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Original research

Comparison of lumen-apposing metal stents versus double-pigtail plastic stents for infected necrotising pancreatitis

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ABSTRACT

Objective Lumen-apposing metal stents (LAMS) are believed to clinically improve endoscopic transluminal drainage of infected necrosis when compared with double-pigtail plastic stents. However, comparative data from prospective studies are very limited.

Design Patients with infected necrotising pancreatitis, who underwent an endoscopic step-up approach with LAMS within a multicentre prospective cohort study were compared with the data of 51 patients in the randomised TENSION trial who had been assigned to the endoscopic step-up approach with double-pigtail plastic stents. The clinical study protocol was otherwise identical for both groups. Primary end point was the need for endoscopic transluminal necrosectomy. Secondary end points included mortality, major complications, hospital stay and healthcare costs.

Results A total of 53 patients were treated with LAMS in 16 hospitals during 27 months. The need for endoscopic transluminal necrosectomy was 64% (n=34) and was not different from the previous trial using plastic stents (53%, n=27)), also after correction for baseline characteristics (OR 1.21 (95% CI 0.45 to 3.23)). Secondary end points did not differ between groups either, which also included bleeding requiring intervention—5 patients (9%) after LAMS placement vs 11 patients (22%) after placement of plastic stents (relative risk 0.44; 95% CI 0.16 to 1.17). Total healthcare costs were also comparable (mean difference −€6348, bias-corrected and accelerated 95% CI −€26 386 to €10 121).

Conclusion Our comparison of two patient groups from two multicentre prospective studies with a similar design suggests that LAMS do not reduce the need for endoscopic transluminal necrosectomy when compared with double-

WHAT IS ALREADY KNOWN ON THIS SUBJECT?

⇒ The endoscopic step-up approach is preferred over a surgical step-up approach in eligible patients with infected necrotising pancreatitis.
⇒ The choice of stents is not finally established, while it is believed that the larger lumen diameter of lumen-apposing metal stents (LAMS) facilitates improved drainage of pancreatic and peripancreatic necrosis and may be superior over the current standard, double-pigtail plastic stents.
⇒ The results of the only randomised trial did, however, indicate a higher complication rate, in particular severe bleeding, when LAMS were used.

WHAT ARE THE NEW FINDINGS?

⇒ In our comparative non-randomised study using data from two prospective trials, the need for endoscopic transluminal necrosectomy in patients with infected necrotising pancreatitis treated with LAMS was not lower compared with plastic stents.
⇒ Clinical outcomes, including total number of interventions, length of hospital stay and total healthcare costs, as well as complications (especially bleeding) did not differ either between groups.

HOW MIGHT IT IMPACT ON CLINICAL PRACTICE IN THE FORESEEABLE FUTURE?

⇒ Based on the results of this study, LAMS and plastic stents can both be used for endoscopic transluminal drainage of infected necrosis.

pigtail plastic stents in patients with infected necrotising pancreatitis. Also, the rate of bleeding complications was comparable.

INTRODUCTION

Necrotising pancreatitis is a potentially lethal disease, with a mortality rate up to 30%.[1–4] Minimally invasive step-up intervention is indicated in the majority of patients with infected pancreatic and peripancreatic necrosis.[5 6] The endoscopic step-up approach is favoured over a surgical step-up approach if technically possible, because it leads to shorter hospital stay and fewer pancreaticocutaneous fistulas.[7 8]

Several innovations were developed to improve the endoscopic step-up approach, including lumen-apposing metal stents (LAMS).[9 10] Theoretically, the wider lumen diameter of LAMS offers improved drainage, facilitates endoscopic transluminal necrosectomy and decreases the risk of stent occlusion. LAMS can also be placed via a single-step electrocautery-assisted device, providing an easier and faster drainage procedure when compared with double-pigtail plastic stents. Finally, endoscopic ultrasound (EUS)-guided transluminal drainage using LAMS does not require fluoroscopic guidance, while this is highly preferred when using plastic stents.

International guidelines are not consistent regarding the use of LAMS. While the European Society of Gastrointestinal Endoscopy guideline suggests that both LAMS and plastic stents can be considered, the Asian consensus guideline state that LAMS should not be used outside clinical trials.[5 11] In contrast, the American Gastroenterological Association guideline concludes that LAMS are preferred.[12] The actual benefit of LAMS is, however, uncertain and not yet proven. Additionally, the price of LAMS is substantially higher than plastic stents. To date, the only high level evidence comes from one single-centre randomised trial that found no difference in total number of procedures, length of hospital stay or overall treatment costs.[13] Moreover, an unusual low need for necrosectomy in patients treated with LAMS (13%) as well as with plastic stents (21%) was reported in this trial. In general, necrosectomy is required in at least 50% of patients, and therefore the potential benefit of LAMS could be underestimated.[7 8] Finally, the trial results raised important safety concerns, as LAMS were associated with higher stent-related complications if not removed within 3 weeks.[13 14]

Clear evidence regarding the routine use of LAMS in patients with infected necrotising pancreatitis is lacking. We performed a prospective multicentre study and compared its findings with a previous study with a similar design, to investigate whether the use of LAMS improves endoscopic transluminal drainage and reduces the need for endoscopic transluminal necrosectomy.

METHODS

Study design

The AXIOMA study was an investigator-initiated multicentre prospective cohort study. We prospectively included consecutive patients with infected pancreatic or peripancreatic necrosis (ie, infected necrosis) who could be drained endoscopically with LAMS in 16 hospitals collaborating with the Dutch Pancreatitis Study Group. We compared this cohort to the patients assigned the endoscopic step-up approach with plastic stents in the TENSION trial.[8] The TENSION trial was a multicentre randomised trial in which the endoscopic step-up approach was compared with the surgical step-up approach in patients with infected necrotising pancreatitis.[8] The study protocol of the AXIOMA study, including in- and exclusion criteria, was identical to the TENSION trial, except for the type of transluminal stent.[8]

An independent Data Safety Monitoring Board assessed patient recruitment and evaluated patient safety after consecutive enrolment of 15 patients. Complications were reported by treating clinicians to the coordinating investigator, who reported these events to the Dutch Central Committee for Research involving human subjects. An independent monitor performed clinical trial monitoring. The AXIOMA study was registered in the Netherlands Trial Registry (registry number NL6878). This investigator-initiated study was funded by an unrestricted grant of Boston Scientific Corporation and Amsterdam UMC, Academic Medical Center, Amsterdam, the Netherlands. Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this study. However, the patient association for pancreatic diseases, the 'Alvleesklierevereniging', was actively involved in meetings of the Dutch Pancreatitis Study Group, including regarding the AXIOMA study and TENSION trial. The study is reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology guidelines.[15]

Study participants

Inclusion criteria were identical to the criteria used in the TENSION trial, in order to create a similar cohort: patients with necrotising pancreatitis, with a strong suspicion or documented evidence of infected necrosis and in whom endoscopic transluminal drainage was deemed indicated and feasible, were eligible for inclusion. Main exclusion criteria were previous invasive intervention for necrotising pancreatitis and chronic pancreatitis according to the M-ANNHEIM criteria (additional criteria provided in online supplemental appendix).[16] We defined infected necrosis as the presence of gas configurations within necrosis on contrast-enhanced CT or a positive culture obtained by fine-needle aspiration. Suspected infected necrosis was defined as clinical signs of persistent sepsis or progressive clinical deterioration despite maximal support on the intensive care unit without any other clear source of infection.

Study procedures

Patients with acute pancreatitis were followed from hospital admission by the study coordinator in the 16 participating centres. Broad-spectrum antibiotics were administered when infected necrosis was suspected or proven. The indication and timing for intervention and eligibility for study inclusion was subsequently evaluated by the nationwide online multidisciplinary expert panel of the Dutch Pancreatitis Study Group.[17] If clinically possible, the intervention was postponed until the stage of walled-off necrosis, when collections were largely or fully encapsulated. After patients provided informed consent, EUS-guided transluminal drainage was performed, similarly to the approach in the TENSION trial, except for the placement of LAMS instead of plastic stents. The LAMS used in this study (Hot AXIOS stent and electrocautery-enhanced delivery system, Boston Scientific) were 15 or 20 mm in diameter and 10 mm in length (online supplemental figure S1). The 20 mm LAMS was preferred when available in the treating hospital. A 7 Fr nasocystic catheter was placed through the LAMS and flushed with 1 L saline/24 hours to keep the fistulous tract open in line with the practice in the TENSION trial. The nasocystic catheter was preferably left in place for irrigation during 1 week. It was allowed to remove the catheter earlier if patients did not tolerate the nasocystic catheter or when the catheter was obstructed. Details

of the study protocol for the plastic stents-group are described in the online supplemental appendix.[8]

If drainage did not lead to clinical improvement after 72 hours, endoscopic transluminal necrosectomy was performed. Clinical improvement was defined as improvement of at least two organ systems (circulatory, pulmonary or renal) or decreased inflammatory markers (C reactive protein (CRP), leucocytes or temperature). Additional percutaneous catheter drainage after endoscopic transluminal drainage was allowed when necrotic collections could not be optimally drained endoscopically. LAMS were removed within 6 weeks. Imaging (preferably magnetic resonance cholangiopancreatography (MRCP)) was conducted to evaluate pancreatic duct integrity prior to stent removal. If the necrotic collection was not fully collapsed or pancreatic duct disruption or disconnection was suspected, the LAMS was, if technically possible, exchanged for plastic stents. In the plastic stents-group, stents were not routinely removed.

