International multicenter comprehensive analysis of adverse events associated with lumen-apposing metal stent placement for pancreatic fluid collection drainage

Alessandro Fugazza, MD,[1] Amrita Sethi, MD,[2] Arvind J. Trindade, MD,[3] Edoardo Troncone, MD,[4] John Devlin, MD,[5] Mouen A. Khashab, MD,[6] Frank P. Vleggaar, MD, PhD,[7] Auke Bogte, MD, PhD,[7] Ilaria Tarantino, MD,[8] Pierre H. Deprez, MD, PhD,[9] Carlo Fabbri, MD,[10] José Ramón Aparicio, MD,[11] Paul Fockens, MD PhD,[12] Rogier P. Voermans, MD, PhD,[12] Will Uwe, MD,[13] Geoffroy Vanbiervliet, MD,[14] Antoine Charachon, MD,[15] Christopher D. Packey, MD, PhD,[2] Petros C. Benias, MD,[3] Yasser El-Sherif, MD,[5] Christopher Paiji, MD,[6] Dario Ligresti, MD,[8] Cecilia Binda, MD,[10] Belén Martínez, MD,[11] Loredana Correale, PhD,[1] Douglas G. Adler, MD, FACG, AGAF, FASGE,[16] Alessandro Repici, MD,[1,17] Andrea Anderloni, MD, PhD[1]

Rozzano, Rome, Palermo, Romagna, Italy; New York, New York; New Hyde Park, New York; Baltimore, Maryland; Salt Lake City, Utah, USA; London, UK; Utrecht, Amsterdam, Netherlands; Brussels, Belgium; Alicante, Spain; Gera, Germany; Nice, France; CH Princesse Grace, Monaco

Background and Aims: High rates of technical and clinical success were reported for lumen-apposing metal stent (LAMS) placement for peripancreatic fluid collection (PFC) drainage. However, data on the adverse event (AE) rates are heterogeneous. The aim of this study was to evaluate the incidence, severity, management, and risk factors of AEs related to the use of LAMSs for drainage of PFCs in a large cohort of patients.

Methods: This is a multicenter, international, retrospective review from 15 centers of all patients who underwent placement of LAMSs for the management of PFCs. A nested case-control study was conducted in patients with (case) or without (control) AEs.

Results: Three hundred thirty-three procedures in 328 patients were performed (5 patients treated with 2 LAMSs). Technical success was achieved in 321 patients (97.9%). Three hundred four patients were finally included in the study (7 excluded for lost to follow-up information; 10 excluded for deaths unrelated to LAMSs). The rate of clinical success was 89.5%. Seventy-nine LAMS-related AEs occurred in 74 of 304 patients (24.3%), after a mean time of 25.3 days (median, 18 days; interquartile range, 6-30) classified as 20 (25.3%) mild, 54 (68.4%) moderate, or 5 (6.3%) severe. On multivariable analysis compared with control subjects, cases were more likely to have walled-off necrosis (WON) versus pancreatic pseudocysts (odds ratio, 2.18; 95% confidence interval, 1.09-4.46; $P = .028$), whereas cases were less likely to have undergone tract (balloon) dilation (yes vs no; odds ratio, .47; 95% confidence interval, .22-.93; $P = .034$).

Conclusions: Data from this large international retrospective study confirm that the use of LAMSs for management of PFCs has excellent technical and good clinical success rates. The rate of AEs, however, is not negligible and should be carefully considered before using these stents for drainage of PFCs and in particular for WON. Further prospective studies are needed to confirm these findings. (Clinical trial registration number: NCT 03544008.) (Gastrointest Endosc 2020;91:574-83.)

(footnotes appear on last page of article)

Use your mobile device to scan this QR code and watch the author interview. Download a free QR code scanner by searching "QR Scanner" in your mobile device's app store.

Pancreatic pseudocyst (PP) and walled-off necrosis (WON) are peripancreatic fluid collections (PFCs) resulting from acute or chronic pancreatitis, which substantially differ in the amount of necrotic content, with more abundant debris in WON and mostly absent in PP.[1] In many cases, in particular when necrotic material is absent, such collections may resolve spontaneously.[2,3] In other cases they can

become symptomatic, causing gastric outlet obstruction, biliary obstruction, pain, or infection, thereby causing significant morbidity and mortality and requiring prompt intervention.[4] Surgical debridement or percutaneous drainage is associated with a significant risk of adverse events (AEs) and mortality, so less-invasive approaches, such as endoscopic drainage, are preferred when the expertise is available.[5-7] Over the past 2 decades, EUS-guided drainage of PFCs and necrotic collections has significantly advanced, using relatively small plastic stents and also larger self-expanding metallic stents (SEMSs). With both methods, drainage of the necrotic collection was feasible and allowed access into the collection to perform endoscopic transmural necrosectomy when needed.[8] However, endoscopic drainage is limited by the absence of dedicated devices, because stents initially used had been created for biliary drainage. Because they were not specifically designed for internal drainage of extraluminal collections, plastic stents and SEMSs are limited by shortcomings and possible AEs, such as obstruction, migration, peritoneal leakage, bleeding, and the need of multiple endoscopic reinterventions.[8]

In recent years a new type of fully covered SEMS has become available, namely the lumen-apposing metal stent (LAMS), with a specific biflanged design that facilitates the creation of a stable and sealed fistula between the gastric or duodenal wall and the target cavity.[9] The use of LAMSs for PFC drainage, and for WON drainage in particular, has brought good results, with a high rate of technical and clinical success and potentially lower risk of fistula occlusion and perforation compared with plastic stents, although high-quality evidence is still missing.[9-13] The same studies have also highlighted the risks associated with the use of LAMSs, such as bleeding, stent obstruction by necrotic tissue, buried stents, or biliary duct compression, thus raising questions regarding the proper indication for these stents and the correct timing for removal.[14,15] Data on AEs with LAMSs in the setting of PFC drainage are heterogeneous, and only a few prospective studies are available. To better understand how to avoid serious AEs and maximize the benefits from the use of LAMSs, we conducted a retrospective multicenter study aimed to evaluate the incidence, severity, management, and risk factors of AEs related to the use of LAMSs for the drainage of PFCs in a large cohort of patients.

