

Use of fully-covered, self-expandable metallic stents for first-line treatment of benign bile duct strictures

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Primary Site: Indiana University Medical Center, Indianapolis, IN

Total number of participating centers: 9

Study design: randomized, controlled, clinical trial

Abbreviations:

| | |
|-------|--|
| PS | plastic stents |
| cSEMS | covered, self-expandable metallic stents |
| OLT | orthotopic liver transplant |
| PSC | primary sclerosing cholangitis |
| CP | chronic pancreatitis |
| ERCP | endoscopic retrograde cholangiopancreatography |
| SEMS | self-expandable metallic stents |
| CBD | common bile duct |
| MRCP | magnetic resonance cholangiopancreatography |
| CT | computed tomography |
| ICER | incremental cost effectiveness ratio |

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Research Aims

Aim #1: Compare the efficacy and safety of serial plastic stent (PS) therapy to fully covered, self-expandable metallic stents (cSEMS) for first-line treatment of benign bile duct strictures.

Hypotheses: 1) Both stents will have comparable safety and efficacy, *and cSEMS will require significantly fewer interventions than will PS to achieve complete resolution of the stricture*; 2) Complication rates will be similar between the two stent types.

Aim #2: Compare direct costs associated with use of plastic stents and cSEMS.

Hypothesis: Early use of cSEMS will be less costly compared to standard endoscopic treatment with serial dilation.

Aim #3: Compare the rate of stent-associated changes in the common hepatic duct.

Hypothesis: cSEMS and PS will have a comparably low rate of stent-associated changes in common hepatic duct.

Background and rationale

Epidemiology and standard approach to benign biliary strictures. The majority of benign bile duct strictures arise from postoperative complications related to cholecystectomy, orthotopic liver transplant (OLT) or biliary reconstruction. Other etiologies include chronic pancreatitis (CP), primary sclerosing cholangitis (PSC) and other, less common cholangiopathies.¹ Benign biliary strictures require intervention to treat jaundice, chronic cholestasis and cholangitis, as well as avoiding the long-term development of secondary biliary cirrhosis.² Traditionally, benign biliary strictures have been treated with surgery, via Roux-en-Y hepaticojejunostomy or choledochoduodenostomy.³ However, among patients with accessible bile ducts, endoscopic placement of multiple bile duct stents has replaced surgery as the first-line treatment for benign bile duct strictures.⁴ Postoperative anastomotic strictures occur in up to 10% of deceased donor liver transplants and 30% of living donor transplants.^{5,6} In addition, bile duct injuries occur in up to 2% of patients undergoing laparoscopic cholecystectomy, leading to a significant long-term reduction in health-related quality of life.⁷ With more than 500,000 cholecystectomies performed in the United States each year, post-operative bile duct injuries affect many patients annually.

The standard endoscopic approach for benign biliary strictures involves the insertion of two plastic 10F stents for one year.⁸ Some experts advocate an even more aggressive approach, serially increasing the number of plastic stents (PS) across the stricture until there is complete fluoroscopic resolution.⁹⁻¹³ Due to problems of PS occlusion, repeat endoscopic retrograde cholangiopancreatography (ERCP) is usually performed every three months to exchange the stents. This process may take one year or longer to resolve the stricture. Each ERCP is associated with significant health care costs, sedation- and procedure-related risks, as well as undue stress and inconvenience to the patient. Nevertheless, approximately 80% of patients with endoscopic treatment of postoperative biliary strictures have long-term clinical resolution. Patients with biliary strictures due to CP have much

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less favorable long-term response rates due to underlying dense fibrosis and calcifications in the pancreatic head.^{9,14,15}

Self-expandable metallic stents. Due to their greater diameter compared to PS, self-expandable metallic stents (SEMS) have superior patency rates and are increasingly preferred for the treatment of unresectable malignant biliary obstruction among patients whose life expectancy is at least three to six months.¹⁶⁻²⁰ However, increased device cost and limited endoscopic removability are well-established disadvantages of SEMS compared to PS. Uncovered SEMS have been used in refractory cases of benign biliary strictures with modest success.²¹⁻²³ Although short-term stricture resolution is reported in up to 80%, these stents have limited removability due to epithelial hyperplasia between the interstices, oftentimes leading to stent occlusion. A systematic review by van Boeckel, et al. summarized the use of uncovered SEMS in 182 patients with benign biliary strictures.²⁴ Despite including many patients who had previously failed treated with PS in their analysis, the technical and clinical success rates were 98.9% and 79.5%, respectively.