Follow-up was completed after 6 months. Outpatient follow-up visits were scheduled at 3 and 6 months after inclusion, to evaluate exocrine and endocrine pancreatic function and to complete two questionnaires (Short-Form-36 (SF-36) and EuroQol Five dimensions (EQ-5D-3L)).[18 19]

End points

The primary end point was the need for endoscopic transluminal necrosectomy. Predefined secondary end points were similar to the TENSION trial and included mortality, new-onset organ failure, bleeding requiring intervention, perforation of a visceral organ and/or enterocutaneous fistula requiring intervention, pancreaticocutaneous fistula, biliary stricture, endocrine and exocrine pancreatic insufficiency, total number of endoscopic, radiological or surgical interventions for infected necrosis (catheter drainage and necrosectomy), total length of intensive care and hospital stay (definitions in online supplemental appendix). Bleeding only requiring blood transfusion (post hoc definition) and bleeding requiring endoscopic, radiological or surgical intervention (similar to the definition in the TENSION trial) are reported separately. LAMS-related complications were post hoc defined as complications that occurred with LAMS in situ. The end points were assessed by an adjudication committee, consisting of five endoscopists and two surgeons. All CT scans and MRIs of the study participants were reviewed and scored by two experienced abdominal radiologists (TLB and MPMK).

Statistical analysis

In the TENSION trial, endoscopic transluminal necrosectomy was performed in 53% of the patients assigned to the endoscopic step-up approach with plastic stents. Based on the findings of another prospective study, we hypothesised that the number of patients needing an endoscopic transluminal necrosectomy procedure could be halved when using LAMS.[20] Assuming a reduction from 53% to 26.5% and using a two-sided significance level of 0.05% and 80% power, we calculated with a χ^2 test that a total of 52 patients needed to be included in the study in addition to the 51 patients assigned to the endoscopic step-up approach with plastic stents from the TENSION trial.

All analyses were done according to the intention-to-treat principle. Patient characteristics are summarised as mean and SD or median and ranges between the 25th and 75th percentile. Results are presented as relative risk (RR) with corresponding CIs or as mean differences with two-sided bias-corrected and accelerated (BCa) 95% CIs calculated by bootstrapping with 5000 samples. Logistic regression analysis was performed to correct for baseline imbalances between groups for the primary end point. An explorative post hoc subgroup analysis was performed to evaluate the primary end point in patients drained with 15 mm vs 20 mm LAMS. There was no missing data for the primary end point, but a few for the secondary end points; all observed data were included in the analysis without imputation. Healthcare costs were calculated from a hospital's perspective, and are presented as mean differences with corresponding two-sided BCa 95% CIs. Unit costs of both groups were price-indexed for the year 2020 and presented in euros. Units and their respective costs are summarised in the online supplemental table S4. All tests were two-sided, with p values <0.05 indicating statistical significance. CIs were not adjusted for multiplicity. Statistical analyses were conducted using R software, V.4.0.3 (R Project for Statistical Computing).

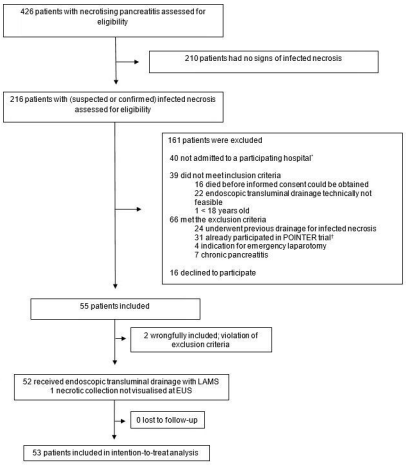

Figure 1 Study enrolment, inclusion and follow-up in LAMS-group. *For clinical and logistical reasons, transfer to a participating hospital participating in AXIOMA study not possible. †Further explained in online supplemental appendix. EUS, endoscopic ultrasound; LAMS, lumen-apposing metal stents.

RESULTS

Study enrolment

From 1 June 2018 to 4 March 2020, a total of 426 patients with necrotising pancreatitis were screened for eligibility. Fifty-three patients were prospectively included in the study (figure 1). Two patients were incorrectly included because percutaneous catheter drainage was preceded prior to study enrolment. Both patients were, after approval of the ethical committee and prior to analysis, replaced with new study participants. The number of included patients finally exceeded the original study sample size, because the last two patients simultaneously consented to enrolment in two different study centres.

One of the 53 enrolled patients did not underwent EUS-guided transluminal drainage with LAMS, because the necrotic collection could not be visualised by EUS. This patient was treated with antibiotics and percutaneous catheter drainage. According to the intention-to-treat principle, outcomes of this patient were included in analysis of the LAMS-group. The remaining 52 patients underwent EUS-guided transluminal drainage with LAMS. Clinical outcomes of the patients in the 53 patients LAMS-group were compared with 51 patients in the plastic stents-group.

Table 1 Baseline characteristics

Characteristics	LAMS (n=53)	Plastic stents* (n=51)
Age—mean±SD	59±13	63±14
Male sex—no. (%)	33 (62)	34 (67)
Body mass index—mean±SD	29±5	30±8
CT severity index† —mean±SD	7±2	7±2
Extent of pancreatic necrosis—no. (%)		
<30%	23 (43)	26 (51)
30%–50%	18 (34)	15 (29)
>50%	12 (23)	10 (20)
Encapsulation—no. (%)		
Medium encapsulated	6 (11)	1 (2)
Largely encapsulated	15 (28)	14 (27)
Fully encapsulated	32 (60)	36 (71)
Necrosis extending >5 cm down the retrocolic gutters—no. (%)	20 (38)	20 (39)
Gas configurations—no. (%)	19 (36)	23 (45)
Disease severity‡		
Admitted to ICU—no. (%)	14 (26)	21 (41)
SIRS§—no. (%)	47 (89)	33 (65)
C reactive protein¶ (mg/L)—median (p25–p75)	248 (144–325)	168 (106–256)
White cell count (10^{-9}/L)**—median (p25–p75)	15 (11–22)	14 (9–17)
Organ failure—no. (%)	12 (23)	13 (25)
Multiple organ failure—no. (%)	7 (13)	9 (18)
Time from onset of symptoms to ETD (days)—median (p25–p75)	36 (26–62)	43 (30–58)

Additional baseline variables are provided in online supplemental table S1.
*Data from plastic stent-group are derived from the multicentre randomised TENSION trial.
†Based on the CT before inclusion; score ranges from 0 to 10, higher scores indicate more extensive pancreatic and peripancreatic necrosis.
‡Data were based on maximum values during the 24 hours before inclusion.
§P=0.005.
¶P=0.017; missing in six patients.
**Missing in two patients.
ETD, endoscopic transluminal drainage; ICU, intensive care unit; LAMS, lumen-apposing metal stents.

Table 2 Primary and secondary end points

Outcome	LAMS (n=53)	Plastic stents* (n=51)	Relative risk (95% CI)	P value
Primary end point				
Need for endoscopic transluminal necrosectomy—no. (%)	34 (64)	27 (53)	1.21 (0.87 to 1.68)	0.320
Secondary end points				
Death—no. (%)	6 (11)	9 (18)	0.64 (0.25 to 1.67)	
New-onset organ failure—no. (%)	9 (17)	7 (14)	1.24 (0.50 to 3.07)	
Pulmonary	7 (13)	4 (8)	1.68 (0.52 to 5.41)	
Cardiovascular	7 (13)	3 (6)	2.25 (0.61 to 8.21)	
Renal	4 (8)	2 (4)	1.92 (0.37 to 10.05)	
New-onset multiple organ failure†—no. (%)	6 (11)	2 (4)	2.89 (0.61 to 13.65)	
Bleeding—no. (%)	9 (17)	11 (22)	0.79 (0.36 to 1.74)	
Bleeding only requiring blood transfusion—no. (%)	4 (8)	0 (0)	–	
Bleeding requiring intervention—no. (%)	5 (9)	11 (22)	0.44 (0.16 to 1.17)	
Perforation of a visceral organ or enterocutaneous fistula—no. (%)	1 (2)	4 (8)	0.24 (0.03 to 2.08)	
Pancreaticocutaneous fistula—no. (%)	3 (6)	2 (4)	1.44 (0.25 to 8.28)	
Biliary stricture—no. (%)	1 (2)	3 (6)	0.32 (0.03 to 2.98)	
Exocrine insufficiency				
Use of enzymes—no. (%)	19 (36)	17 (34)	1.05 (0.62 to 1.79)	
Faecal elastase <200 mg/g—no. (%)‡	23 (48)	23 (52)	0.92 (0.61 to 1.38)	
Endocrine insufficiency—no. (%)	11 (21)	10 (20)	1.06 (0.49 to 2.28)	

Data are n (%).
*Data from the plastic stents-group are derived from the multicentre randomised TENSION trial.
†New-onset organ failure was defined as organ failure not present at randomisation.
‡Missing in five patients in LAMS-group and seven patients in the plastic stents-group
LAMS, lumen-apposing metal stents.