METHODS

The present study is a multicenter, international, retrospective review from 15 secondary and tertiary care centers (11 in Europe, 4 in the United States) of all patients treated in these institutions with LAMSs (AXIOS or electrocautery-enhanced [EC]-AXIOS system; Boston Scientific Corp, Marlborough, Mass, USA) for the management of PPs or WON between March 2013 and October 2017. Intraprocedural and postprocedural AEs were recorded, classified, and graded according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon.[16] The institutional review board of each hospital approved the observational study (NCT03544008), and the protocol was performed in accordance with the Declaration of Helsinki.

Study device

The AXIOS stent is a SEMS made up of braided nitinol that is fully covered with silicone, with wide flanges on both ends to provide anchoring between the GI and cyst lumens. The stent is preloaded in a 9F or 10.8F catheter with a through-the-scope delivery system compatible with therapeutic echoendoscopes having a working channel of 3.7-mm diameter or larger. The delivery system allows for endoscopic control and uses a locked 2-step release system to prevent unintended deployment of the second flange. The novel EC-LAMS stent incorporates an electrocautery wire into the distal tip of the delivery catheter, enabling a lumen-to-lumen passage of the device followed by immediate deployment of the stent, thus allowing for drainage to be performed as a single-maneuver procedure. These stents are available in different diameters and lengths: 6 × 8 mm, 8 × 8 mm, 10 × 10 mm, 15 × 10 mm, and the novel 20 × 10 mm and the 10-mm, 15-mm, and 20-mm diameter stents, believed to be more appropriate for PFCs.

Procedures

All EUS procedures were performed by experienced endoscopists in the endoscopy suite with a therapeutic echoendoscope. Only mature PFC (ie, after at least 4 weeks from the index pancreatitis, as defined by the Atlanta classification[1]) were included in the study. Under EUS guidance, the PFC was studied and drained from either the stomach or duodenum. Two different deployment techniques were used in function of the stent used at the discretion of the endoscopist.

When a standard LAMS (AXIOS) was used, an initial puncture with a 19-gauge needle through the GI wall into PFC followed by insertion of a .025-inch or .035-inch guidewire was performed. After that, the tract was dilated using a cystotome and dilation balloon, followed by insertion of the delivery system and deployment of the stent.

With the cautery-enhanced LAMS (EC-AXIOS) a free-hand technique was used, with direct access into the PFC by puncture with the device on the pure-cut setting, followed immediately by deployment of the stent without any exchange of devices. For both systems deployment of the second flange was released either endoscopically or with the intrascope channel stent release technique.[17]

Complementary maneuvers performed during the same or further procedures were at the discretion of the endoscopist and included the following: balloon dilation of the LAMS, hydrogen peroxide irrigation of the PFC, placement of nasocystic drainage tube or double-pigtail stent through the LAMS, and/or extraction of

necrotic debris. Placement of a concomitant percutaneous drainage was added in some cases. All patients were under broad-spectrum antibiotic therapy at the moment of LAMS placement. The type, dosage, and course of the antibiotic therapy were at the discretion of the endoscopist and/or of the medical team (eg, gastroenterology unit, intensive care unit) that was taking care of the patient at each institution.

Data

All data were extracted and compiled into a central database. Patient-related data included patient demographics, type of PFC, size and location of the collection, presence of disruption of pancreatic duct, previous imaging (CT, magnetic resonance imaging, MRCP), presence of abnormal vessels on imaging (including portal vein thrombosis, splenic vein thrombosis, perigastric varices, pseudoaneurysm, or others), etiology of pancreatitis, and indication for drainage. Procedural data included type and size of the LAMS used, approach, endoscopic appearance of the cavity, complementary maneuvers during the procedure, and/or subsequent placement of a concomitant percutaneous drainage. Postprocedural data included length of hospitalization, successful stent removal after resolution of PFC, recurrence of PFC during follow-up, AEs with severity graded according to the ASGE lexicon's severity grading system,[16] and their management. AEs were classified as early, when presenting within 14 days, and late, when presenting after 14 days from LAMS placement. Patients were followed up with periodic laboratory analyses, clinic visits, and imaging (CT and/or magnetic resonance imaging) at the discretion of the responsible endoscopist at each participating hospital in an ambulatory setting.

Definitions

AEs were defined as all symptomatic events related to the use of LAMSs such as bleeding, infection, stent occlusion, and stent migration resulting in prolongation of hospital stay and requiring medical therapy or further procedure or action to resolve the event or to treat the symptoms. The ASGE lexicon's severity grading system was used to grade the AEs.[16]

Technical success was defined as successful LAMS placement into the PFC across the gastric or duodenal wall. Clinical success was defined as WON or PP <2 cm on axial imaging 1 to 6 months after stent insertion without need for further interventional radiologic, endoscopic, or surgical procedures. A nested case-control analysis was conducted in patients with (case) or without (control) AEs, looking for factors associated with occurrence of AEs. Cases and their control subjects were recruited from each institution.

