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Soft self-expandable metal stent to treat painful pancreatic duct strictures secondary to chronic pancreatitis: a prospective multicenter trial

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Abstract

Background and Aims: Fully covered self-expandable metal stents (FCSEMSs) may offer a treatment option for pain associated with a dilated pancreatic duct (PD) in chronic pancreatitis (CP), but optimal patient selection and FCSEMS design, efficacy, and safety remain uncertain. We studied an investigational pancreatic FCSEMS for treatment of CP-associated pain.

Methods: Patients with painful CP, a dominant distal PD stricture, and PD dilation upstream were enrolled in a prospective, multicenter, single-arm trial studying 6-month indwell of a 4- to 6-cm-long soft pancreatic FCSEMS. Primary efficacy and safety endpoints were pain reduction 6 months after FCSEMS indwell (performance goal ≥53%) and PD stenting–related serious

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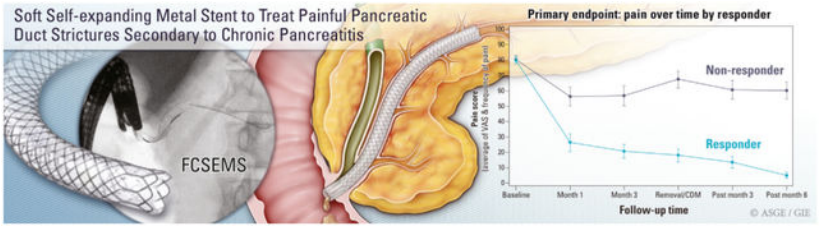
adverse events (SAEs), respectively (performance goal <32%). The primary efficacy endpoint was assessed in patients with sufficiently severe and frequent pain at FCSEMS placement as a first stent or in exchange of a plastic stent.

Results: Among 67 patients (mean age, 52.7 ± 12.5 years; mean time since CP diagnosis, 6.4 ± 6.4 years), 34 (50.7%) had plastic stent placement within 90 days of FCSEMS placement, and 46 patients were eligible for the primary efficacy endpoint analysis. Technical success was 97.0% (65/67). The observed primary efficacy (26.1%, 12/46) and safety endpoints (31.3%, 21/67) failed to meet the a priori study hypotheses. Study stent migration occurred in 47.7% of patients (31/65).

Conclusions: Six-month treatment with an FCSEMS did not lead to an expected degree of pain reduction, and migrations and SAEs were common. Further study is needed to clarify optimal decompressive strategy, FCSEMS design, and patient selection. (Clinical trial registration number: NCT02802020.)

GRAPHICAL ABSTRACT



Abdominal pain is the most common symptom of chronic pancreatitis (CP), observed as the initial presentation in approximately 75% of patients and present during the clinical course of disease in 85% to 97%.[1] CP-associated pain is believed to be caused by parenchymal and ductal hypertension and parenchymal inflammation, but the pathogenesis is multifactorial and complex.[2] For example, pain may be associated with pancreatic duct (PD) dilation and impaired drainage because of strictures or stones; however, pain can occur in the absence of PD dilation and may not resolve after stone removal and ductal decompression.[3] Clinical decision-making for CP is complex, and the implementation of endotherapy, extracorporeal shock wave lithotripsy (ESWL), and surgical and medical treatment varies among specialists.[4] A 2021 systematic review of randomized clinical trials comparing endoscopic therapy versus surgery for the treatment of CP in adult patients with dilation in the main PD concluded that surgical interventions showed superior results when compared with endotherapy in terms of complete long-term pain relief.[5] However, not all patients are agreeable to or fit for surgery, and effective nonsurgical options need to continue to be evaluated and developed. For example, patients with obstructive stones may be offered ESWL alone without any endoscopic or surgical intervention as a first therapeutic approach,[6] illustrating the fact that morphologic selection is important.

The 2020 American College of Gastroenterology guideline for diagnosis and management of CP recommended surgical intervention over endoscopic therapy in patients with obstructive CP for the long-term relief of pain if first-line endoscopic approaches to PD drainage have been exhausted or unsuccessful.[7] Endoscopic decompressive procedures include ERCP with pancreatic sphincterotomy, stone clearance (including pancreatoscopy-guided lithotripsy[8,9]),

stricture dilation, and PD stenting as well as interventional EUS procedures for placement of a transluminal stent to allow for PD decompression.[7] Plastic stents have been used for this indication since the early 1990s,[10] whereas fully covered self-expandable metal stents (FCSEMSs) have been studied more recently. A 2021 retrospective study of 80 CP patients reported that in comparison with plastic stents, FCSEMS placement for persistent main PD strictures had favorable long-term clinical efficacy, with its typical adverse events like spontaneous migration and de novo strictures.[11] Similarly, a 2021 meta-analysis concluded "FCSEMS are comparable to multiple plastic stents in the treatment of symptomatic refractory PD strictures. However, use of FCSEMS is associated with increased risk of adverse events (p 854)."[12]

Three-month use of a modified flared FCSEMS was associated with frequent migration and de novo PD strictures.[13,14] Subsequently, a modified, non-flared, short, fully covered metal stent was developed for treatment of refractory benign PD strictures.[15] Among 27 patients in whom this FCSEMS was successfully placed through the major (n = 27) or minor (n = 5) duodenal papilla, all achieved pain relief and stricture resolution without stent migration by the time of FCSEMS removal at 3 months after placement, with 5 patients showing asymptomatic de novo focal PD strictures on pancreatograms obtained at that time.[15]

To further investigate treatment for PD strictures in patients with painful CP, we conducted a prospective, single-arm trial to test the efficacy and safety of 6-month treatment using a new "soft" FCSEMS. The study was conducted under an Investigational Device Exemption protocol approved by the U.S. Food and Drug Administration and Competent Authorities of other participating countries. The Investigational Device Exemption protocol provided detailed and stringent definitions of primary effectiveness and safety endpoints, both of which were failed in the study. A post-hoc analysis aimed to suggest potential future study designs (see Supplementary Methods, available online at www.giejournal.org).