Outcomes

Baseline characteristics

Baseline characteristics were mostly equally distributed between patients treated with LAMS and plastic stents (table 1 and online supplemental table S1). More patients in the LAMS-group met the systemic inflammatory response syndrome (SIRS) criteria (89% vs 65%, p=0.005) and had higher CRP levels at inclusion (median 245 (p25–p75 114–325) vs median 168 (p25–p75 106–256), p=0.017) when compared with the plastic stents-group. Twenty-five patients (47%) were drained with 15 mm LAMS and 27 patients (51%) with 20 mm LAMS.

Primary and secondary end points

The primary end point did not differ between groups: 34 patients (64%) in the LAMS-group vs 27 patients (53%) in the plastic stents-group needed an endoscopic transluminal necrosectomy (RR 1.21; 95% CI 0.87 to 1.68, p=0.320) (table 2). After correction for baseline characteristics (age, sex, timing of drainage, extent of necrosis and necrosis extending >5 cm down the retrocolic gutters) and baseline imbalances (SIRS and CRP), the OR for need for endoscopic transluminal necrosectomy in the LAMS-group versus plastic stents-group was 1.21 (95% CI 0.45 to 3.23).

No difference was found in mortality rate: six patients (11%) died in the LAMS-group vs nine patients (18%) in the plastic stents-group (RR 0.64; 95% CI 0.25 to 1.67). Nine patients (17%) developed new-onset organ failure in the LAMS-group vs seven patients (14%) in the plastic stents-group (RR 1.24; 95% CI 0.50 to 3.07).

Bleeding occurred in 9 patients (17%) in the LAMS-group vs 11 patients in the plastic stents-group (22%) (RR 0.79; 95% CI 0.36 to 1.74). Four patients (8%) developed a bleeding requiring only a blood transfusion in the LAMS-group versus none of the patients in the plastic stents-group (online supplemental figure S2). The remaining 5 patients (9%) in the LAMS-group required an (endoscopic, radiological or surgical) intervention to manage the bleeding vs 11 patients (22%) in the plastic stents-group (RR 0.44; 95% CI 0.16 to 1.17), after a mean of 26 days (median 20 days; p25–p75 14–26) and 37 days (median 26 days; p25–p75 18–55) postdrainage (mean difference −11 days; 95% CI −34 to 18), respectively. Six of 9 patients (67%) had indwelling LAMS and 9 of 11 patients (82%) indwelling plastic stents at the time of the bleeding. Pseudoaneurysms were present in 5 of 9 patients (56%) in the LAMS-group and 10 of 11 patients (91%) in the plastic stents-group. Additional predefined major complications did not differ between groups (table 2).

Other LAMS-related complications were reported in four patients (8%): stent migration occurred in two patients (4%), who were both treated conservatively. Perforation with LAMS in situ did not occur. The LAMS was found buried under overgrowing gastric mucosa in two patients (4%), but could be removed successfully. Complications other than the predefined

Table 3 Secondary end points related to healthcare utilisation

Outcome	LAMS (n=53)	Plastic stents* (n=51)	Relative risk/Mean difference (95% CI)
Interventions for infected necrosis			
Total number interventions (catheter drainage and necrosectomy)—mean (BCa 95% CI)	4.9 (3.8 to 6.4)	4.3 (3.4 to 5.6)	0.6 (–1.1 to 2.3)
Total number of drainage procedures—mean (BCa 95% CI)	2.5 (1.9 to 3.6)	2.5 (2.0 to 3.6)	0 (–1.0 to 1.1)
ETD procedures—mean (BCa 95% CI)	1.1 (1.0 to 1.3)	1.3 (1.1 to 1.7)	–0.2 (–0.6 to 0.0)
Total number of necrosectomies—mean (BCa 95% CI)	2.4 (1.7 to 3.4)	1.8 (1.2 to 2.6)	0.6 (–0.5 to 1.6)
ETN procedures—mean (BCa 95% CI)	2.3 (1.7 to 3.3)	1.8 (1.2 to 2.6)	0.6 (–0.4 to 1.7)
Need for additional PCD—no. (%)	17 (32)	14 (27)	1.17 (0.65 to 2.12)
Need for VARD—no. (%)	2 (4)	2 (4)	0.96 (0.14 to 6.58)
Hospital admission			
Length of ICU admission (days)—mean (BCa 95% CI)	8 (4 to 14)	13 (7 to 26)	– 6 (–17 to 2)
Length of hospital stay (days)—mean (BCa 95% CI)	43 (34 to 55)	53 (42 to 68)	–10 (–27 to 5)
Healthcare costs			
Initial endoscopic drainage procedure—mean (BCa 95% CI)	€5056 (€4479 to €5153)	€2813 (€2490 to 2934)	€2244 (€1941 to €2491)
Total healthcare costs—mean (BCa 95% CI)	€46 860 (€37 991 to €59 680)	€53 208 (€41 479 to €72 123)	-€6348 (-€26 386 to €10 121)

Data are n (%) or mean (BCa 95% CI).
*Data from the plastic stent-group are derived from the multicentre randomised TENSION trial.
BCa, bias-corrected and accelerated CI; ETD, endoscopic transluminal drainage; ICU, intensive care unit; LAMS, lumen-apposing metal stents; PCD, percutaneous catheter drainage; VARD, video-assisted retroperitoneal debridement.

primary and secondary end points are summarised in online supplemental table S2.

Length of intensive care stay (mean 8 days vs 13 days; mean difference −6 (95% CI −17 to 2)) and hospital stay (mean 43 days vs mean 53 days; mean difference −10 (95% CI −27 to 5)) did not differ between groups. The mean number of endoscopic, radiological or surgical interventions for infected necrosis (catheter drainage and necrosectomy) was 4.9 (95% CI 3.8 to 6.4) in the LAMS-group vs 4.3 (95% CI 3.4 to 5.6) in the plastic stents-group (table 3). Seventeen patients (32%) needed percutaneous catheter drainage in the LAMS-group vs 14 patients (27%) in the plastic stents-group-group.

The LAMS was removed after a mean of 47 days (median 41 days; p25–p75 34–50). In 27 patients (51%), the LAMS was exchanged for plastic stents (online supplemental figure S3). During follow-up, two patients (4%) in the LAMS-group versus none in the plastic stents-group developed a symptomatic recurrence of pancreatic fluid collections that required intervention. Both patients had a disrupted or disconnected pancreatic duct on MRCP. The LAMS was previously successfully replaced with plastic stents in one of the patients who developed a recurrence, while this was not possible in the other patient.

At 6 months follow-up, there were no differences in the development of endocrine and exocrine pancreatic insufficiency between groups. The results of the SF-36 and EQ-5D-3L questionnaires and the post hoc analysis are summarised in online supplemental tables S3 and S6.

Costs

The mean costs for the initial endoscopic transluminal drainage procedure were higher for the LAMS-group, with a statistically significant mean difference of €2244 (BCa 95% CI €1941 to €2491) (table 3 and online supplemental table S5). Total healthcare costs were €46 860 (BCa 95% CI €37 991 to €59 680) for the LAMS-group and €53 208 (BCa 95% CI €41 479 to €72 123) for the plastic stents-group (mean difference −€6348, BCa 95% CI −€26 386 to €10 121).

DISCUSSION

This study compared clinical outcome after endoscopic transluminal drainage with LAMS with plastic stents in patients with infected necrotising pancreatitis. The results suggests that LAMS do not reduce the need for endoscopic transluminal necrosectomy as compared with plastic stents. Complication rates, including the risk of bleeding, were comparable between groups. While the initial drainage procedure was more expensive when using LAMS, we found no difference in total healthcare costs.

Our results partly confirm, and contradict the findings of the only single-centre randomised trial that has been performed so far on this topic.[13 14] First, our results confirm that drainage with LAMS did not have the expected clinical advantages in terms of lowering the requirement for endoscopic transluminal necrosectomy. Furthermore, our results support the findings that overall treatment costs are similar, even though the LAMS device is more expensive. In fact, the higher costs of LAMS are probably a minor component of the total treatment costs for patients with necrotising pancreatitis.