In response to issues of epithelial hyperplasia and tumor ingrowth in cases of malignant obstruction, newer metallic stent designs have incorporated a partial or fully covered, nonporous membrane (i.e., covered SEMS (cSEMS)). These designs offer the potential for removability.²⁵⁻²⁸ Clinical trials of cSEMS have shown similar or superior patency rates compared to uncovered SEMS for malignant biliary obstruction.²⁹⁻³² The partially covered Wallstent™ (Boston Scientific, Natick, MA) has been used for refractory cases of benign bile duct strictures due to CP. Among 14 patients, all demonstrated short-term resolution of their cholestasis; however, stent patency progressively declined over time (37.5% at 36 months of follow-up) as a result of epithelial hyperplasia along the uncovered margins of the stent.³³ In a second series of 79 patients (32 with CP), stricture resolution was shown in 75% (77% of patients with CP) after a median follow-up of 12 months (range 3-26 months). Among 65 of 79 patients who underwent attempted stent removal, 90% were successful.²⁸

Preliminary data

Fully covered metallic stents. More recently, fully covered metallic stents were designed to prevent tumor ingrowth and epithelial hyperplasia. There is a growing body of literature to support their safety and short-term efficacy for benign indications.³⁴ Among 41 patients with benign biliary strictures (17 with CP) who underwent placement of a fully covered SEMS (Viabil, ConMed, Utica, NY), 83% (65% in CP) demonstrated stricture resolution after a median follow-up of 3.8 months (range 1.2 – 7.7 months). As expected, all cSEMS were successfully removed; one stent unraveled during its extraction, but was otherwise accomplished without adverse effects. Fully covered SEMS have been used in refractory cases of postoperative bile leaks; among 16 patients who previously failed standard sphincterotomy and stent therapy, a fully covered stent was placed.³⁵ After a minimum follow-up of 6 months, 88% of leaks had resolved and all stents were removed endoscopically.

Local experience. In a query of the Indiana University ERCP database, > 2,800 ERCPs are performed annually. Over the past 24 months, 121 patients have undergone one or more ERCPs for a benign biliary stricture secondary to CP. In addition, 286 patients with postoperative bile duct strictures secondary to

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liver transplant (187), cholecystectomy (89) or other (3) have undergone at least one ERCP at our facility (table 1). These numbers support the feasibility of our recruitment goal and importance of optimizing the efficiency of our approach to the endoscopic therapy of biliary strictures.

| Etiology | Patients | # procedures (median, range) | Complications |
|------------------------|----------|------------------------------|---|
| Chronic pancreatitis | 121 | 3 (1,11) | Bleeding (1) |
| Post-operative (total) | 286 | 3 (1,17) | (non-transplant): Pancreatitis (1), Cholangitis (1) |
| Post-liver transplant | 187 | 3 (1,17) | Perforation (2), Bleeding (2) |
| Total | 407 | 3 (1,17) | |

Indiana University has participated in a multi-center, prospective cohort study evaluating the safety of removing fully covered SEMS that were placed for malignant and benign disease.³⁶

Among 182 patients who underwent placement of a fully covered SEMS (29 at Indiana University), all 36 patients (9 at Indiana University) with attempted removal were successful, after a median stenting period of 106 days (range 6-355). During the stenting period, occlusion developed in 13% of cases (compared to 27% matched patients with uncovered SEMS). The removability of fully covered SEMS has been confirmed in other, smaller series.^{34,37-41} The published experience using fully covered metallic stents in benign disease include > 100 reported cases of successful placement and removal of fully covered SEMS for benign biliary strictures or leaks, with limited serious complications (table 2).