METHODS

Study design

We conducted a prospective, multicenter, single-arm clinical trial to evaluate the safety and efficacy of the WallFlex Pancreatic RX Fully Covered Soft Stent System (Boston Scientific Corporation, Marlborough, Mass, USA) (Fig. 1) to treat PD strictures in adults with painful CP (U.S. Food and Drug Administration Investigational Device Exemption no. G150185; clinicaltrials.gov NCT02802020). After presenting with a plastic stent and pancreatic stone clearance if needed, the FCSEMS was placed with intended implantation for 6 months. FCSEMSs were available in 6-mm or 8-mm diameter and 4-cm, 5-cm, or 6-cm length. After a 6-month indwell, the FCSEMS was removed. Patients were observed for an additional 6 months after stent removal or after observation of complete distal (outward) migration (CDM).

Patient population

Eligible patients were adults aged ≥18 years with a CP-induced Cremer type IV stricture[16] (distal dominant stricture with upstream ductal dilation) and upstream PD ≥5 mm in

diameter, endoscopic pancreatic sphincterotomy in the past or at study baseline, and pain occurring at least weekly and rated ≥20 on the visual analog scale pain score (1–100 scale[17]) at study baseline (ie, at time of FCSEMS placement for stenting treatment–naïve patients or at time of initial stent placement for patients with a prior plastic pancreatic stent). Prior clearance of PD stones was performed where applicable. If PD stone clearance before placement of the study stent included ESWL, then a plastic pancreatic stent could be placed immediately after ESWL at the discretion of the investigator. However, if new PD stones requiring ESWL subsequently formed before the intended FCSEMS placement, the patient was excluded from the study to be treated per standard of practice outside of the study. Other exclusion criteria were pancreatic or periampullary cancer with or without associated PD strictures, biliary strictures caused by CP and requiring treatment, perforated duct, Ansa pancreatica, pancreatic cysts, duodenal/groove pancreatitis, autoimmune pancreatitis, PD stenoses not located in the head of the pancreas, prior failed access during an attempted ERCP, cumulative plastic pancreatic stent indwell exceeding 90 days within 1 year before enrollment into the study, prior pancreatic metal stent(s), recent acute relapsing pancreatitis, contraindication to endoscopic techniques, inability to comply with study follow-up, or enrollment in another investigational study that would directly interfere with the current study.

All investigational sites obtained approval from their local institutional review boards before recruitment of participants for the study. The study was registered in the clinicaltrials.gov database on June 16, 2016 and was conducted under a U.S. Food and Drug Administration–approved protocol. Competent Authorities in other participating countries also approved the protocol. All enrolled patients provided written informed consent for their procedures and for participation in the study. All authors had access to the study data and reviewed and approved the final manuscript. The study was sponsored by the manufacturer of the FCSEMS used in this study (Boston Scientific).

Study visits

Baseline screening visit.—A screening assessment was performed to document study eligibility, informed consent, baseline demographics, and medical and procedural history including prior endoscopic pancreatic sphincterotomy, prior plastic stenting, and prior PD stone clearance.

Pancreatic study stent placement.—Pancreatic study stent placement could be performed on the same day as screening at the discretion of the treating physician or in a separate visit soon afterward. Investigators were advised to place a 6-mm diameter study stent if the upstream dilated PD was ≤6 mm, and an 8-mm diameter study stent if the dilated PD was >6 mm. Technical success was defined as successful placement of the stent across the intended stricture confirmed on endoscopy and fluoroscopy.

Longitudinal assessments during stent indwell and stent removal.—The following assessments were performed at baseline and longitudinally in follow-up visits at 1, 3, and 6 months (stent removal visit): weight, concomitant medications (including injectable narcotics), average daily narcotic dose for rhe prior month, SF-12 quality of life (QOL)

score, Izbicki pain score,[18] and PD imaging (pre- and postprocedure). Adverse event/device event assessment was conducted as occurring. After stent removal at 6 months, placement of a nasopancreatic drain was optional, followed by pancreatographic assessment of the PD stricture 24 to 72 hours after study stent removal.

Visits after stent removal.—Follow-up visits were performed 3 months and 6 months after FCSEMS removal or observation of CDM. The final visit 6 months after stent removal included PD imaging.

Study endpoints

Primary efficacy endpoint: pain reduction.—The self-reported pain score (0–100) was the mean of the visual analog scale and Izbicki frequency of pain subscore (sum treated as a continuous variable). The remaining 2 components of the full Izbicki pain score system[18] were not used because they were unsuitable for our cohort (ie, the Izbicki analgesic medication component did not include all medications taken by our patients, and the inability to work component included duration >6 months that could not be assessed in our 6-month study). The primary efficacy endpoint was the proportion of patients who had complete (pain score ≤10) or partial (pain score >10 but reduced at least 50% compared with pain as baseline) pain relief by 6 months after FCSEMS removal or observation of CDM or partial stent migration.

Primary efficacy endpoint failure included any of the following: (1) no pain relief, (2) complete or partial pain relief in the setting of a 50% higher average daily narcotic dose compared with the patient's daily average narcotic dose in the month before baseline and at 6 months after stent removal/observation of CDM, (3) stent migration in the setting of recurring pain (visual analog scale pain score ≥20), and (4) restenting in the setting of recurring pain. Patients were excluded from the intention-to-treat (ITT) analysis of the primary pain endpoint for insufficient pain level after plastic stent placement (which precluded accurate assessment of study FCSEMS efficacy) or nonevaluable status because of death or loss to follow-up.