Nevertheless, our results contradict the trial's previous findings which demonstrated a higher rate of complications when using LAMS. Our findings indicate similar outcomes for LAMS and plastic stents, without an apparent higher risk of complications or severe bleeding, when the LAMS was removed within 6 weeks. Bleeding is the most feared complication associated with LAMS. It is believed that, as soon as the necrotic collection has collapsed, the opposite cavity wall is exposed to the distal end of the LAMS, which could cause tissue and vascular injury.[13 14] Noteworthy, our results demonstrated that only 67% of patients with indwelling LAMS developed a bleeding; a causal relationship was therefore not evident in our study. LAMS should be removed as early as possible when no longer needed; the authors of the aforementioned randomised trial confirmed in another prospective study that delayed removal was associated with more complications.[21] Based on our study, the 6 weeks interval seems safe. A longer period is usually not required, because exchange for plastic stents is possible when the necrotic collection is not

fully resolved. In conclusion, we confirm the results of a recent systematic review of mainly retrospective studies, reporting that there is no increased bleeding risk when using LAMS.[22] The results of two ongoing randomised trials will provide more information on LAMS safety.[23 24]

However, one important difference between the currently available randomised trial and our study must be taken into consideration. In our study, nasocystic catheters were placed through the LAMS for irrigation, similar to the practice in the plastic stents-group.[8] We choose this approach to strengthen our methodology and minimise differences between groups. However, there is currently no high-level evidence on the advantages of irrigation with a nasocystic catheter on clinical outcome, nor on the most optimal duration, type and volume of irrigation fluids. Moreover, it is currently unclear whether nasocystic irrigation offers any advantages when combined with a LAMS. Similarly, the placement of plastic stents within the LAMS has recently been suggested to improve drainage and prevent damaging the opposite cavity wall.[25 26] Nonetheless, high quality evidence to support this practice is currently lacking.

Necrosis of the pancreatic parenchyma frequently leads to loss of pancreatic duct integrity and is associated with recurrence of pancreatic fluid collections.[27 28] In line with the current guidelines, we therefore choose to exchange LAMS for plastic stents in case of a persistent collection or a proven disrupted duct, to maintain a permanent fistula between the pancreatic duct and the GI tract.[5] Given the low recurrence rate in our study and the inability to replace the LAMS with plastic stents in some patients, the exchange seems not necessary in all patients. Another recent retrospective study including 274 patients also challenged this practice: while approximately 75% of patients had a disrupted or disconnected pancreatic duct following acute necrotising pancreatitis, LAMS were not exchanged for plastic stents.[29] Recurrence of pancreatic fluid collections was, however, noticed in 13% of patients, with only 7% requiring further intervention.

We acknowledge several limitations of this study, despite its multicentre and prospective design. First, our study design, including the use of a historic control group, limits the interpretation of the results. As a consequence, we had to control for some baseline differences. Possible presence of confounding effects despite the similar study designs cannot be ruled out. We also acknowledge that the study was not powered to detect a difference in complications.

Second, we acknowledge that the use of a nasocystic catheter can be seen as a technical variant, which limits the external validity of our results. The LAMS used in this study might be designed to be used without a nasocystic catheter, especially because it was expected that the larger lumen of the LAMS would facilitate drainage, making additional flushing unnecessary. Because the nasocystic catheter was only in situ for 1 week, we do not expect that our study results would have changed without the placement of a nasocystic catheter.

Third, we used both the 15 and 20 mm LAMS in the study, which potentially could have affected clinical outcome. During the course of the study, not all hospitals in the Netherlands had immediate access to the 20 mm LAMS. In view of insufficient evidence about the advantages of the larger lumen, we decided to continue with both stents, reflecting routine clinical practice in the Netherlands. Moreover, outcome did not differ between stent size (online supplemental table S6).

Last, we did not measure the duration of the endoscopic transluminal drainage procedure, which could be a potential important advantage. However, significant reduction of procedural time in favour of LAMS was already proven in the only randomised trial and confirmed in daily clinical practice.[13]

In summary, our study suggests that the use of LAMS does not substantially reduce the need for endoscopic transluminal necrosectomy and leads to similar patient outcomes, complications and healthcare costs when compared with double-pigtail plastic stents in patients with infected necrotising pancreatitis.

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Contributors This study was primarily designed by LB, RCV, MGB, JEvH, J-WP, FPV, MBo, PF and RPV, and was subsequently discussed in research meetings with

all authors. The study was conducted by LB, RCV, MGB, MAB, TLB, SAWB, VCC, WC, CHD, SMvD, HMvD, CvE, E-JvG, MH, WLH, PH, JEvH, MAJMJ, JECK, MPMK, EK, SK, ML, VBN, LP, J-WP, RQ, RJdR, HCvS, CJSW, MS, HCT, BW, DSU, NGV, FV, RLJvW, MBr, PF and RPV. The data were collected and analysed by LB who also drafted the manuscript under supervision of RPV. All authors contributed to the interpretation of the data and to the draft of the manuscript. All authors have approved of the final manuscript. The guarantor of the article is RPV.

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REFERENCES

1 Schepers NJ, Bakker OJ, Besselink MG, *et al*. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. *Gut* 2019;68:1044–51.
2 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.
3 Gurusamy KS, Belgaumkar AP, Haswell A, *et al*. Interventions for necrotising pancreatitis. *Cochrane Database Syst Rev* 2016;4:CD011383.
4 Bang JY, Wilcox CM, Arnoletti JP, *et al*. Superiority of endoscopic interventions over minimally invasive surgery for infected necrotizing pancreatitis: meta-analysis of randomized trials. *Dig Endosc* 2020;32:298–308.
5 Arvanitakis M, Dumonceau J-M, Albert J, *et al*. Endoscopic management of acute necrotizing pancreatitis: European Society of gastrointestinal endoscopy (ESGE) evidence-based multidisciplinary guidelines. *Endoscopy* 2018;50:524–46.
6 Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013;13:e1–15.
7 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.
8 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. *The Lancet* 2018;391:51–8.
9 Binmoeller KF, Shah J. A novel lumen-apposing stent for transluminal drainage of nonadherent extraintestinal fluid collections. *Endoscopy* 2011;43:337–42.
10 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.
11 Teoh AYB, Dhir V, Kida M, *et al*. Consensus guidelines on the optimal management in interventional EUS procedures: results from the Asian EUS group RAND/UCLA expert panel. *Gut* 2018;67:1209–28.
12 Baron TH, DiMaio CJ, Wang AY, *et al*. American gastroenterological association clinical practice update: management of pancreatic necrosis. *Gastroenterology* 2020;158:67–75.
13 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.
14 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.
15 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–9.
16 Schneider A, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. *J Gastroenterol* 2007;42:101–19.
17 van Grinsven J, van Brunschot S, van Santvoort HC, *et al*. The value of a 24/7 online nationwide multidisciplinary expert panel for acute necrotizing pancreatitis. *Gastroenterology* 2017;152:685–8.
18 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
19 Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. *Ann Med* 2001;33:337–43.
20 Abu Dayyeh BK, Mukewar S, Majumder S, *et al*. Large-caliber metal stents versus plastic stents for the management of pancreatic walled-off necrosis. *Gastrointest Endosc* 2018;87:141–9.
21 Bang JY, Hawes RH, Varadarajulu S. Lumen-apposing metal stent placement for drainage of pancreatic fluid collections: predictors of adverse events. *Gut* 2020;69:1379–81.
22 Guzmán-Calderón E, Chacaltana A, Díaz R, *et al*. Head-To-Head comparison between endoscopic ultrasound guided lumen apposing metal stent and plastic stents for the treatment of pancreatic fluid collections: a systematic review and meta-analysis. *J Hepatobiliary Pancreat Sci* 2022;29:198–211.
23 Zhu H-Y, Xie P, Song Y-X, *et al*. Lumen-apposing metal stents (LAMS) versus plastic stents for EUS-guided drainage of walled-off necrosis (WON) (LVPWON): study protocol for a multicenter randomized controlled trial. *Trials* 2018;19:549.
24 Gornals JB, Perez-Miranda M, Vazquez-Sequeiros E, *et al*. Multicenter study of plastic vs. self-expanding metal stents in endoscopic ultrasound-guided drainage of walled-off pancreatic necrosis - PROMETHEUS: a randomized controlled trial protocol. *Trials* 2019;20:791.
25 Puga M, Consiglieri CF, Busquets J, *et al*. Safety of lumen-apposing stent with or without coaxial plastic stent for endoscopic ultrasound-guided drainage of pancreatic fluid collections: a retrospective study. *Endoscopy* 2018;50:1022–6.
26 Ali SE, Benrajab K, Mardini H, *et al*. Anchoring lumen-apposing metal stent with coaxial plastic stent for endoscopic ultrasound-guided drainage of pancreatic fluid collections: any benefit? *Ann Gastroenterol* 2019;32:620–5.
27 Arvanitakis M, Delhaye M, Bali MA, *et al*. Pancreatic-fluid collections: a randomized controlled trial regarding stent removal after endoscopic transmural drainage. *Gastrointest Endosc* 2007;65:609–19.
28 Bang JY, Wilcox CM, Navaneethan U, *et al*. Impact of disconnected pancreatic duct syndrome on the endoscopic management of pancreatic fluid collections. *Ann Surg* 2018;267:561–8.
29 Basha J, Lakhtakia S, Nabi Z, *et al*. Impact of disconnected pancreatic duct on recurrence of fluid collections and new-onset diabetes: do we finally have an answer? *Gut* 2021;70:447–9.