| Study (n) | Stent type | Removal rate (%) | Clinical success (%) | Serious complications (%) |
|--|---|------------------|----------------------|---------------------------|
| Chaput, et al., 2010 (n=22) ⁴² | Fully covered Wallflex™ | 22/22 (100%) | 22/22 (100%) | 0/22 |
| Phillips MS, et al., 2010 (n=17) ⁴³ | Viabil™ | 17/17 (100%) | 16/17 (94%) | 6/17 |
| Poley JW, et al., 2010 (n=11) ⁴⁴ | M.I.Tech | 11/11 (100%) | 8/11 (73%) | 1/11 |
| Goldberg EM, et al., 2010 (n=9) ⁴⁵ | Fully covered Wallflex™ | 9/9 (100%) | 8/9 (89%) | 0/9 |
| Garcia-Cano J, et al., 2010 (n=10) ⁴⁶ | Fully covered Wallflex™ | 10/10 (100%) | 10/10 (100%) | None |
| Kuo, et al., 2006 (n=6) | Viabil™ | 6/6 (100%) | Not available | 0/6 (0%) |
| Baron, et al., 2006 (n=3) | Partially covered Wallstent™ (2), Viabil™ (1) | 3/3 (100%) | 3/3 (100%) | 0/3 (0%) |
| Kahaleh, et al., 2008 (n=79) | Partially covered Wallstent™ | 63/65 (97%) | 59/79 (75%) | 6/79 (8%) |
| Mahajan, et al., 2009 (n=44) | Viabil™ | 41/41 (100%) | 34/44 (77%) | 1/44 (2%) |
| Garcia-Cano, et al., 2009 (n=12) | Fully covered Wallflex™ | 12/12 (100%) | Not available | 0/12 (0%) |
| Kasher, et al., 2009 (n=182) | Viabil™ | 36/36 (100%) | Not available | 3/36 (8%) |
| Traina, et al., 2009 (n=16) | Niti-S™ | 16/16 (100%) | 14/16 (88%) | 0/16 (0%) |
| Cahen, et al., 2008 (n=6) | Hanaro™ | 4/6 (67%) | 3/6 (50%) | 2/6 (33%) |
| Phillips, et al., 2009 (n=16) | Viabil™ | 13/13 (100%) | 12/13 (92%) | 3/13 (23%) |

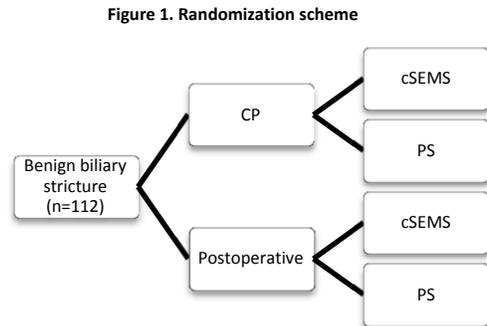
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using fully covered SEMS for the initial treatment of benign biliary strictures. First, a tapered deployment catheter is likely to obviate the need for pre-treatment with balloon or passage dilation, thereby reducing the number of devices at the time of initial ERCP. Second, the superior patency of cSEMS is expected to lower the cumulative number of ERCPs required to fully dilate a benign biliary stricture. The initial increased cost of a cSEMS compared to one or more PS should be offset by the need to perform fewer procedures. Finally, the early and sustained radial force of a metallic stent may result in prolonged maintenance of bile duct patency during long term follow-up. This benefit is likely to be accentuated in patients with CP, where the success of current endoscopic approaches is marginal. Given these potential advantages, a randomized clinical trial comparing early use of a cSEMS with serial PS treatment is indicated.

Study plan

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Study design. We propose conducting a randomized, controlled trial comparing standard endoscopic management of benign biliary strictures with placement of a fully covered SEMS (fully covered Wallflex™, Boston Scientific, Natick, MA) during the initial endoscopic intervention. Randomization will be stratified based on the etiology of biliary stricture (CP and postoperative) (figure 1). Patients and physicians will not be blinded to their randomization group since the interval between endoscopic interventions will be different for each group. The objectivity of the primary outcome of stricture resolution greatly reduces the potential for biased ascertainment from the non-blinded nature of this study.