Statistical analysis

Descriptive analysis was carried out by calculating mean and standard deviation for continuous variables and proportions for categorical variables. We used univariate and multivariable logistic regression analysis to identify risk factors for AEs from possible variables. For the purpose of this analysis, patients were separated according to a binary variable: those with any AE (mild/moderate/severe) and those without AEs. Lack of individual matching for all centers permitted the use of unconditional logistic modeling.[18] The univariate model used independent variables related to patient and procedure characteristics. Crude odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Any factors associated with AEs with $P \leq .100$ on univariate analysis were entered into a multivariable logistic regression analysis to determine any independent predictors of AEs. Adjusted ORs and their 95% CIs were obtained from multiple logistic regression model. In our study there was a possible source of nonindependence of data. Patients treated in a particular center may be more alike compared with patients treated in another center because of differences in treatment policies. As a result, patients treated in the same center are dependent (clustered) rather than independent. Therefore, an adjustment by using clustered standard error was required for this hospital effect in estimating regression parameters.

Secondary outcome measures included cumulative frequencies and times (from stent insertion to occurrence) of different types of AEs (ie, stent migration, bleeding, infection, and stent occlusion). Times were summarized using descriptive statistics with mean and variability. A linear regression model was used to estimate time with type of AEs. For additional verification, frequencies of different types of AEs among early ($\leq$14 days) and late (>14 days) events were determined; differences between the 2 groups were assessed using the χ^2 test.

All analyses were done using R software, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at $\leq$.05.

There was multiple testing of outcome data arising from individual patients. The *P* values for the univariate statistical tests are not corrected for multiple testing, because those tests were taken as exploratory. The subsequent multivariable logistic regression analysis was considered the main definitive result because it determined those variables independently associated with the occurrence of AEs after adjusting for the contributions of the other variables in the model. Other statistical results including those comparing times from stent insertion with occurrence of AEs are secondary, to be taken as descriptive only, and not requiring correction of their *P* values for multiple comparisons.

RESULTS

During the study period 333 procedures were performed in 328 patients (116 women [35.4%]; mean age, 56.0; standard deviation, 16.0; range, 4-86) were performed. Five patients (1.5%) were treated with 2 LAMSs in different sessions. Overall, technical success was obtained in 321 patients (97.9%).

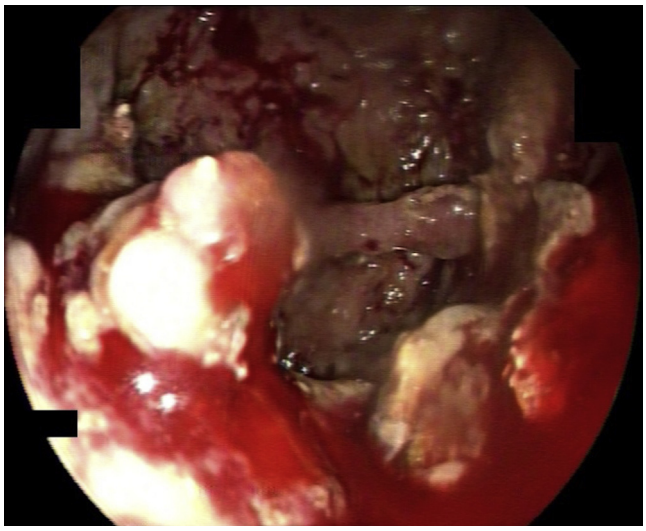

Figure 1. EGD revealed correct placement of the lumen-apposing metal stent, fully opened, crossable by standard gastroscope. In the fluid collection cavity, an oozing bleeding from a large arterial vessel was visible.

Among the 7 of 328 patients (2.1%) with technical failure, 4 patients subsequently underwent a new LAMS placement with or without concomitant coaxial plastic stents. The remaining 3 patients underwent successful plastic stent placement. No LAMS-related AEs were seen among the 7 patients with technical failure. The median follow-up length was 153 days (mean, 258 days; interquartile range, 92-365).

After exclusions for technical failure (7 patients, 2.1%), lost to follow-up information (7 patients, 2.1%), and deaths unrelated to LAMSs (2 patients [.6%] for cardiac arrest and 8 patients [2.4%] who presented with sepsis and multiorgan failure [MOF] before any intervention received intensive care support and finally died), 304 patients were included in the analysis, constituting our study population. The rate of clinical success was 89.5% (272/304).

One or more LAMS-related AEs were noted in 74 of 304 patients (24.3%). These 74 cases included 79 AEs (5 patients with 2 AEs) consisting of 22 (27.8%) cases of bleeding (Fig. 1), 20 (25.3%) stent migrations (Fig. 2), 19 (24.1%) infections, 14 (17.7%) stent occlusions, 3 (3.8%) with buried stent syndrome (Fig. 3), and 1 (1.3%) occlusion of the pylorus (Table 1). The control group consisted of 230 patients without any of these conditions. Baseline characteristics for cases and control subjects are given in Table 2.

For the 74 patients who experienced AEs, the mean age was 56 years (standard deviation, 17) and 25 (33.8%) were female patients. Forty-four patients (59%) underwent drainage for WON. PPs were drained in the remaining 30 patients (41%). The most common etiologies of pancreatitis were gallstone (35.1%), alcohol (33.8%), and idiopathic (17.6%). Major indications for drainage were abdominal pain (33.8%), gastric outlet obstruction (28.4%), and symptoms suggestive of infection (27%).

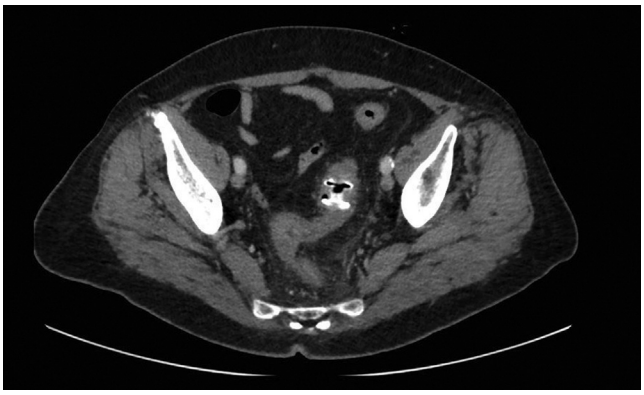

Figure 2. CT shows migration of the lumen-apposing metal stent in the sigmoid colon.