SUPPLEMENTARY APPENDIX

"Comparison of lumen-apposing metal stents versus double-pigtail plastic stents for infected necrotising pancreatitis"

This study was registered in the Netherlands Trial Registry, NL6878.

Boxhoorn L, *et al. Gut* 2022;0:1–7. doi: 10.1136/gutjnl-2021-325632

CONTENT

METHODS

Eligibility criteria

Inclusion criteria

- Documented or suspected infected pancreatic and peripancreatic necrosis (i.e. infected necrosis) and an indication for intervention (see Box S1. for definitions)
- Endoscopic transluminal drainage is technically feasible as deemed by nationwide online multidisciplinary expert panel and/or treating physician
- ≥18 years old

Exclusion criteria

- Previous invasive intervention for necrotising pancreatitis (e.g. percutaneous catheter drainage of (peri)pancreatic necrosis prior to study participation. Ascites drainage and emergency laparotomy without opening the omental bursa was permitted)
- Indication for emergency laparotomy for abdominal catastrophe (e.g. bleeding, bowel perforation, abdominal compartment syndrome)
- Documented chronic pancreatitis according to the M-ANNHEIM criteria [1]
- Participation in other interventional studies which might affect primary or secondary outcome*

* The Dutch Pancreatitis Study Group simultaneously conducted a randomised trial investigating the timing of catheter drainage in patients with infected necrotising pancreatitis (POINTER trial) (overlap period of 16 months; from June 2018 until October 2019).[2] Within the first 35 days of acute pancreatitis, patients were eligible for participation in this trial. Patients included in the POINTER trial were not included in the AXIOMA study.

Study procedures

Process of evaluating study participants prior to inclusion

Hospitalised patients with acute pancreatitis were followed from hospital admission in the collaborating hospitals of the Dutch Pancreatitis Study Group by the study coordinator. Similar to the TENSION trial, the nationwide online multidisciplinary expert panel of Dutch Pancreatitis Study Group was consulted when patients developed necrotising pancreatitis and infected necrosis was suspected or proven.[3] The members of the expert panel individually assessed whether they suspected infected necrosis, the indication for intervention, and the eligibility for inclusion in the AXIOMA study. The expert panel was also used to identify eligible patients in non-participating centers. These patients could then be transferred if clinically appropriate to a study center.

Endoscopic step-up approach with LAMS

The endoscopic step-up approach with LAMS was performed according to the step-up approach in the TENSION trial, with the exception of the placement of LAMS instead of double-pigtail plastic stents.[4] The first step in endoscopic step-up approach was endoscopic ultrasound (EUS)-guided transluminal drainage. The size, location and content of the collection were visualised by EUS after patients were sedated. The LAMS in this study (Hot AXIOS stent and electrocautery-enhanced delivery system, Boston Scientific, Natick, Massachusetts, USA) were 15 or 20 mm in diameter. The delivery catheter was advanced into the necrotic collection after puncturing the gastro-intestinal tissue walls using the electrocautery tip. Next, the distal flange was deployed under endoscopic ultrasound guidance. Finally, the proximal flange was released (either within the endoscope or within the gastrointestinal lumen) under endoscopic guidance. If possible, (aspirated) fluid was sent for fluid analysis, including at least a Gram stain and culture. Finally, a 7 Fr nasocystic catheter was positioned within the necrotic collection and flushed with 1 liter saline/24 hours to keep the fistulous tract open. The nasocystic catheter was left in situ for irrigation for 1 week. It was allowed to remove the catheter sooner if patients did not tolerate the nasocystic catheter or when the catheter was obstructed.

Endoscopic transluminal necrosectomy was performed if endoscopic transluminal drainage did not lead to considerable clinical improvement after 72 hours. Clinical improvement was defined in accordance with the TENSION trial: improved function of at least two organ systems (circulatory, pulmonary, renal) or improvement of two out of three parameters of infection (CRP, leucocytes or

temperature) within 72 hours.[4] Clinical failure was defined as the absence of clinical improvement according to the aforementioned criteria. If there was no clinical improvement 72 hours post-drainage, a contrast-enhanced CT was made to identify the most likely cause of deterioration. Endoscopic transluminal necrosectomy was performed when the contrast-enhanced CT showed that the LAMS was properly positioned and no undrained necrotic collections, that were not in communicating with the one drained via the LAMS, were visualised. During this procedure, the endoscope was introduced through the LAMS into the necrotic collection. Subsequently, endoscopic transluminal necrosectomy was performed with endoscopic devices such as a polypectomy snare, Dormia basket, Roth net or grasping forceps at the discretion of the endoscopist.

Endoscopic step-up approach with double-pigtail plastic stents

The endoscopic step-up approach with double-pigtail plastic stents was performed according to the step-up approach described in the TENSION trial.[4]

The size, location and content of the collection were visualised by EUS after patients were sedated. The necrotic cavity was punctured through the gastric or duodenum wall under EUS guidance with a 19G EUS needle or needle knife at the endoscopists' discretion. In addition, (aspirated) fluid was sent for fluid analysis, including at least a Gram stain and culture. Subsequently, the tract was dilated with a 10 Fr cystotome and 8 mm balloon. At least two 7 Fr double-pigtail plastic stents were then placed in the necrotic collection. Finally, a 7 Fr nasocystic catheter was positioned within the necrotic collection and flushed with 1 liter saline/24 hours to keep the fistulous tract open. The nasocystic catheter was left in situ for irrigation for 1 week. It was allowed to remove the catheter sooner if patients did not tolerate the nasocystic catheter or when the catheter was obstructed.

Endoscopic transluminal necrosectomy was performed if endoscopic transluminal drainage did not lead to considerable clinical improvement after 72 hours, using the aforementioned criteria. If there was no clinical improvement 72 hours post-drainage, a contrast-enhanced CT was made to identify the most likely cause of deterioration. Endoscopic transluminal necrosectomy was performed when the contrast-enhanced CT showed that the plastic stents were properly positioned and no undrained necrotic collections, that were not in communicating with the one drained via the plastic stents, were visualised. During this procedure, the fistulous tract was dilated up to 18 mm. Thereafter, the endoscope was introduced into the necrotic collection. Subsequently, endoscopic transluminal necrosectomy was

performed with endoscopic devices such as a polypectomy snare, Dormia basket, Roth net or grasping forceps at the discretion of the endoscopist.

Additional interventions

Patients were assigned to the endoscopic step-up approach as the initial and preferred technique. However, all clinically indicated procedures for infected necrosis, including percutaneous catheter drainage and if needed video-assisted retroperitoneal debridement (i.e. the surgical step-up approach), were allowed throughout the course of the disease after the first endoscopic transluminal drainage procedure. This approach was mainly used in patients with necrosis extending to the paracolic gutter or other locations, which were not optimally drained by the endoscopic route. The decision to perform percutaneous catheter drainage or step-up to video-assisted retroperitoneal debridement was discussed with the local multidisciplinary team of gastroenterologists, surgeons and (interventional) radiologists. The procedures were performed by experienced interventional radiologists (image-guided percutaneous catheter drainage) or experienced HPB-surgeons (video-assisted retroperitoneal debridement).

LAMS removal

The LAMS cannot be left in situ for long-term as is commonly desired in case of a disrupted or disconnected pancreatic duct to prevent a recurrence of pancreatic fluid collections, because of the risk of complications.[5] The LAMS had to be removed after 6 weeks following the initial drainage procedure. Prior stent removal, imaging (preferably MRI/MRCP) was conducted to asses pancreatic duct integrity prior to stent removal. If the necrotic collection was not fully collapsed or pancreatic duct disruption or disconnected was suspected, the LAMS was exchanged for plastic stents.

Removal of plastic stents

The plastic stents were usually left in situ indefinitely. The decision to remove plastic stents during follow-up was left at the discretion of the endoscopist in combination with the findings on follow-up imaging.