Primary safety endpoint: rate of related serious adverse events.—The primary safety endpoint was the rate of serious adverse events (SAEs) related to the FCSEMS or study procedures from FCSEMS placement to the end of study follow-up. Pain believed to be caused by FCSEMS pancreatic stent expansion was reported but did not count toward the endpoint if all 3 of the following conditions applied[19]: pain managed by medication, with the exception of injectable narcotic use for more than 24 hours; pain not causing pancreatic FCSEMS removal; and pain resolved by 72 hours after pancreatic FCSEMS placement.

Secondary endpoints.—Secondary efficacy endpoints were technical success, stent migrations, restenting after removal of FCSEMSs or observation of CDM, and change in weight and self-reported QOL, assessed at each visit.

Statistical analysis

A literature search on plastic pancreatic stenting in CP yielded 10 articles reporting on pain reduction representing 392 assessable patients.[19–28] A meta-analysis yielded a point estimate of 66% (95% confidence interval, 53–76) for the proportion of patients who satisfied predefined pain relief success. Based on the meta-analysis findings, we hypothesized that "pain reduction" (as defined in study endpoints above) would be achieved in a performance goal of at least 53% of patients receiving the study FCSEMS. Assuming an observed pain reduction rate of 75% and using an exact test with a 1-sided alpha of .025, 43 patients were required to obtain power of at least 80%.

Using the same literature search, we found 9 articles representing 386 patients[19–26,28] that reported on the rate of device- or procedure-related SAEs. This meta-analysis yielded a point estimate of 25% (95% confidence interval, 19–32). Therefore, we hypothesized that the proportion of patients reporting 1 or more related SAE(s) would be below a performance goal of 32%. Assuming an observed SAE rate of 15% and using an exact test with a 1-sided alpha of .025, 57 patients were required to obtain power of at least 80%. Taking the larger of the 2 sample size calculations and adding 10% for attrition, 64 patients would be enrolled. In addition, we estimated that 20% to 30% of patients would not meet the pain requirement for a priori primary efficacy endpoint hypothesis testing at FCSEMS placement in cases of prior plastic stenting. Thus, a maximum of 92 patients could be enrolled.

Continuous variables were analyzed and are reported as means and standard deviations or median and ranges. Binary variables are reported as frequencies. Primary endpoints were tested using the Fisher exact test, where a $P < .025$ meant the performance goal was met. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA; https://www.sas.com).

RESULTS

Baseline patient and stent placement procedural characteristics

Of 93 patients screened for study eligibility (Fig. 2), 65 were from U.S. sites, 10 from Belgium, 7 from India, 7 from Italy, 2 from The Netherlands, and 2 from Canada. Sixty-seven eligible patients were enrolled between January 2017 and August of 2020, with a mean age of 52.7 ± 12.5 years. The mean time since first CP diagnosis was 6.4 ± 6.4 years (Fig. 2, Table 1). Thirty-four patients had prior plastic stent placement within 90 days of study entry.

Thirty FCSEMS placements (44.8%) were on inpatients, with a median total hospital stay of 2.0 days (range, 1.0–7.0) (Table 2). The FCSEMS was placed through the major papilla in most cases (71.2%, 47/66). Sixty-seven patients (100.0%) had a pancreatic sphincterotomy at some point, including 12 performed during the study stent placement. Forty patients (59.7%) had a biliary sphincterotomy at some point, including 6 performed during the study stent placement. A plastic biliary stent was placed in 1 patient. Most patients had normal PD anatomy (61.2%, 41/67) and 17 (25.4%) had pancreas divisum (Fig. 3). Forty-seven patients had other endoscopic procedures performed at the time of FCSEMS placement, including balloon sweep in 31 (46.3%), and pancreatic stone extraction in 27 (40.3%).

Primary efficacy endpoint

Twenty-one of 67 patients were excluded from the ITT analysis of the primary pain endpoint because of insufficient pain levels after plastic stent placement, death, or loss to follow-up (Fig. 2). Among the 46 patients who were eligible for the primary efficacy endpoint ITT analysis of the efficacy hypothesis of the study, 12 (26.1%) achieved complete or partial pain relief by 6 months after FCSEMS removal or observation of CDM and had less than a 50% increase in narcotic dose. This result did not meet the performance goal of 53.0% ($P = .999$) (Table 3).

Primary safety endpoint

The overall SAE rate did not meet the safety performance goal ($P = .513$) (Table 3). FCSEMS- or procedure-related SAEs occurred in 21 patients (31.3%) (Table 4). Pain was the most commonly reported SAE (14.9%, 10/67), followed by post-ERCP pancreatitis (11.9%, 8/67), CP exacerbation (4.5%, 3/67), and other (4.5%, 3/67) (Table 4). One patient had a study stent placed after significant acute on chronic inflammatory changes had improved with prolonged non-stimulatory feeding. Shortly after placement she developed cholestatic liver enzymes and bile duct dilation that improved after a biliary sphincterotomy with the study stent left in place. She subsequently developed acute on CP complicated by fluid collections and mesenteric vein thromboses requiring hospital admissions. She completed a scheduled stent removal as an outpatient. Two weeks later she was emergently admitted from home to a local hospital but succumbed to overwhelming sepsis and multiorgan failure. Postmortem study revealed abdominal sepsis as her cause of death.