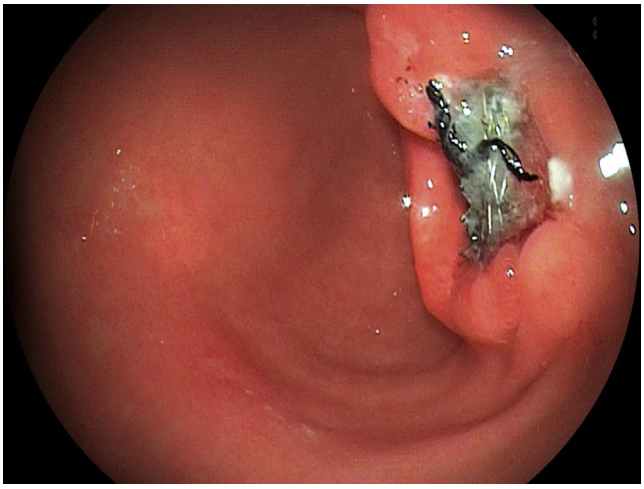

Figure 3. EGD revealed a buried stent syndrome with gastric mucosa partially covering the lumen-apposing metal stent.

Fluid collection extension into the paracolic gutter was observed in 6.8% of cases. In most cases (91.9%), EUS-guided drainage were performed with the EC-LAMSs. Twenty-eight patients (37.8%) required endoscopic necrosectomy. Concomitant percutaneous drainage was used in 12.2% of cases.

According to the ASGE lexicon,[16] 20 AEs (25.3%) were classified as mild, 54 (68.4%) as moderate, and 5 (6.3%) as severe. Regarding all 79 included AEs, 46 (58.2%) were managed endoscopically, 27 (34.2%) were managed conservatively, and 6 (7.6%) were managed through interventional radiology. No AE required surgical management.

All results of the univariate analysis are shown in Table 2. On univariate analysis, case and control groups did not differ statistically in terms of age, gender, indication for collection drainage, etiology of pancreatitis, fluid location and mean size, stent type and diameter, and endoscopic necrosectomy. There were, however, some differences. Compared with control subjects, cases were more likely (at $P \leq .100$) to have drainage of WON

TABLE 1. Characteristics of main adverse events, with severity grade index and their management

Adverse event	No. of events (%)	Early (<14 days)	Late (>14 days)	Severity grade index	Management
Bleeding	22 (27.8)	13	9	3 severe 17 moderate 2 mild	12 endoscopy 5 interventional radiology 5 conservative
Stent migration	20 (25.3)	6	14	8 moderate 12 mild	8 endoscopy 12 conservative
Infection	19 (24.1)	11	8	2 severe 12 moderate 5 mild	10 endoscopy 8 conservative 1 interventional radiology
Stent occlusion	14 (17.7)	3	11	13 moderate 1 mild	13 endoscopy 1 conservative

versus PP (OR, 1.66; 95% CI, .98-2.86; $P = .062$) and to need concomitant percutaneous drainage (OR, 2.13; 95% CI, .85-5.01; $P = .098$) but were less likely to have PFCs extending up to the paracolic gutter (OR, .44; 95% CI, .14-1.10; $P = .100$), to undergo nasocystic tube placement (OR, .40; 95% CI, .16-1.01; $P = .046$), and to undergo pneumatic tract dilation (OR, .61; 95% CI, .33-1.08; $P = .092$). On multivariable analysis (Table 3), PFC classification (WON vs pseudocyst; OR, 2.18; 95% CI, 1.09-4.46; $P = .028$) and pneumatic tract dilation (yes vs no; OR, .47; 95% CI, .22-.93; $P = .034$) remained statistically significant.

Among cases, AEs were diagnosed after a mean time of 25.3 days (median, 18 days; interquartile range, 6-30) from the time of stent placement. The mean days of diagnosis for each AE was 16.0 days for bleeding (interquartile range, .0-75), 45.0 for stent migration (interquartile range, 2-146), and 23.8 for stent occlusion (interquartile range, 1-60). Stent migration was significantly associated with longer time from stent insertion as compared with other events ($P = .026$).

The cumulative incidence of AEs during the study period is shown in Figure 4. Early AEs, within 14 days from LAMS placement, were observed in 34 of 79 cases (43.0%). Among early AEs, bleeding (13/34, 39.4%) and infection (11/34, 32.3%) were the most commonly diagnosed. Stent migration and stent occlusions represented 17.6% (6/34) and 8.8% (3/34) of early AEs, respectively. Severe/moderate AEs had (not significantly) shorter time (22.0 days; 95% CI, 14.5-50.3) to diagnosis as compared with mild AEs (36.5 days; 95% CI, 22.6-50.4; $P = .071$).

