− 343/− 406
Global cost:				
€	1 159 796	1 100 158	2 259 955	59 637
$	1 371 691	1 301 157	2 672 848	70 533

Data are mean (SD). Costs are in the 2021 value for the euro (€). Costs were converted to U.S dollars ($) with the use of the European Central Bank (1 € equivalent to 1.1827 U.S $, as average exchange rate, 2021). Cost analysis of the services provided, through records of care activity and Relative Units of Value (RUV) catalogs. Analysis performed using SAP Profitability and Cost Management 10.0 (PCM). *DPS* double-pigtail plastic stent. *LAMS* lumen apposing metal stent

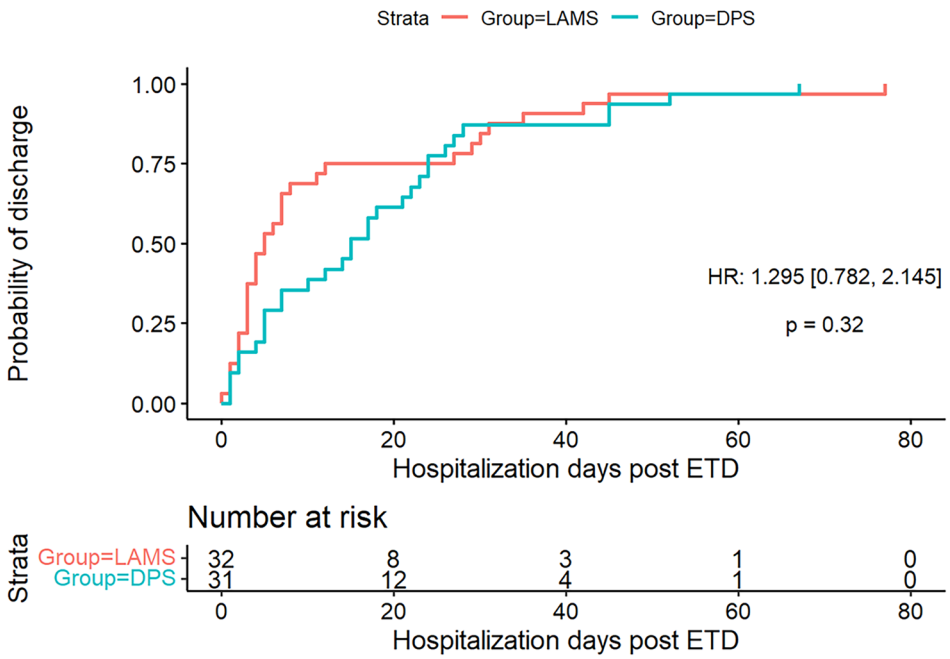


Fig. 2 Kaplan–Meier. Hospitalization days post-ETD. *DPS* double-pigtail plastic stent. *ETD* endoscopic transluminal drainage. *LAMS* lumen-apposing metal stent. *p*-value of log-rank test

pancreatic or peripancreatic necrosis that were drained using LAMS and compared to a historic cohort of patients assigned to an endoscopic step-up approach with DPS in the TENSION trial. [1] This study included more severely ill patients than did the American single-center trial and our study. This difference must be noted because ill patients are associated with more complications, ICU stays, and greater global hospital stay [12, 14].

With the increasing use of LAMS, significant LAMS-related AEs have been reported [5–7, 18]. In our trial, the percentage of reported SAEs was higher, compared with previous trials [12, 13]. The rigor of the external monitoring in the collection of SAEs and the nature of necrotizing pancreatitis surely contributed to the increase of reported SAEs. Furthermore, the risk of severe bleeding in LAMS, with removal after 3 weeks was not higher in contrast to the mentioned trial [12]. In this line, our trial, along with recent reports (including a metanalysis and a UK and Ireland LAMS registry), provides more evidence for leaving LAMS in situ beyond 4 weeks if required clinically, and 6 weeks seems to be safe [9, 13, 14, 20].

In this trial, in contrast to the AXIOMA and the Danish study, no nasocystic catheters were used in any of the index procedures. There is no high-level evidence, and it is expected that LAMS has been designed to be used without it [21, 22]. Similarly, despite a recent randomized trial focused on coaxial DPS within LAMS strategy (less stent occlusion), no placement of DPS within LAMS were allowed in the index procedure with the aim of minimizing differences between the groups [23, 24].

In contrast to recent guidelines and to the American trial, in our trial LAMS were not exchanged for DPS, similarly to our clinical practice [10–12]. As a result, after 12 months of follow-up, although the recurrence rate was considerable, no cases required intervention. A recent reports evaluated the recurrence of collection after metal stent removal, but

no significant differences were found and reintervention was rarely required [25, 26]. For these reasons, according to our results and the technical difficulty of replacing LAMS with DPS, this exchange strategy seems not to be necessary in all cases.