Secondary endpoints

Technical success.—Technical success of FCSEMS placement was attained in 65 patients (97.0%). FCSEMS sizes (diameter × length) were 6 mm × 4 cm in 26 patients (40.0%), 6 mm × 6 cm in 19 patients (29.2%), 6 mm × 5 cm in 8 patients (12.3%), 8 mm × 6 cm in 6 patients (9.2%), 8 mm × 4 cm in 5 patients (7.7%), and 8 mm × 5 cm in 1 patient (1.5%). Of the remaining 2 patients, 1 had an aborted ERCP after failed cannulation and died of an unknown cause on day 57. In the second patient, the FCSEMS dislodged after attempted insertion through a tight stricture; instead, 2 plastic stents were placed and removed after 42 days. At 42 days, 1 prophylactic plastic stent was placed, but pain never resolved, and the patient exited the study 6 months after the initial FCSEMS placement attempt.

At intended FCSEMS removal, 38 patients (58.5%) underwent endoscopic stent removal and 28 (43.1%) were observed to have undergone CDM. All FCSEMS removals and CDMs were uneventful.

Stent migration.—Stent migration was observed in 31 of 65 patients (47.7%), including 28 CDMs (Table 4), 1 partial distal migration, and 2 proximal migrations. CDMs were uneventful with all migrated FCSEMSs spontaneously passing. Of 28 CDMs, 11 were asymptomatic, not associated with recurrence of pain, and observed at the time of intended endoscopic FCSEMS removal.

Restenting.—Eleven patients had restenting during study follow-up: 7 at the time of FCSEMS removal or observation of CDM and 1 each at 6, 8, 13, and 114 days after FCSEMS removal or observation of CDM. Most restenting procedures occurred within 14 days of the FCSEMS removal or observation of CDM.

Secondary strictures.—Secondary strictures located at the intraductal edge of the FCSEMS were reported in 5 patients at the time of stent removal or observation of CDM. All 5 were restented with a single plastic pancreatic stent. Of these, 3 were restented for <1 month for maintenance of PD drainage or PD stones, 1 was restented for 63 days, and 1 exited the study with the plastic stent in place. At the end of follow-up, the latter 2 cases reported no pain.

Weight and QOL.—Twenty-four of 61 patients (39.3%) were reported to have weight gain by 6 months after FCSEMS removal or observation of CDM, with a mean weight change compared with baseline of −1.3 ± 6.9 kg (range, −16.2 to 19.0). Self-reported QOL score was reported as improved compared with baseline in 71.7% of patients (43/60) by 6 months after FCSEMS removal or observation of CDM. Median change in QOL score increased to +16.4 (range, −46.0 to 79.3) at 6 months.

DISCUSSION

In this study, patients with CP who showed early pain reduction during 6-month indwell of an FCSEMS and subsequently maintained good pain relief until 6 months after FCSEMS removal represented only one-third of those eligible for the primary efficacy analysis. This is clearly inferior to the expected outcomes. In addition, procedure-related SAEs were observed in almost one-third of patients, and study stent migrations occurred in nearly half of patients (although most were asymptomatic).

Because pain is the most frequent cause for hospitalization and the strongest predictor of poor QOL in patients with CP,[1] effective pain management is a key treatment goal. Although surgery is considered the most definitive treatment, endotherapy is usually undertaken initially given the invasiveness of surgery and the relatively low morbidity and mortality of endoscopy.[29] The best responders to endoscopic therapy are patients with obstructing stones located in the head of the pancreas, complete stone clearance and absence of main PD stricture, with a short disease duration and a low frequency of pain attacks before endoscopic therapy, together with the discontinuation of alcohol and tobacco.[30] In patients with uncomplicated painful CP and a dilated main PD, endoscopic therapy is recommended as first-line treatment after failed medical therapy after discussions by a multidisciplinary team.[30] In obstructive CP, endotherapy is the preferred initial treatment and provides early and sustained pain relief in 88% and 67% of patients, respectively.[31]

Optimal timing of surgery is uncertain, but 2018 evidence-based guidelines from a United European Gastroenterology working group concluded that surgery is superior to endoscopy in terms of mid-term and long-term pain relief in patients with painful CP and that early surgery is favored over surgery at a more advanced stage of the disease.[30] Consistent with this recommendation, a 2020 randomized clinical trial reported that complete or partial pain

relief at the end of follow-up was achieved in 58% of patients (23/40) in an early surgery group versus 39% of patients (16/41) in the endoscopy-first approach group ($P = .10$).[32] However, at the end of follow-up, pain scores and the proportion of patients with complete or partial pain relief, pancreatic function, and QOL were not significantly different between groups in this randomized clinical trial.[32] A 2021 meta-analysis[5] concluded that endoscopic interventions can be considered first in cases with the possibility of reaching PD clearance or relief of obstruction, because decompression surgery would not achieve additional benefit for this symptom if it does not improve after endoscopic therapy. Surgery could then be performed when there is a recurrence of a stricture or pancreatolithiasis or in the event of a failure with endoscopic treatment. The authors acknowledged that this approach is recommended in several published clinical practice guidelines.[7,33,34]

Using SEMSs for stricture calibration might shorten the calibration period and avoid repeated procedures for stent exchange. However, our results did not suggest a benefit for FCSEMS therapy in all patients with CP-associated pain. The 2 groups that appeared to benefit showed an early response after FCSEMS placement or plastic stent placement with subsequent exchange for an FCSEMS, with pain relief that was durable throughout the 6-month post–stent removal follow-up period. These preliminary findings might warrant future studies in patients with painful CP who have a favorable pain response to initial ductal decompression with a single plastic stent and randomly comparing 180-day treatment with multiple plastic stents versus a single FCSEMS or randomly comparing early surgery with 180-day FCSEMS treatment with multiyear follow-up in a similar patient population.