Supportive treatment

Patients were treated in accordance with the International Association of Pancreatology (IAP)/American Pancreatic Association (APA) and the European Society of Gastrointestinal

Endoscopy (ESGE) guidelines.[5, 6] In accordance with the guidelines, the initial treatment of patients with acute pancreatitis is supportive and includes fluid resuscitation therapy, pain management and nutritional support (either oral or by feeding tube). Antibiotic prophylaxis was not given, but selective decontamination of the digestive tract was allowed when patients were admitted at the intensive care unit.[5] In clinically deteriorating patients with signs of infection, blood-, urine-, sputum-, and/or ascites cultures were collected and diagnostic imaging (e.g. chest X-ray and abdominal contrast-enhanced CT) was performed. In case of diagnostic uncertainty, fine-needle aspiration could be performed. Targeted antibiotics were given when a primary focus of infection was found. In case of high suspicion of infected necrosis and persistent clinical deterioration, broad-spectrum antibiotics were started, as advised in the IAP/APA and ESGE guidelines [5, 6]

Box S1. Inclusion and exclusion criteria: definitions

	Definition
Pancreatic necrosis	Diffuse or focal area(s) of non-enhancing pancreatic parenchyma as detected on contrast-enhanced CT.
Peripancreatic necrosis	Persistent peripancreatic fluid collections on contrast-enhanced CT in the absence of pancreatic parenchymal non-enhancement.
Infected necrosis	• Documented infected necrosis is defined as a positive culture of pancreatic necrosis or peripancreatic necrosis obtained by fine-needle aspiration or the presence of gas in the necrotic collection on contrast-enhanced CT. • Suspected infected necrosis is defined as persistent sepsis, new onset sepsis or progressive clinical deterioration without other causes for infection.

Box S2. Definitions of the primary and secondary endpoints [4]

Endpoint	**Definition**
Primary endpoint	The need for endoscopic transluminal necrosectomy
Secondary endpoints	
New onset organ failure	Organ failure occurring after randomisation and not present 24 hours before randomisation: **- Pulmonary**: a PaO2 < 60 mmHg despite FiO2 30% or the need for mechanical ventilation **- Cardiovascular**: a systolic blood pressure < 90 mmHg despite adequate fluid resuscitation or need for vasopressor support **- Renal**: a serum creatinine > 177 mmol/L after rehydration or need for hemofiltration or hemodialysis (not applicable if patients already suffered from renal insufficiency before developing acute pancreatitis [creatinine > 177 umol/L])
Multiple organ failure	Failure of 2 or more organ systems (respiratory, cardiovascular or renal) at the same moment.
Bleeding requiring intervention	Bleeding requiring surgical, radiological, or endoscopic intervention.
Perforation of a visceral organ requiring intervention	Perforation requiring surgical, radiologic, or endoscopic intervention.
Enterocutaneous fistula requiring intervention	Secretion of fecal material from a percutaneous drain or drainage canal after removal of drains or from a surgical wound, either from small or large bowel; confirmed by imaging or during surgery.
Pancreaticocutaneous fistula	Output through a percutaneous drain or drainage canal after removal of drains from a surgical wound, or any measurable volume of fluid with an amylase content >3 times the serum amylase level.
Biliary stricture	Biliary stricture requiring ERCP or PTC.
Exocrine pancreatic insufficiency	• Oral pancreatic-enzyme supplementation required to treat clinical symptoms of steatorrhea 6 months after randomization; this requirement was not present before onset of acute pancreatitis • Fecal elastase <0.2 gram and the need for pancreatic enzyme supplementation; this requirement was not present before onset of acute pancreatitis.
Endocrine pancreatic insufficiency	The need for insulin or oral anti-diabetic drugs; this requirement was not present before onset of acute pancreatitis.

Total number of endoscopic, radiological or surgical interventions	Total number of endoscopic, radiological or surgical interventions for infected necrosis (catheter drainage and necrosectomy).
Length of intensive care stay	Length of admission at the intensive care unit during 6 months follow-up.
Length of hospital stay	Length of hospital stay during 6 months follow-up.
Post-hoc defined secondary endpoints	
Bleeding only requiring blood transfusion	Bleeding requiring blood transfusion only, not requiring surgical, radiologic, or endoscopic intervention.
Direct LAMS-related complications	Complications that occurred with LAMS in situ.

Table S1. Baseline characteristics (continued)

Characteristics	LAMS (*n* = 53)	Plastic stents (*n* = 51)
Cause of pancreatitis – no. (%)		
Gallstones	31 (58)	26 (51)
Alcohol abuse	9 (17)	7 (14)
Other*	13 (25)	18 (35)
ASA classification on admission – no. (%)		
I: Healthy status	7 (13)	7 (14)
II: Mild systemic disease	23 (43)	26 (51)
III: Severe systemic disease	22 (42)	18 (35)
IV: Severe systemic disease with constant treat to life	1 (2)	0 (0)
Disease severity~		
APACHE II score¥ – median (p25–p75)	10 (8–13)	9 (6–13)
Modified Glasgow score† – median (p25–p75)	2 (1–3)	2 (1–3)
Modified MODS score‡ – median (p25–p75)	0 (0–1)	0 (0–1)
SOFA score – median (p25–p75)	0 (0–2)	0 (0–4)

Data are n (%), mean ± SD or median (p25–p75).
APACHE = Acute Physiology and Chronic Health Evaluation, ASA = American Society of Anesthesiologists, MODS = multiple organ dysfunction syndrome, SOFA = Sequential Organ Failure Assessment.
* Includes medication, hypertriglyceridemia, and unknown aetiology.
~ Data were based on maximum values during the 24 hours before inclusion.
¥ APACHE II score ranges from 0 to 71, higher scores indicate more severe disease.
† Modified Glasgow scores range from 0 to 8, higher scores indicate more severe disease.
‡ Modified MODS scores range from 0 to 24, higher scores indicate more severe disease.

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Table S2. Complications other than primary and secondary endpoints

Complications	**LAMS (*n* = 53)**	**Plastic stents (*n* = 51)**
Readmissions – no. (%)	27 (51)	31 (61)
Gastrointestinal		
Ascites – no. (%)	5 (9)	7 (13)
Abdominal compartment syndrome – no. (%)	2 (4)	2 (4)
Bleeding in the liver – no. (%)	0 (0)	1 (2)
Cholangitis or cholecystitis – no. (%)	5 (9)	4 (8)
Bile duct injury – no. (%)	1 (2)	0 (0)
Clostridium infection – no. (%)	1 (2)	0 (0)
Ileus/gastroparesis – no. (%)	5 (9)	1 (2)
Ischaemic colitis – no. (%)	0 (0)	1 (2)
Jaundice – no. (%)	0 (0)	1 (2)
Spleen abcess – no. (%)	0 (0)	1 (2)
Cardiovascular		
Atrial fibrillation or other heart arrhythmias – no. (%)	3 (6)	3 (6)
Congestive heart failure, volume overload or cardiac asthma – no. (%)	7 (13)	1 (2)
Hypertension – no. (%)	1 (2)	0 (0)
Splenic vein or deep venous thrombosis – no. (%)	3 (6)	4 (8)
Pulmonary		
Exacerbation of chronic obstructive pulmonary disease	0 (0)	3 (6)
Hydro-pneumothorax	0 (0)	1 (2)
Pneumonia – no. (%)	4 (8)	16 (31)
Pleural effusion – no. (%)	10 (19)	3 (6)
Pleura empyema – no. (%)	1 (2)	1 (2)
Pulmonary embolus – no. (%)	0 (0)	1 (2)

Neurologic		
Cerebrovascular accident – no. (%)	1 (2)	0 (0)
Delirium – no. (%)	3 (6)	0 (0)
Trauma capitis – no. (%)	1 (2)	0 (0)
Urinary tract		
Urinary tract infection – no. (%)	1 (2)	6 (12)
Pyelonephritis – no. (%)	0 (0)	1 (2)
Other		
Bacteremia – no. (%)	7 (13)	11 (22)
Oral candidiasis – no. (%)	2 (4)	0 (0)
Critical illness neuropathy – no. (%)	2 (4)	0 (0)
Decubitus – no. (%)	2 (4)	0 (0)
Electrolyte disorders[2] – no. (%)	14 (26)	
Gout – no. (%)	1 (0)	0 (0)
Line infection or phlebitis – no. (%)	4 (8)	0 (0)
Toxicoderma – no. (%)	0 (0)	1 (2)
Pediculosis pubis – no. (%)	1 (0)	0 (0)

Data are n (%).
[1] Only pleural effusion requiring intervention was reported in TENSION trial
[2] Not reported as complication in TENSION trial

Table S3. Results of SF-36 and EQ-5D-3L questionnaires of patients treated with LAMS or plastic stents at 3 and 6 months follow-up.