DISCUSSION

In the last 2 decades endoscopic drainage of PFCs has become widespread. Additionally, the availability of devices specifically designed for transmural drainage, such as LAMSs, has substantially contributed to the diffusion of these procedures. As the use of LAMSs has increased, more safety data regarding clinically relevant AEs at unexpectedly high rates have raised concerns about LAMS safety, highlighting the need of further and focused studies. In this work, we reported data from a wide cohort of patients treated with LAMSs for symptomatic mature PFCs (ie, pseudocyst or WON), and factors related to AEs were investigated through a nested case-control study. In our cohort, the overall rate of AEs was 24.3%, whereas data from published series reported rates from 3% to 53%.[9-15,19-23] Most of these studies were not prospective and the definitions of AEs were not uniform, preventing generalizability of LAMS-related AEs. For instance, some published series did not report or analyze the stent occlusion rate or buried stent syndrome as an AE.[10,19]

It is known that the clinical outcomes of collections containing solid debris are worse than drainage of pseudocysts.[24,25] In fact, the solid necrotic material may not drain spontaneously through the stent, requiring additional procedures, such as endoscopic necrosectomy, in around 60% of patients.[20] Although a lower clinical success rate for WON compared with PP has already been described, it is not clear whether WON drainage procedures are burdened by an increased risk of AEs. In our study, drainage of WON compared with PP is associated with an increased risk of AEs in both univariate and multivariate analysis, whereas none of the other additional procedures usually performed to facilitate drainage of collections (ie, endoscopic necrosectomy, plastic stent through the LAMS) increased such risk.

Consistently, nasocystic tube drainage and pneumatic dilation of the stent reduce the risk of AEs, even if only the latter has been confirmed in multivariate analysis (OR, .47; 95% CI, .22-.93; $P = .034$). As reported above, this could be attributed to the presence of necrotic material that can obstruct the stent, impairing the drainage of the collection and increasing the risk of AEs such as infection and stent occlusion. Larger and well-designed studies are needed to address this critical point. Bleeding is one of the most feared AEs related to SEMSs and LAMSs in the setting of PFC drainage. Bleeding can

TABLE 2. Demographic data and analyzed variables of case and control groups

Variable	Case (n = 74)	Control (n = 230)	Univariable analysis		
			Odds ratio	95% Confidence interval	*P* value
Mean age, y (SD)					
	56 (17)	56 (16)	1.00	(.99-1.02)	.787
Gender					
Male	49 (66.2)	150 (65.2)	1		
Female	25 (33.8)	80 (34.8)	.99	(.54-1.77)	.969
Indication for PFC drainage					
Abdominal pain	25 (33.8)	74 (32.2)	1		
Gastric outlet obstruction	21 (28.4)	46 (20.0)	1.35	(.68-2.64)	.425
Symptoms suggestive of infected collection	20 (27)	88 (38.2)	.65	(.32-1.26)	.280
Early satiety	5 (6.8)	16 (7.0)	.93	(.28-2.64)	.946
Jaundice	2 (2.7)	2 (.9)	2.96	(.34- 25.7)	.273
rapid increase in size	1 (1.4)	4 (1.7)	.74	(.04-5.29)	.819
PFC location					
Head	16 (21.6)	37 (16.1)	1		
Tail	17 (23.0)	49 (21.3)	.80	(.36-180)	.592
Body	41 (55.4)	144 (62.6)	.66	(.34-1.32)	.229
PFC classification					
PP	30 (41.0)	123 (53.5)	1		
WON	44 (59.0)	107 (46.5)	1.66	(.98-2.86)	.062
Mean PFC size (SD)	113.5 (44.2)	113.6 (64.0)	1	(.99-1.00)	.799
Mean length of hospitalization, days (SD)	8.3 (14.1)	9.2 (18.3)	1	(.99-1.02)	.797
Mean procedure time, min (SD)	31.6 (20.3)	32.1 (21.1)	1	(.99-1.02)	.795
Recurrent WON or pseudocyst					
No	63 (85)	214 (93.0)	1		
Yes	11 (15)	16 (7.00)	2.15	(.90-4.93)	.073
Stent type					
EC-LAMS (hot AXIOS)	68 (91.9)	208 (90.4)	1	—	—
LAMS (cold AXIOS)	6 (8.1)	22 (9.6)	.83	(9.30-2.03)	.706
Stent diameter					
≤10 mm	25 (33.8)	62 (27.0)	1		
>10 mm	49 (66.2)	168 (73.0)	.72	(.41-1.28)	.259
Drainage approach					
Transgastric	70 (94.6)	217 (94.3)	1		
Transduodenal	4 (5.4)	13 (5.7)	.83	(.30-2.65)	.726
Tract dilation					
No	54 (73.0)	147 (64.0)	1		
Yes	20 (27.0)	83 (36.0)	.61	(.33-1.08)	.092
Necrosectomy					
Yes	28 (37.8)	78 (33.9)	1		
No	46 (62.2)	152 (66.1)	.9	(.53-1.54)	.691
Hydrogen peroxide irrigation					
Yes	16 (21.6)	59 (25.7)	1		
No	58 (78.4)	171 (74.3)	1.02	(.57-2.07)	.950

(*continued on the next page*)

TABLE 2. Continued

Variable	Case (n = 74)	Control (n = 230)	Univariable analysis		
			Odds ratio	95% Confidence interval	*P* value
Nasocystic tube					
Yes	9 (12.2)	12 (5.2)	1		
No	65 (87.8)	218 (94.8)	.40	(.16-1.01)	.046
Pigtail stents placed through the LAMS					
Yes	9 (12.2)	25 (10.9)	1		
No	65 (87.8)	205 (89.1)	.87	(.40-2.07)	.748
Concomitant percutaneous drainage					
No	65 (87.8)	216 (94.0)	1		
Yes	9 (12.2)	14 (6.0)	2.13	(.85-5.01)	.098
Extension of fluid collection to paracolic gutter					
No	59 (79.7)	167 (72.6)	1		
Yes	5 (6.8)	32 (13.9)	.44	(.14-1.10)	.100
Not reported	10 (13.5)	31 (13.5)	.91	(.42-1.96)	.420

Values are n (%) unless otherwise defined.
SD, Standard deviation; *PFC*, pancreatic fluid collection; *PP*, pseudocyst; *WON*, walled-off necrosis; *EC-LAMS*, electrocautery-enhanced lumen-apposing metal stent; *LAMS*, lumen-apposing metal stent.