Our study had several limitations. This was a single-arm study conducted by expert endoscopists at large university medical centers. The results might not be replicable at centers with lower procedural volumes, less experience with pancreatic endotherapy, or with fewer specialty resources. Pain relief reported by the end of study could be attributable to an increase in narcotic dose when that occurred. The 6-month follow-up period after FCSEMS removal may have been short for adequate estimation of PD stricture recurrences. Several authors disclosed financial relationships with the manufacturer of the study FCSEMS.

In conclusion, in patients with painful CP, a PD stricture, and upstream PD dilation who received 6-month treatment with a new FCSEMS, the performance goal for the primary endpoint of pain relief was not reached, and SAEs were common. Further study is needed to clarify optimal FCSEMS design and appropriate patient populations for this treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA SHARING

The data, analytic methods, and study materials for this study may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (http://www.bostonscientific.com/en-US/data-sharing-requests.html).

Abbreviations:

CDM	complete distal migration
CP	chronic pancreatitis
ESWL	extracorporeal shock wave lithotripsy
FCSEMS	fully covered self-expandable metal stent
ITT	intention-to-treat
PD	pancreatic duct
QOL	quality of life
SAE	serious adverse event

REFERENCES

1. Drewes AM, van Veldhuisen CL, Bellin MD, et al. Assessment of pain associated with chronic pancreatitis: an international consensus guide line. Pancreatology 2021;21:1256–84. [PubMed: 34391675]
2. Strate T, Yekebas E, Knoefel WT, et al. Pathogenesis and the natural course of chronic pancreatitis. Eur J Gastroenterol Hepatol 2002;14: 929–34. [PubMed: 12352211]
3. Goulden MR. The pain of chronic pancreatitis: a persistent clinical challenge. Br J Pain 2013;7:8–22. [PubMed: 26516493]
4. Issa Y, van Santvoort HC, Fockens P, et al. Diagnosis and treatment in chronic pancreatitis: an international survey and case vignette study. HPB 2017;19:978–85. [PubMed: 28821411]
5. Mendieta PJO, Sagae VMT, Ribeiro IB, et al. Pain relief in chronic pancreatitis: endoscopic or surgical treatment? A systematic review with meta-analysis. Surg Endosc 2021;35:4085–94. [PubMed: 33948714]
6. Dumonceau JM, Costamagna G, Tringali A, et al. Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic treatment: a randomised controlled trial. Gut 2007;56:545–52. [PubMed: 17047101]
7. Gardner TB, Adler DG, Forsmark CE, et al. ACG clinical guideline: chronic pancreatitis. Am J Gastroenterol 2020;115:322–39. [PubMed: 32022720]
8. Beyna T, Neuhaus H, Gerges C. Endoscopic treatment of pancreatic duct stones under direct vision: revolution or resignation? Systematic review. Dig Endosc 2018;30:29–37. [PubMed: 28656688]

9. Gerges C, Pullmann D, Bahin F, et al. SpyGlass DS-guided lithotripsy for pancreatic duct stones in symptomatic treatment-refractory chronic calcifying pancreatitis. Endosc Int Open 2019;7:E99–103. [PubMed: 30705939]
10. Cremer M, Deviere J, Delhaye M, et al. Stenting in severe chronic pancreatitis: results of medium-term follow-up in seventy-six patients. Endoscopy 1991;23:171–6. [PubMed: 1860448]
11. Lee SH, Kim YS, Kim EJ, et al. Long-term outcomes of fully covered self-expandable metal stents versus plastic stents in chronic pancreatitis. Sci Rep 2021;11:15637. [PubMed: 34341385]
12. Sofi AA, Khan MA, Ahmad S, et al. Comparison of clinical outcomes of multiple plastic stents and covered metal stent in refractory pancreatic ductal strictures in chronic pancreatitis—a systematic review and meta-analysis. Pancreatology 2021;21:854–61. [PubMed: 33941467]
13. Moon SH, Kim MH, Park DH, et al. Modified fully covered self-expandable metal stents with antimigration features for benign pancreatic-duct strictures in advanced chronic pancreatitis, with a focus on the safety profile and reducing migration. Gastrointest En dosc 2010;72:86–91.
14. Tringali A, Vadala di Prampero SF, Landi R, et al. Fully covered self-expandable metal stents to dilate persistent pancreatic strictures in chronic pancreatitis: long-term follow-up from a prospective study. Gastrointest Endosc 2018;88:939–46. [PubMed: 30142349]
15. Lee YN, Moon JH, Park JK, et al. Preliminary study of a modified, non-flared, short, fully covered metal stent for refractory benign pancreatic duct strictures (with videos). Gastrointest Endosc 2020;91:826–33. [PubMed: 31738924]
16. Cremer M, Toussaint J, Hermanus A, et al. Primary chronic pancreatitis. A classification based on endoscopic pancreatography [in French]. Acta Gastroenterol Belg 1976;39:522–46. [PubMed: 1023728]
17. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: What is moderate pain in millimetres? Pain 1997;72:95–7. [PubMed: 9272792]
18. Bloechle C, Izbicki JR, Knoefel WT, et al. Quality of life in chronic pancreatitis—results after duodenum-preserving resection of the head of the pancreas. Pancreas 1995;11:77–85. [PubMed: 7667246]
19. Costamagna G, Bulajic M, Tringali A, et al. Multiple stenting of refracttory pancreatic duct strictures in severe chronic pancreatitis: long-term results. Endoscopy 2006;38:254–9. [PubMed: 16528652]
20. Eleftheriadis N, Dinu F, Delhaye M, et al. Long-term outcome after pancreatic stenting in severe chronic pancreatitis. Endoscopy 2005;37:223–30. [PubMed: 18556820]
21. Vitale GC, Cothron K, Vitale EA, et al. Role of pancreatic duct stenting in the treatment of chronic pancreatitis. Surg Endosc 2004;18:1431–4. [PubMed: 15791364]
22. Topazian M, Aslanian H, Andersen D. Outcome following endoscopic stenting of pancreatic duct strictures in chronic pancreatitis. J Clin Gastroenterol 2005;39:908–11. [PubMed: 16208117]
23. Farnbacher MJ, Muhldorfer S, Wehler M, et al. Interventional endoscopic therapy in chronic pancreatitis including temporary stenting: a definitive treatment? Scand J Gastroenterol 2006;41:111–7. [PubMed: 16373284]
24. Ishihara T, Yamaguchi T, Seza K, et al. Efficacy of s-type stents for the treatment of the main pancreatic duct stricture in patients with chronic pancreatitis. Scand J Gastroenterol 2006;41:744–50. [PubMed: 16716976]
25. Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med 2007;356:676–84. [PubMed: 17301298]
26. Weber A, Schneider J, Neu B, et al. Endoscopic stent therapy for patients with chronic pancreatitis: results from a prospective follow-up study. Pancreas 2007;34:287–94. [PubMed: 17414050]
27. Seza K, Yamaguchi T, Ishihara T, et al. A long-term controlled trial of endoscopic pancreatic stenting for treatment of main pancreatic duct stricture in chronic pancreatitis. Hepatogastroenterology 2011;58:2128–31. [PubMed: 22234084]
28. Gabbrielli A, Pandolfi M, Mutignani M, et al. Efficacy of main pancreatic-duct endoscopic drainage in patients with chronic pancreatitis, continuous pain, and dilated duct. Gastrointest Endosc 2005;61:576–81. [PubMed: 15812411]