	At 3 months after inclusion [#]			At 6 months after inclusion[#]		
SF-36 (Dutch standard)	**LAMS (n=30)**	**Plastic stents (n=31)**	**P-value**	**LAMS (n=31)**	**Plastic stents (n=25)**	**P-value**
Physical Component	47 ± 11	42 ± 11	0.062	47 ± 11	43 ± 10	0.257
Mental Component	40 ± 6	39 ± 13	0.944	41 ± 7	49 ± 11	0.003
EQ-5D (Dutch standard)	**LAMS (n=31)**	**Plastic stents (n=32)**	**P-value**	**LAMS (n=31)**	**Plastic stents (n=25)**	**P-value**
EQ-5D score (Dutch standard)	0.75 ± 0.19	0.65 ± 0.31	0.375	0.72 ± 0.26	0.76 ± 0.27	0.364
Perceived health score	71 ± 18	64 ± 19	0.160	72 ± 17	72 ± 18	1.000

Data are mean ± SD
[#]Number of patients with completed questionnaires

Table S4. Dutch unit costs for used resources

Resource	Unit	Costs (€, 2020)	Source
Hospital stay[1]			
Intensive care unit stay	Day	1282,62	DCM 2015
General ward stay	Day	514,78	DCM 2015
Outpatient hospital care[1]			
Outpatient clinic visit	Visit	98,41	DCM 2015
Telephone consultation	Consultation	49,21	DCM 2015
Emergency department visit	Visit	280,10	DCM 2015
Laboratory tests[1]			
All chemistry costs per admission day	Test	23,32	Institutional cost ledger
Microbiology			
Blood culture[1]	Test	30,09	Institutional cost ledger
Fecal culture	Test	90,77	Institutional cost ledger
Culture <2 medium[1]	Test	15,10	Institutional cost ledger
Culture 2-3 media[1]	Test	20,43	Institutional cost ledger
Culture 3> media[1]	Test	25,28	Institutional cost ledger
Diagnostic imaging[1]			
CT abdomen	Test	215,61	Institutional cost ledger
CT chest	Test	202,20	Institutional cost ledger
Abdominal ultrasound	Test	115,50	Institutional cost ledger
X-ray chest	Test	47,26	Institutional cost ledger
X-ray abdomen	Test	48,15	Institutional cost ledger
MRI/MRCP	Test	353,09	Institutional cost ledger
Endoscopy[1]			
Endoscopic retrograde cholangiopancreatography (ERCP)	Procedure	1234,62	Institutional cost ledger
Endoscopic ultrasound	Procedure	894,59	Institutional cost ledger
Endoscopic feeding tube placement	Procedure	282,39	Institutional cost ledger
Gastroscopy	Procedure	509,30	Institutional cost ledger
Colonoscopy	Procedure	505,26	Institutional cost ledger
Radiological interventions			

Pleural drainage[2]	Procedure	784,11	Institutional cost ledger
Ascites drainage[2]	Procedure	1023,74	Institutional cost ledger
Ultrasound-guided transhepatic biliary drainage[1]	Procedure	431,18	Institutional cost ledger
Ultrasound-guided gallbladder drainage[1]	Procedure	431,18	Institutional cost ledger
Vascular embolisation[2]	Procedure	1807,45	Institutional cost ledger
Interventions for infected necrosis[2]			
Percutaneous catheter drainage[3]	Procedure	1023,74	Institutional cost ledger
Endoscopic transluminal drainage • Double-pigtail plastic stents • Lumen-apposing metal stent	Procedure	2988,35 5153,36	Institutional cost ledger (plastic stents) Top-down cost calculation (LAMS)
Endoscopic transluminal necrosectomy	Procedure	2988,35	Institutional cost ledger
Videoscopic-assisted retroperitoneal debridement	Procedure	2327,96	APEC Trial [7]
Surgical procedures			
Open cholecystectomy[1]	Procedure	3455,83	Institutional cost ledger
Laparoscopic cholecystectomy[1]	Procedure	3068,33	Institutional cost ledger
Exploratory laparotomy[2]	Procedure	7597,60	Institutional cost ledger
Laparoscopic-assisted loop ileostomy[2]	Procedure	6083,79	Institutional cost ledger
Laparoscopic gastroenterotomy[2]	Procedure	3841,7	Institutional cost ledger
Pancreaticoduodenectomy (Whipple)[2]	Procedure	7872,20	Institutional cost ledger
Laparotomy and splenectomy[2]	Procedure	7077,16	Institutional cost ledger
Laparotomy for incarcerated incisional hernia[2]	Procedure	3692,96	Institutional cost ledger
Thoracothomy[2]	Procedure	3649,66	Institutional cost ledger
Placement of vacuum-assisted closure system[2]	Procedure	1499,73	Institutional cost ledger

DCM: Dutch Costing Manual for health care research.
Culture <2 medium: line tip, catheter tip, culture 2-3 media: urine, throat, rectum, culture >3 media: Ascites, drain fluid, pleural effusion, sputum, wound, pus.
[1] Average costs of academic and teaching hospital.
[2] Unit costs from the academic hospital.
[3] Unit costs were calculated by combining the costs of abdominal CT and ultrasound-guided drainage of abdominal collection.

Table S5. Mean healthcare costs by treatment strategy

Outcome	**LAMS (*n* = 53)**	**Plastic stents (*n* = 51)**	**Cost difference**
	Mean costs in € (BCa 95%CI)	*Mean costs in € (BCa 95%CI)*	*Mean costs in € (BCa 95%CI)*
Interventions for infected necrosis	**€14,119**	**€10,473**	**€3646 (€87 to €7444)**
Initial endoscopic transluminal drainage procedure	**€5056**	**€2813**	**€2244 (€1941 to €2491)**
Endoscopic transluminal drainage	€5630	€3984	
Endoscopic transluminal necrosectomy	€6992	€5274	
Percutaneous catheter drainage	€1410	€1124	
Video-assisted retroperitoneal debridement	€88	€91	
Endoscopy	**€1349**	**€1321**	**€28 (- €518 to €505)**
ERCP	€676	€412	
EUS	€135	€123	
Endoscopic feeding tube placement	€202	€537	
Gastroscopy	€308	€250	
Colonoscopy	€29	€0	
Radiological interventions	**€523**	**€897**	**- €374 (- €832 to €107)**
Pleural drainage	€192	€138	
Ascites drainage	€212	€301	
Ultrasound-guided PTC drainage	€16	€59	
Ultrasound-guided gallbladder drainage	€0	€8	

Vascular embolization	€102	€390	
Surgical procedures[1]	**€1290**	**€754**	**€536 (- €290 to €1410)**
Laboratory	**€996**	**€1239**	**- €243 (- €631 to €126)**
Microbiology	**€429**	**€755**	**- €326 (- €849 to €25)**
Diagnostic imaging	**€1018**	**€1098**	**- €80 (- €411 to €315)**
CT abdomen	€911	€1015	
CT thorax	€107	€83	
Abdominal ultrasound	€61	€66	
X-ray chest	€156	€259	
X-ray abdomen	€51	€83	
MRI/MRCP	€313	€14	
Hospital stay	**€28,116**	**€37,757**	**- €9641 (- €25,381 to €3198)**
Intensive care unit stay	€9801	€17,202	
General ward stay	€18,056	€20,440	
Emergency department visit	€259	€115	
Outpatient hospital care	**€368**	**€234**	**€133 (- €40 to €282)**
Outpatient clinic visit	€260	€208	
Telephone consultation	€108	€26	
Total health-care costs	**€46,860 (€37,991 to €59,680)**	**€53,208 (€41,479 to €72,123)**	**- €6348 (- €26,386 to €10,121)**

[1] Includes all surgical procedures as presented in Table S3.

Table S6. Post-hoc subgroup analysis for patients drained with 15 mm vs. 20 mm LAMS

Outcome	**15 mm (*n* = 25)**	**20 mm (*n* = 27)**	**Risk ratio (95%CI)**	**P-value**
Primary end point				
Need for endoscopic transluminal necrosectomy – no. (%)	15 (60)	19 (70)	1.17 (0.78 to 1.75)	0.562