The use of DEN should be reserved for those patients who do not adequately respond to ETD [8]. In our trial, the number of sessions intended to treat the collection and the total of interventions were similar in the two groups. It must be noted that the removal stents procedures were greater in LAMS, and the strategy of indwelling stents was considered in the DPS group.

A shorter procedure time was observed in LAMS. The reason is obvious attending to the LAMS-delivery-system, avoiding the need to use the Seldinger technique. This benefits severely ill patients with poor clinical status [12].

Fluoroscopy is not essential using LAMS, and for this reason it was used less in the LAMS group [26]. However, it was used in 70% of the LAMS group, because the majority EUS-guided procedures were performed in rooms where fluoroscopy is available. By contrast, in almost all DPS, fluoroscopy was needed.

Hospitalization median after the index procedure (5 vs. 15 days) and for the global hospitalization (34 vs. 38 days), were similar between groups and to the trials [12, 13]. This can explain that overall costs between groups were similar, despite LAMS are more expensive.

Our study has some limitations. Sterile collections were included which may have led to comparison of patients with different degrees of severity. The trial ended before the calculated sample size was reached and this may have led to underestimation of the effect of LAMS in demonstrating its superiority in terms of clinical success (as a primary outcome). In contrast, bleeding was more likely to occur in LAMS group, although without significant difference maybe also due to insufficient sample size. Second, although the preferred LAMS size for an ETD should be larger, other smaller diameters were used. But at the start of this trial, 20 mm LAMS were not available, and not all the centers had immediate access to this size. Furthermore, in our study and in the Dutch study, no differences in clinical outcome were encountered between LAMS sizes. Lastly, considering short-term success as a primary outcome may cause confusion, but it was based on the existing literature (up to protocol approval) and the hypothesis that better and faster drainage of using LAMS could be proved in only one month.

Finally, it must be noted that the clinical outcomes of these collections depended on different variables, and LAMS vs. DPS discussion, is only one aspect of the whole management of these patients. An adequate treatment protocol standardization is still lacking [28].

The multicenter design and randomization nature strengthens the quality and generalizability of the results. Furthermore, follow-up of 12 months can guarantee a proper data for recurrences. Thus, this time length may be enough to detect benefits or AEs of the LAMS group in the long term.

In clinical practice, LAMS is gaining popularity over DPS. This trial has demonstrated that both stents are valid with similar total cost. In summary, no significant difference in any outcome measure were encountered, except for procedural duration. Therefore, results from this study did not prove the significant superiority of LAMS. Safety of treating WON patients does not appear to be impaired by using LAMS.

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Author contributions EVS, MPM, JJV, and JBG conceived the project. SV, MPM, EVS, JJV, PH, CT, and JBG participated in the design of the study. The study design was discussed in research meetings with all authors. JGV, FBC, AGG, JME, AT, FGH, MPM, CGA, JJV, AGS, JRF, JFV, MM, IMS, CSH, MMP, ASY, SRO, and JB promoted the enrolment of patients, conducted the study, and acquired the data. JGV, and JBG collected, interpreted, and analyzed the data, and verified the underlying data. JGV, FBC, PH, SV, and JBG coordinated the study. JGV, CT, and JBG did the statistical analysis. RM, JGV, and JBG calculated the cost analysis. JBG drafted the manuscript under supervision of EVS. All authors read, revised, and provided a critical review of the draft manuscript. All authors approved the final manuscript. JBG had final responsibility for the decision to submit for publication.

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Declarations

Disclosures M. Perez-Miranda is consultant and speaker for Medtronic, Olympus, Taewoong, Boston Sc and M. I. Tech; E Vazquez-Sequeiros is consultant for Boston Sc; F Gonzalez-Huix is consultant for Boston Sc; JB Gornals is consultant for Boston Sc and Fujifilm; JG Velasquez is a PhD student at the Universitat de Barcelona, and this paper is part of his doctoral project. JB Gornals acts as a PhD Director. Francesc Bas-Cutrina, Ana Garcia Garcia De Paredes, Jose-Miguel Esteban, Alvaro Teran, Carlos Guarner-Argente, Juan J Vila, Albert Garcia-Sumalla, Jose Ramon Foruny, Joaquin Fisac-Vazquez, Maria Moris, Isabel Miquel-Salas, Carlos De-la-Serna Higuera, Marianette Murzi-Pulgar, Andres Sanchez-Yague, Silvia Salord, Sandra Ruiz-Osuna, Juli Busquets, Mireia Sanllorente-Melenchon, Sebas Videla, Ramon Moreno, Cristian Tebe-Cordomi, Pilar Hereu have no conflict of interest or financial ties to disclose.

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