29. Poley JW, Cahen DL, Metselaar HJ, et al. A prospective group sequential study evaluating a new type of fully covered self-expandable metal stent for the treatment of benign biliary strictures (with video). Gastrointest Endosc 2012;75:783–9. [PubMed: 22325806]

30. Dominguez-Munoz JE, Drewes AM, Lindkvist B, et al. Recommendations from the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis. Pancreatology 2018;18:847–54. [PubMed: 30344091]

31. Nabi Z, Lakhtakia S. Endoscopic management of chronic pancreatitis. Dig Endosc 2021;33:1059–72. [PubMed: 33687105]

32. Issa Y, Kempeneers MA, Bruno MJ, et al. Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial. JAMA 2020;323:237–47. [PubMed: 31961419]

33. Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) guideline—updated August 2018. Endoscopy 2019;51:179–93. [PubMed: 30654394]

34. Lohr JM, Dominguez-Munoz E, Rosendahl J, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur Gastroenterol J 2017;5:153–99.

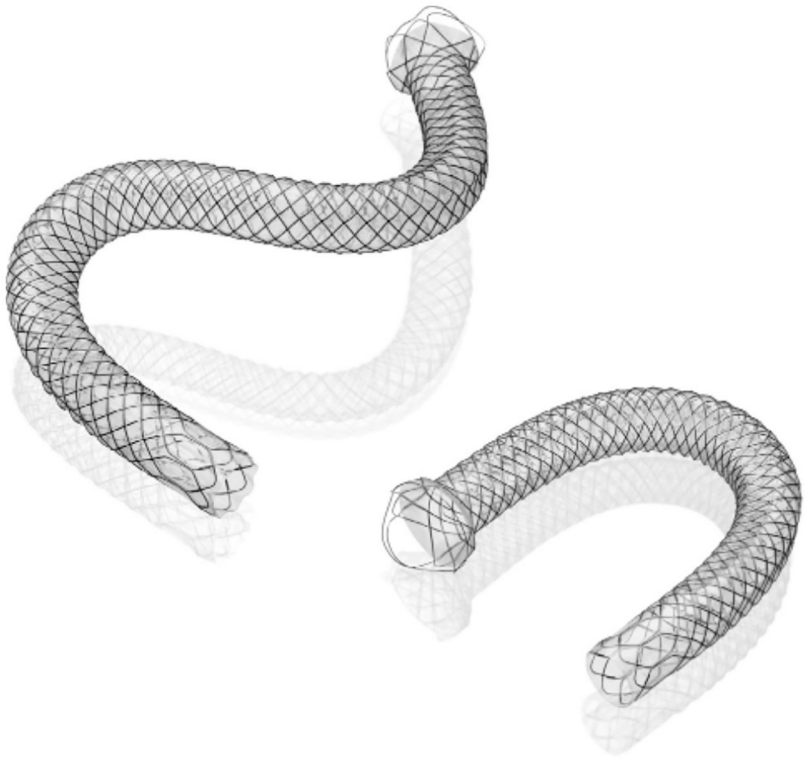

Figure 1.
Pancreatic “soft” fully covered self-expandable metal stent tested in this study. The membrane extends proximally over the metal meshes with the aim of reducing friction with the pancreatic duct epithelium.