Figure S1. Hot AXIOS Stent and Electrocautery-Enhanced Delivery System

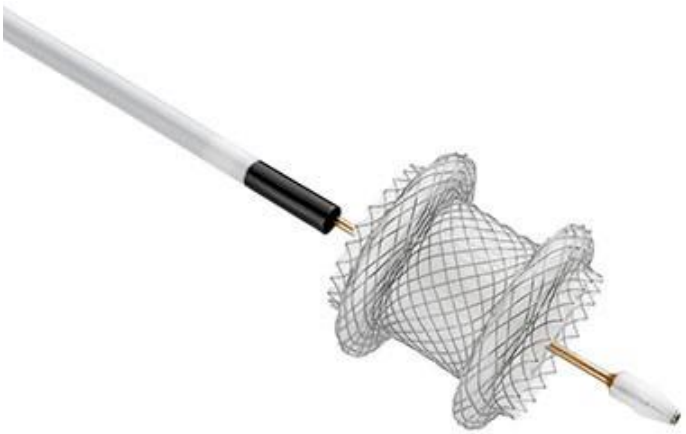
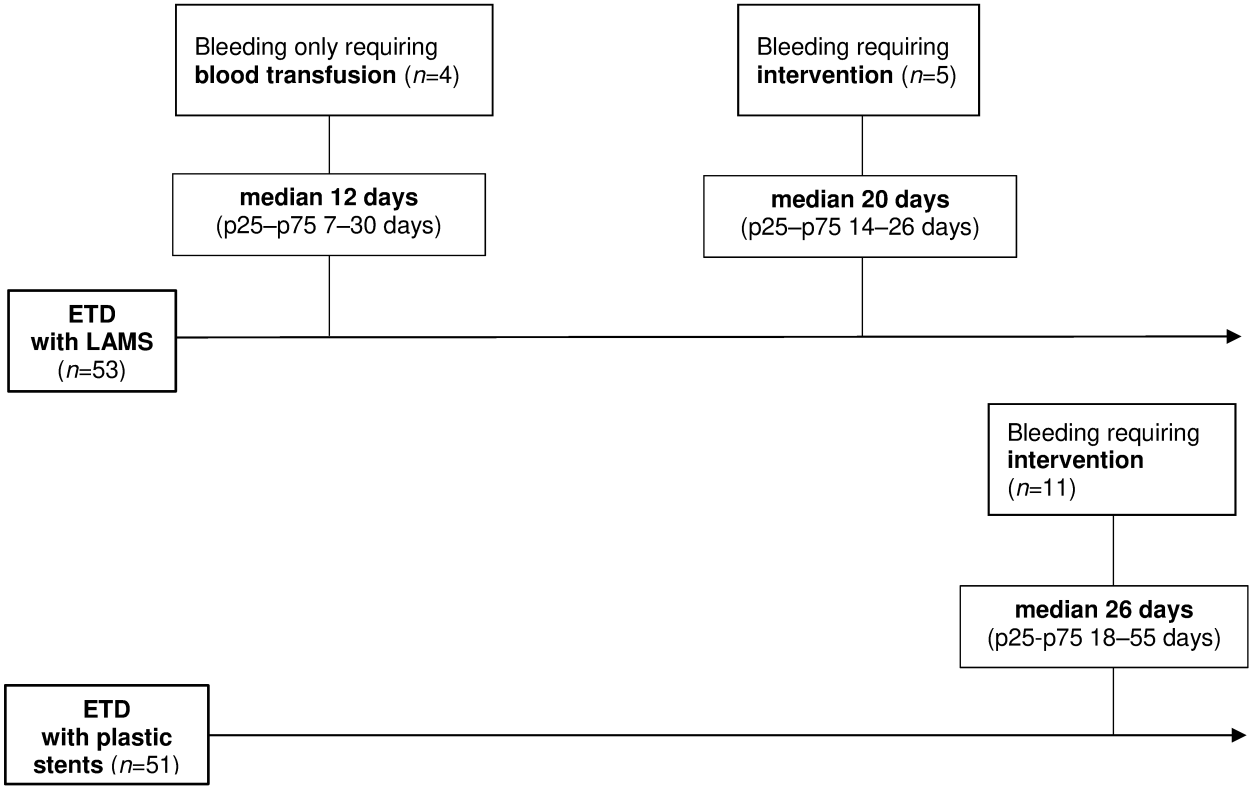
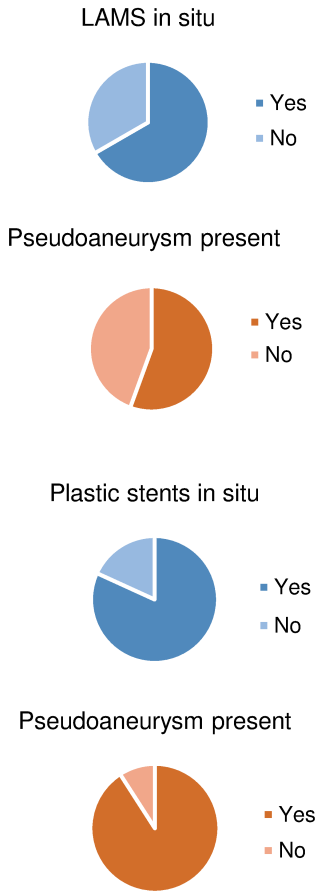


Image courtesy of Boston Scientific, Massachusetts, USA.

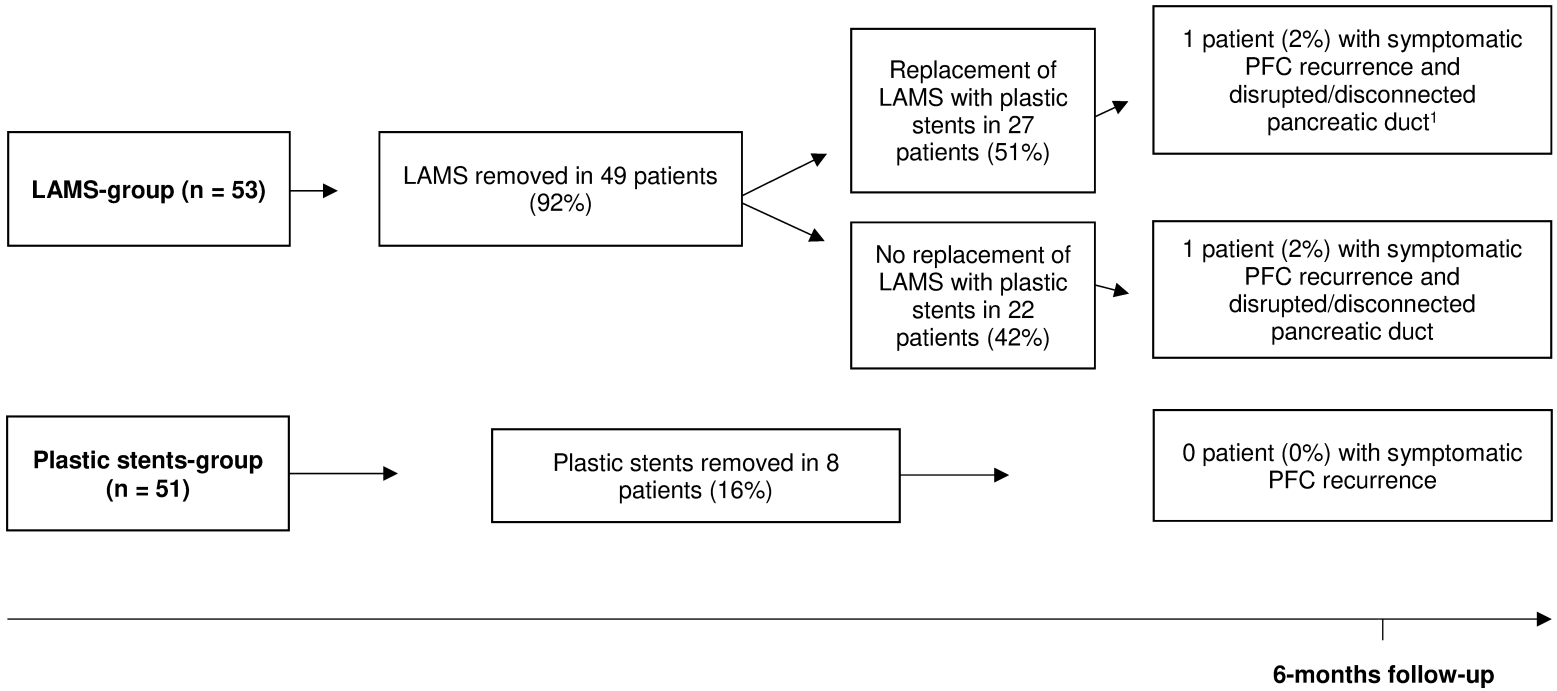
Figure S2. Bleeding in LAMS vs. plastic stents-group





ETD = endoscopic transluminal drainage; LAMS = lumen-apposing metal stent

Figure S3. LAMS removal and recurrence of pancreatic fluid collections



LAMS = lumen-apposing metal stent; PFC = pancreatic fluid collection
[1] Plastic stents removed at the end of follow-up in 1 patient (2%) without PFC recurrence

REFERENCES

1 Schneider A, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol 2007;**42**:101-19.

2 Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bollen TL*, et al.* Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis. N Engl J Med 2021;**385**:1372-81.

3 van Grinsven J, van Brunschot S, van Santvoort HC, Dutch Pancreatitis Study G. The Value of a 24/7 Online Nationwide Multidisciplinary Expert Panel for Acute Necrotizing Pancreatitis. Gastroenterology 2017;**152**:685-8 e6.

4 van Brunschot S, van Grinsven J, van Santvoort HC, Bakker OJ, Besselink MG, Boermeester MA*, et al.* Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. The Lancet 2018;**391**:51-8.

5 Arvanitakis M, Dumonceau JM, Albert J, Badaoui A, Bali MA, Barthet M*, et al.* Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. Endoscopy 2018;**50**:524-46.

6 Working Group IAPAPAAPG. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;**13**:e1-15.

7 Schepers NJ, Hallensleben NDL, Besselink MG, Anten M-PGF, Bollen TL, da Costa DW*, et al.* Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. The Lancet 2020;**396**:167-76.