originate from the gastric wall, which is easier to manage endoscopically, or from the cavity, where the retroperitoneal vessels are usually larger and the possibilities of successful endoscopic hemostasis are significantly reduced. In these cases, radiologic embolization is often required. It has been hypothesized that the LAMSs could result in a rapid collapse of the cavity, resulting in the risk of contact between the retroperitoneal vessels and the distal flange of the stent.[26] The prolonged contact and movement relative to the stent could result in erosion and rupture of the vessels, thus causing acute severe bleeding. Considering this hypothesis, bleeding may be associated with the stent indwell time, with greater risk in case of late removal. This point has been stressed in many studies, and early removal of the LAMS after 4 weeks is emerging as a proposed strategy in clinical practice.[14,23,27] In our study, bleeding represents 27.8% of all AEs (22/79), with an overall risk of 22 of 304 (7.2%) and 3 cases (3/304, .98%) classified as severe. Published series and randomized trials reported a bleeding risk ranging from 0% to 21%.[9-12,14,15,19-23] Interestingly, 13 of 22 cases (59%) of bleeding were reported in the first 14 days from the positioning of the stent. Although early removal of the stent after the resolution of the collection could be a reasonable strategy, these data highlight that bleeding caused by LAMSs cannot be considered exclusively as a late AE. Recently, Dhir and colleagues[27] described a protocol of early removal of the metal stent after 3.5 weeks and reported a bleeding risk of 3.5%, thus confirming the presence of residual risk. Of note, 1 case of bleeding from our cohort was reported at the time of LAMS removal; therefore, endoscopists should be aware of such an AE in every step of the PFC management.

LAMSs were conceived with a specific antimigratory design to overcome the high risk of migration reported for SEMSs. However, several studies reported risk of migration up to 20%.[14,21,22] In this study we reported an overall risk of migration of 6.6% (20/304), which is in line with most published series.[9-15,19-23] The LAMS can migrate into the GI lumen, where it can be easily retrieved, or into the cavity. In the latter case, it is necessary to enter the cavity to retrieve the stent, such as during necrosectomy, with possible further risks and AEs. No cases of migration into the cavity were reported in our cohort, and in most cases migration was a minor AE, treated conservatively in 12 of 20 patients (60%) because the collection had resolved. Of note, stent migration occurred most commonly as a late AE, with a mean time of diagnosis of 45 days (range, 2-146), and was significantly associated with longer time from stent insertion as compared with other events.

Traditionally, endoscopic transmural drainage of PFCs has been a complex multistep procedure that requires access to the cavity, over-the-wire dilation of the tract, and finally stent positioning through the dilated tract. In case of the need for necrosectomy, removal of most stents and hydraulic dilation of the tract to 12 mm or more are required. These procedures involve multiple steps with an inherent small risk of fluid leakage between the gut wall and the collection. In our study population, 276 of 304 procedures (90.8%) were performed with the enhanced-cautery delivery system, which allows the catheter to enter the cavity with a "free-hand" technique and subsequently to deliver the stent without the

TABLE 3. Results from the multivariable analysis

Variable	Odds ratio	95% Confidence interval	*P* value
PFC classification			
Pseudocyst	1		
WON	2.18	(1.09-4.46)	.028
Recurrent WON or PP			
No	1		
Yes	1.79	(.62-4.80)	.259
Tract dilation			
No	1		
Yes	.47	(.22-.93)	.034
Nasocystic tube			
Yes	1		
No	.72	(.26-2.09)	.522
Concomitant percutaneous drainage			
No	1		
Yes	1.51	(.49-4.38)	.456
Extension of fluid collection to paracolic gutter			
No	1		
Yes	.43	(.14-2.10)	.097
Not reported	.94	(.43-1.07)	.975

PFC, Pancreatic fluid collection; *WON*, walled-off necrosis; *PP*, pancreatic pseudocyst.

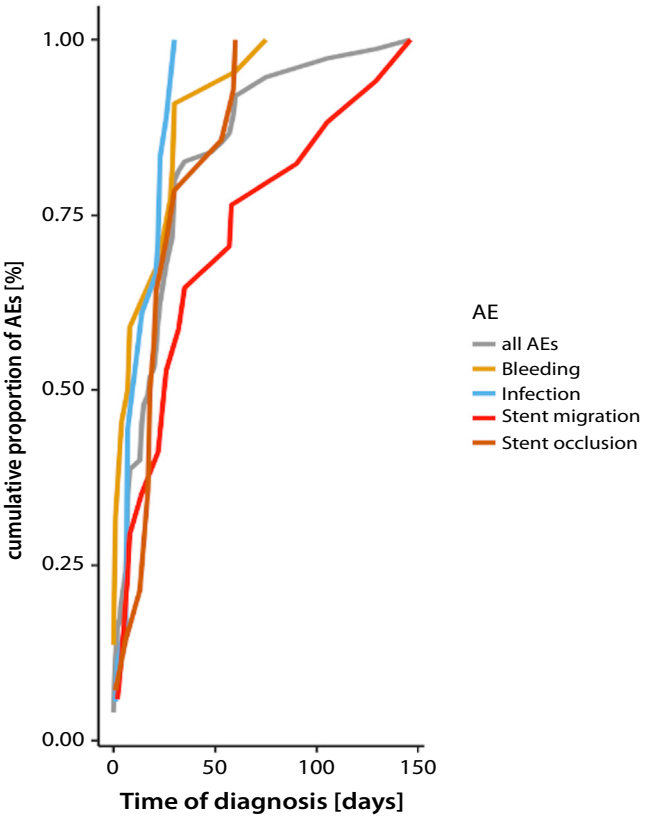

Figure 4. Cumulative proportion of adverse events after lumen-apposing metal stent placement. *AE*, Adverse event.

need for device exchange. It is interesting to note that despite the significant number of procedures reported in this study, no cases of procedure-related perforation or peritonitis were described, which have occasionally been reported during the multistep drainage procedure. Overall, no AEs required surgical management.