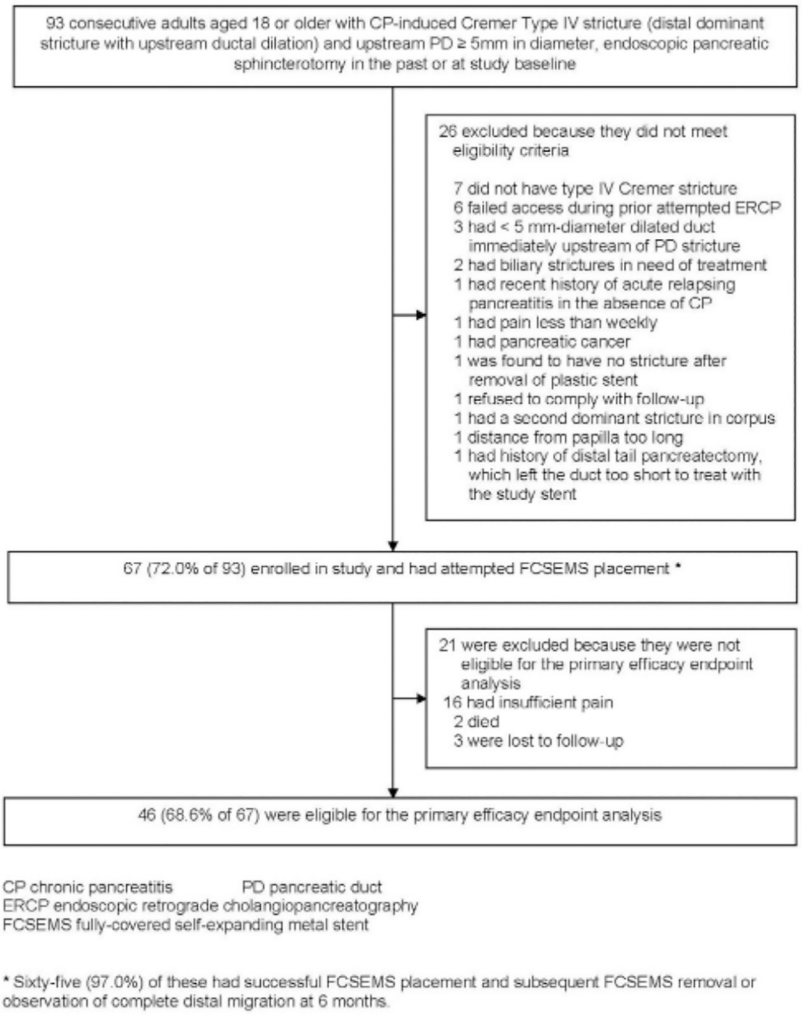

Figure 2.

Patient flow through the study. *CP*, Chronic pancreatitis; *PD*, pancreatic duct; *FCSEMS*, fully covered self-expandable metal stent.

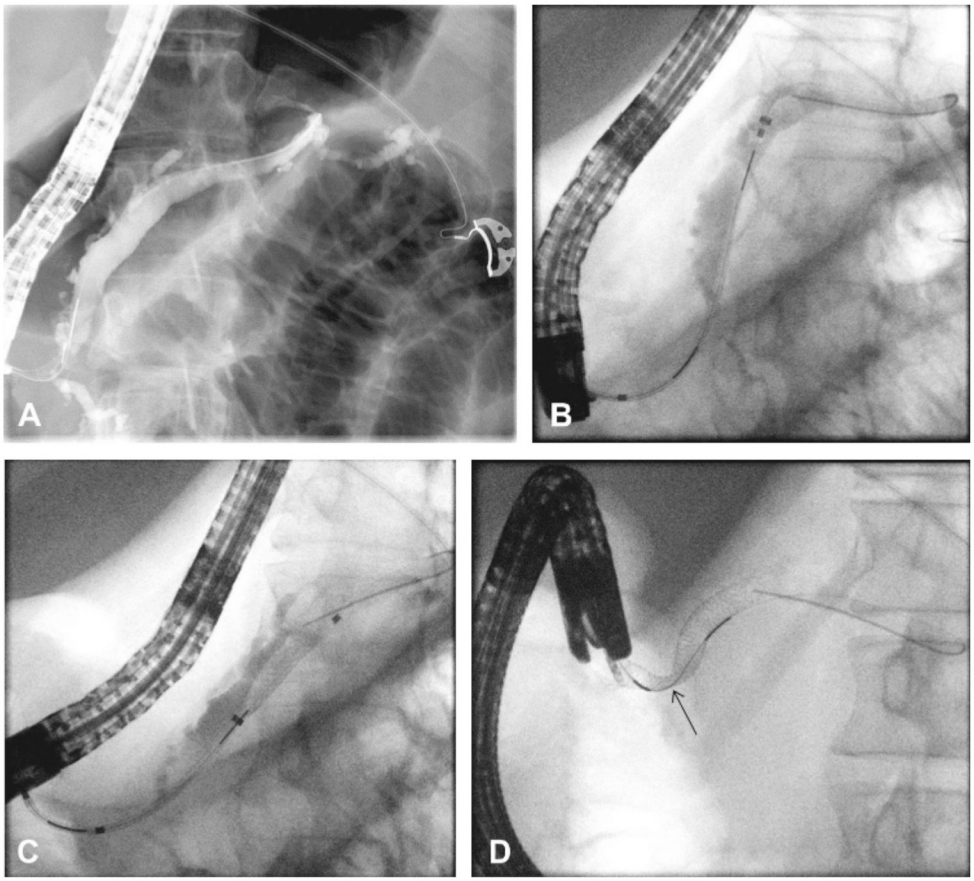

Figure 3.

A, High-grade stricture of the dorsal pancreatic duct in a chronic pancreatitis patient with divisum. **B** and **C,** Stent placement. **D,** Expanded stent in good position. The *arrow* demonstrates the stricture site, which will be progressively dilated with the self-expandable metal stent.

TABLE 1.