In our cohort, we reported a non-negligible mortality rate (12 events: 2 cardiac arrests and 10 MOFs), none of which was related to LAMSs. The main indication of the drainage in these patients was the infection of the collection, complicated by MOF, which finally led to death. As mentioned, infected pancreatic necrosis is a severe clinical condition. It has been reported to have an overall mortality of 15% in patients with infected necrosis, which reached 35% in patients with MOF.[28] In a recent study the overall mortality in patients with infected necrosis who underwent endoscopic drainage was about 18%.[20] Focusing on PFC drainage with LAMSs, published cohorts reported a lower risk of mortality, which ranged from 0% in most studies to 5%.[9-15,19-23] In our study the overall mortality risk was 3.7%. Of note, these cases were mostly complicated patients who necessitated intensive care unit placement before the endoscopic procedure or with advanced cancer and in whom the events leading to MOF and death were not related to the procedure and/or to the stent. The best approach to drain these high-risk patients is not yet defined, but it has been hypothesized that a shorter procedure, without the need for general anesthesia, could limit postoperative stress and could be beneficial for prognosis.[20,29,30] In this setting, delivery of a LAMS with an enhanced-cautery system provides expedited drainage, with an even faster procedure. Our study did not report a protective effect of the use of EC-LAMSs compared with "cold" LAMSs, even if the total number of procedures with "cold" LAMSs was probably too small to make this comparison.

The present study has some limitations, mainly related to the retrospective design. It should also be noted that only one type of commercially available LAMSs was included in this analysis. Moreover, the involvement of several centers with many different operators and clinical settings could have determined some heterogeneity in the data. At the same time, the involvement of several centers could make the results more generalizable. On the other hand, the strengths of this work include the relevant number of patients involved, the standardized definition of AEs, and the design allowing for evaluation of AE-associated risk factors. In conclusion, the findings discussed in this work expand our knowledge about PFC management with LAMSs and could guide further prospective studies aimed to maximize clinical success and to minimize the risk of AEs for patients with PFCs.

REFERENCES

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.
2. Yeo CJ, Bastidas JA, Lynch-Nyhan A, et al. The natural history of pancreatic pseudocysts documented by computed tomography. Surg Gynecol Obstet 1990;170:411-7.
3. Cheruvu CV, Clarke MG, Prentice M, et al. Conservative treatment as an option in the management of pancreatic pseudocyst. Ann R Coll Surg Engl 2003;85:313-6.
4. Alali A, Mosko J, May G, et al. Endoscopic ultrasound-guided management of pancreatic fluid collections: update and review of the literature. Clin Endosc 2017;50:117-25.
5. Gomatos IP, Halloran CM, Ghaneh P, et al. Outcomes from minimal access retroperitoneal and open pancreatic necrosectomy in 394 patients with necrotizing pancreatitis. Ann Surg 2016;263:992-1001.
6. Varadarajulu S, Christein JD, Wilcox CM. Frequency of complications during EUS-guided drainage of pancreatic fluid collections in 148 consecutive patients. J Gastroenterol Hepatol 2011;26:1504-8.
7. Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA 2012;307:1053-61.
8. McVay T, Adler DG. EUS-guided drainage of pancreatic fluid collections: double pigtails, metal biliary, or dedicated transluminal stents? Endosc Ultrasound 2015;4:1-3.
9. Itoi T, Binmoeller KF, Shah J, et al. Clinical evaluation of a novel lumen-apposing metal stent for endosonography-guided pancreatic pseudocyst and gallbladder drainage (with videos). Gastrointest Endosc 2012;75:870-6.
10. Rinninella E, Kunda R, Dollhopf M, et al. EUS-guided drainage of pancreatic fluid collections using a novel lumen-apposing metal stent on an electrocautery-enhanced delivery system: a large retrospective study (with video). Gastrointest Endosc 2015;82:1039-46.
11. Gornals JB, De la Serna-Higuera C, Sanchez-Yague A, et al. Endosonography-guided drainage of pancreatic fluid collections with a novel lumen-apposing stent. Surg Endosc 2013;27:1428-34.
12. Shah RJ, Shah JN, Waxman I, et al. Safety and efficacy of endoscopic ultrasound-guided drainage of pancreatic fluid collections with lumen-apposing covered self-expanding metal stents. Clin Gastroenterol Hepatol 2015;13:747-52.
13. Yang J, Chen YI, Friedland S, et al. Lumen-apposing stents versus plastic stents in the management of pancreatic pseudocysts: a large, comparative, international, multicenter study. Endoscopy 2019;51:1035-43.
14. Garcia-Alonso FJ, Sanchez-Ocana R, Penas-Herrero I, et al. Cumulative risks of stent migration and gastrointestinal bleeding in patients with lumen-apposing metal stents. Endoscopy 2018;50:386-95.
15. Siddiqui AA, Kowalski TE, Loren DE, et al. Fully covered self-expanding metal stents versus lumen-apposing fully covered self-expanding metal stent versus plastic stents for endoscopic drainage of pancreatic walled-off necrosis: clinical outcomes and success. Gastrointest Endosc 2017;85:758-65.
16. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010;71:446-54.
17. Anderloni A, Attili F, Carrara S, et al. Intra-channel stent release technique for fluoroless endoscopic ultrasound-guided lumen-apposing metal stent placement: changing the paradigm. Endosc Int Open 2017;5:E25-9.
18. Breslow NE, Day NE. Statistical methods in cancer research. Volume I—the analysis of case-control studies. IARC Sci Pub 1980;5:338.
19. Lakhtakia S, Basha J, Talukdar R, et al. Endoscopic "step-up approach" using a dedicated biflanged metal stent reduces the need for direct necrosectomy in walled-off necrosis (with videos). Gastrointest Endosc 2017;85:1243-52.
20. van Brunschot S, van Grinsven J, van Santvoort HC, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet 2018;391:51-8.
21. Chandran S, Efthymiou M, Kaffes A, et al. Management of pancreatic collections with a novel endoscopically placed fully covered self-expandable metal stent: a national experience (with videos). Gastrointest Endosc 2015;81:127-35.
22. Mukai S, Itoi T, Sofuni A, et al. Clinical evaluation of endoscopic ultrasonography-guided drainage using a novel flared-type biflanged metal stent for pancreatic fluid collection. Endosc Ultrasound 2015;4:120-5.
23. Bang JY, Navaneethan U, Hasan MK, et al. Non-superiority of lumen-apposing metal stents over plastic stents for drainage of walled-off necrosis in a randomised trial. Gut 2019;68:1200-9.
24. Varadarajulu S, Bang JY, Phadnis MA, et al. Endoscopic transmural drainage of peripancreatic fluid collections: outcomes and predictors of treatment success in 211 consecutive patients. J Gastrointest Surg 2011;15:2080-8.
25. Yang D, Perbtani YB, Mramba LK, et al. Safety and rate of delayed adverse events with lumen-apposing metal stents (LAMS) for pancreatic fluid collections: a multicenter study. Endosc Int Open 2018;6:E1267-75.
26. Bang JY, Hasan M, Navaneethan U, et al. Lumen-apposing metal stents (LAMS) for pancreatic fluid collection (PFC) drainage: may not be business as usual. Gut 2017;66:2054-6.
27. Dhir V, Adler DG, Dalal A, et al. Early removal of biflanged metal stents in the management of pancreatic walled-off necrosis: a prospective study. Endoscopy 2018;50:597-605.
28. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology 2011;141:1254-63.
29. Bang JY, Arnoletti JP, Holt BA, et al. An endoscopic transluminal approach, compared with minimally invasive surgery, reduces complications and costs for patients with necrotizing pancreatitis. Gastroenterology 2019;156:1027-40.e3.
30. van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med 2010;362:1491-502.