Patient demographics and baseline characteristics on the intention-to-treat analysis set (N = 67)

Characteristics	Values
Age, y	52.7 ± 12.5 (67) (20–76.0)
Male sex	62.7 (42/67)
Time since CP diagnosed, y	6.4 ± 6.4 (23, .1–27.7)
Race	
Not Hispanic or Latino	100.0 (67/67)
Ethnicity	
Asian	10.4 (7/67)
Black or African American	9.0 (6/67)
White	80.6 (54/67)
Weight, kg	71.5 ± 18.4 (67) (45.0–115.6)
CP etiology	
Gallstones	1.5 (1/67)
Alcoholic	49.3 (33/67)
Current alcohol consumption	11.9 (8/67)
Smoking	35.8 (24/67)
Hereditary	4.5 (3/67)
Other	11.9 (8/67)
Unknown	28.4 (19/67)
CP calcific	71.6 (48/67)
Unknown	1.5 (1/67)
Type of calcification	
Ductal	41.7 (20/48)
Parenchymal	18.8 (9/48)
Both	39.6 (19/48)
Surgical candidate	68.7 (46/67)
Unknown	13.4 (9/67)
Smoking status	

Characteristics	Values
Current	53.7 (36/67)
Previous	25.4 (17/67)
Never	20.9 (14/67)
Narcotic dose, morphine milligram equivalents	31.9 ± 52.3 (65) (.0–240.0)
Time since first narcotic medication, *y*	4.8 ± 7.3 (28) (.0–35.6)
Steatorrhea	19.4 (13/67)
Diabetes status	
Diabetic	37.3 (25/67)
Insulin dependent	29.9 (20/67)
Oral medication	7.5 (5/67)
Pancreas divisum	26.9 (18/67)
Prior pancreatic sphincterotomy performed	70.1 (47/67)
Prior biliary or pancreatic sphincterotomy performed	71.6 (48/67)
History of pancreatic duct stones	55.2 (37/67)
Unknown	6.0 (4/67)
Stone clearance procedures performed	79.5 (31/39)
Extracorporeal shock wave lithotripsy	51.6 (16/31)
Balloon	64.5 (20/31)
Basket	16.1 (5/31)
Other	3.2 (1/31)
Current pancreatic stones	62.7 (42/67)
Largest stone, mm	6.2 ± 3.9 (40) (1.0–20.0)

Values are mean ± standard deviation (n) (range) or % (n/N).

CP, Chronic pancreatitis.

TABLE 2.

Study stent procedure characteristics on intention-to-treat analysis set (N = 67)

Characteristic	Values
Inpatient procedure	44.8 (30/67)
Inpatient stay, days	2.0 (30) (1.0–7.0)
Procedure time, min	25.0 (30) (1.0–7.0)
Placement of stent in papilla	
Major	71.2 (47/66)
Minor	28.8 (19/66)
Pancreatogram performed before stent	98.5 (65/66)
Prophylactic antibiotics administered	64.2 (43/67)
Prophylactic nonsteroidal anti-inflammatory drugs administered	53.7 (36/67)
Biliary sphincterotomy performed before or during study	59.7 (40/67)
Pancreatic sphincterotomy performed before or during study	100.0 (67/67)
Previously placed pancreatic stent removed	56.7 (38/67)
Biliary stent placed (plastic)	1.5 (1/67)
Pancreatogram performed after stent placement	51.5 (34/66)
Anatomy of pancreatic duct	
Normal	61.2 (41/67)
Patent Santorini	6.0 (4/67)
Pancreas divisum	25.4 (17/67)
Other	6.0 (4/67)
Other endoscopic procedures performed	70.1 (47/67)
Pancreatic stone extraction (other than extracorporeal shock wave lithotripsy)	40.3 (27/67)
Balloon sweep	46.3 (31/67)
Other	23.9 (16/67)

Values are mean ± standard deviation (n) (range) or % (n/N).

TABLE 3.

Primary efficacy and safety endpoint analysis

	Rate % (n/N)	Performance goal (%)	Lower 95% confidence interval (%)	*P* value*
Primary efficacy endpoint†				
Intention-to-treat	26.1 (12/46)	53.0	14.3	.999
			Upper 95% confidence interval (%)	
Primary safety endpoint‡				
Intention-to-treat	31.3 (21/67)	32.0	43.8	.513

*$P < .025$ meant the performance goal was met.

†Based on mean of visual analog scale pain score and Izbicki frequency of pain subscore, with scores ranging from 0 to 100. For patients with a prior plastic pancreatic stent, baseline was considered to be the time of study stent placement. For patients without a plastic pancreatic stent, baseline was the time of enrollment. Defined as either complete (pain score ≤10) or partial (pain reduced by 50%) pain relief reported at 6 months after removal without an increase in narcotics dose by 50%.

‡Rate of related serious adverse events with pain believed to be caused by the WallFlex Pancreatic stent expansion were reported but did not count toward the endpoint if all 3 of the following conditions applied: pain could be managed by medication, with the exception of injectable narcotic use for more than 24 hours; pain did not cause WallFlex Pancreatic stent removal; and pain resolved by 72 hours after WallFlex Pancreatic stent placement.

TABLE 4.

Main serious adverse events related to fully covered self-expandable metal stent or study procedures on intention-to-treat analysis set (n = 67)

Serious adverse event*	No. of events	Percentage (n/N patients)
Any serious adverse event	29	31.3 (21/67)
Pain	12	14.9 (10/67)
Post-ERCP pancreatitis	8	11.9 (8/67)
Chronic pancreatitis exacerbation	3	4.5 (3/67)
Duodenal ulceration	1	1.5 (1/67)
Elevated liver function tests	1	1.5 (1/67)
Ampullary occlusion of the bile duct†	1	1.5 (1/67)
Peripancreatic fluid collection†	1	1.5 (1/67)
Portal vein and superior mesenteric vein thrombosis†	1	1.5 (1/67)
Fatal multiorgan failure from sepsis†	1	1.5 (1/67)

*Rows are not mutually exclusive.

†These serious adverse events occurred in 1 patient.