Abbreviations: AE, adverse event; ASGE, American Society for Gastrointestinal Endoscopy; LAMS, lumen-apposing metal stent; PFC, peripancreatic fluid collection; MOF, multiorgan failure; OR, odds ratio; PP, pancreatic pseudocyst; SEMS, self-expanding metallic stent; WON, walled-off necrosis.

DISCLOSURE: *The following authors disclosed financial relationships relevant to this publication: A. Sethi: Consultant for Boston Scientific, Olympus, and Fujifilm. A. J. Trindade: Consultant for Olympus America, Pentax America, C2 Therapeutics, and CSA Medical. M. A. Khashab: Consultant for Boston Scientific, Olympus, and Medtronic. F. P. Vleggaar, C. Fabbri, J. R. Aparicio, D. G. Adler: Consultant for Boston Scientific. R. P. Voermans: Consultant for and research grant recipient from Boston Scientific. G. Vanbiervliet: Consultant for Boston Scientific and Cook Medical. P. C. Benias: Consultant for Fujinon Medical, Apollo Endo Surgery, and Boston Scientific. A. Repici: Consultant for Boston Scientific and Fujifilm. A. Anderloni: Consultant for Boston Scientific and Olympus. All other authors disclosed no financial relationships.*

0016-5107/$36.00
https://doi.org/10.1016/j.gie.2019.11.021

Received July 2, 2019. Accepted November 9, 2019.

Current affiliations: Digestive Endoscopy Unit, Department of Gastroenterology, Humanitas Research Hospital, Rozzano, Italy (1), Division of Digestive and Liver Disease, Columbia University Medical Center-NYPH, New York, New York, USA (2), Division of Gastroenterology, Long Island Jewish Medical Center, Zucker School of Medicine at Hofstra/Northwell, Northwell Health System, New Hyde Park,

New York, USA (3), Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy (4), Institute of Liver Studies, Kings College Hospital, London, UK (5), Therapeutic Endoscopy, Division of Gastroenterology and Hepatology, Johns Hopkins Hospital, Baltimore, Maryland, USA (6), Department of Gastroenterology and Hepatology, University Medical Center, Utrecht, Netherlands (7), Endoscopy Service, Department of Diagnostic and Therapeutic Services, IRCCS-ISMETT, Palermo, Italy (8), Department of Hepatogastroenterology, Cliniques universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium (9), Unit of Gastroenterology and Digestive Endoscopy, Forlì-Cesena Hospitals, AUSL, Romagna, Italy (10), Endoscopy Unit, Digestive Service, Alicante University General Hospital, Alicante, Spain (11), Department of Gastroenterology & Hepatology, Amsterdam University Medical Centers AMC, Amsterdam, Netherlands (12), Department of Gastroenterology, Municipal Hospital, Gera, Germany (13), Digestive Endoscopy Unit, l'Archet University Hospital, Nice, France (14), Service d'Hépato-gastro-entérologie, CH Princesse Grace, Monaco (15), Division of Gastroenterology and Hepatology, University of Utah School of Medicine, Salt Lake City, Utah, USA (16), Humanitas University, Rozzano, Italy (17).

Reprint requests: Alessandro Fugazza, MD, Digestive Endoscopy Unit, Departement of Gastroenterology, Humanitas Research Hospital, Rozzano(MI), Italy. E-mail: alessandro.fugazza@humanitas.it.