Study sites. To reach our targeted sample size, we have recruited eight tertiary care medical centers with the infrastructure and patient population to support this protocol. *Prior to initiating the multicenter trial, we plan enroll the first 20 patients at our institution (10 randomized each to the PS and cSEMS groups) to confirm the safety and feasibility of our proposed study design.* Indiana University will serve as the coordinating center. All collaborative institutions will be distributed a sample copy of the protocol and informed consent. Collaborative institutions will be responsible for providing the coordinating center their OHRP-approved Assurance. Collaborative institutions will also be responsible that the protocol is reviewed and approved by the local IRB at the collaborating institution prior to the enrollment of subjects in compliance with HHS regulations. Collaborative institutions are responsible for forwarding approved documents to the coordinating center.

Eligibility criteria. Eligibility criteria are summarized in table 3. All patients with a benign, Bismuth type I bile duct stricture (defined as a common bile duct or common hepatic duct stricture whose proximal margin is ≥ 2 cm from the hepatic bifurcation) will be asked to participate. Patients must also have objective signs or symptoms related to the biliary stricture, such as laboratory evidence of cholestasis, jaundice, or cholangitis. Laboratory evidence may include an elevation in alkaline phosphatase aspartate transaminase (AST), *or* alanine transaminase (ALT) greater than the upper limits of the normal laboratory reference range (specific to each institution) *or* an elevation in serum total bilirubin greater than the upper limits of the normal laboratory reference range. Symptoms of cholestasis may include jaundice, pruritis, abdominal pain of suspected biliary origin, or some combination. Patients with radiographic evidence of common bile duct stenosis on magnetic retrograde cholangiopancreatography (MRCP) or computed tomography (CT) scan will be included if there are supporting symptoms or laboratory evidence of cholestasis. At the discretion of the treating physician, post-liver transplant patients should also undergo an evaluation for hepatic artery thrombosis (e.g., duplex sonography) prior to enrollment.

| Table 3. Eligibility criteria |
|---|
| Inclusion criteria |
| <ul style="list-style-type: none"> • Bismuth Type I benign bile duct stricture (see definition) • Objective signs/symptoms related to the stricture |
| Exclusion criteria |

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| |
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| <ul style="list-style-type: none"> • Suspected malignant etiology for the stricture |
| <ul style="list-style-type: none"> • Prior endotherapy within one year of presentation except in the following two scenarios: <ul style="list-style-type: none"> ○ Early (< 30 days) stent placement following liver transplant ○ In patients with chronic pancreatitis, single plastic stent placed during presenting ERCP while evaluating for malignancy |
| <ul style="list-style-type: none"> • Bismuth Type II-IV stricture |
| <ul style="list-style-type: none"> • Proximal common hepatic duct diameter < 6 mm |
| <ul style="list-style-type: none"> • Intact gallbladder <ul style="list-style-type: none"> ○ Except in cases where a stent can be deployed > 1cm below the cystic duct insertion |
| <ul style="list-style-type: none"> • Age < 18 years, pregnancy, incarceration, inability to provide informed consent |
| <ul style="list-style-type: none"> • Karnofsky score ≤ 40 |
| <ul style="list-style-type: none"> • Inability to pass a guidewire proximal to the stricture |
| <ul style="list-style-type: none"> • Stricture > 8cm in length |
| <ul style="list-style-type: none"> • Life expectancy < 1 year |
| <ul style="list-style-type: none"> • Concomitant nonanastomotic biliary strictures (e.g., biliary cast syndrome) |

Patients will be excluded if a malignant etiology of their stricture is suspected. In addition, recent (defined as < 1 year) endoscopic therapy to the same stricture or a Bismuth type II – IV stricture will be excluded. Since the smallest diameter cSEMS is 8 mm in diameter, patients will be excluded if the proximal common hepatic duct is < 6 mm in greatest diameter. Finally, we will exclude patients for age < 18 years, pregnancy, incarceration or those unable to provide informed consent. Additional exclusion criteria are detailed in table 3.

Subject Recruitment. Patients will be recruited from the gastroenterology clinics and endoscopy units at the participating medical centers. We will not advertise outside of our patient population and patients will not be offered reimbursement to participate. Only patients who would otherwise undergo an ERCP for evaluation and treatment of a CBD stricture will be considered.

Study procedures

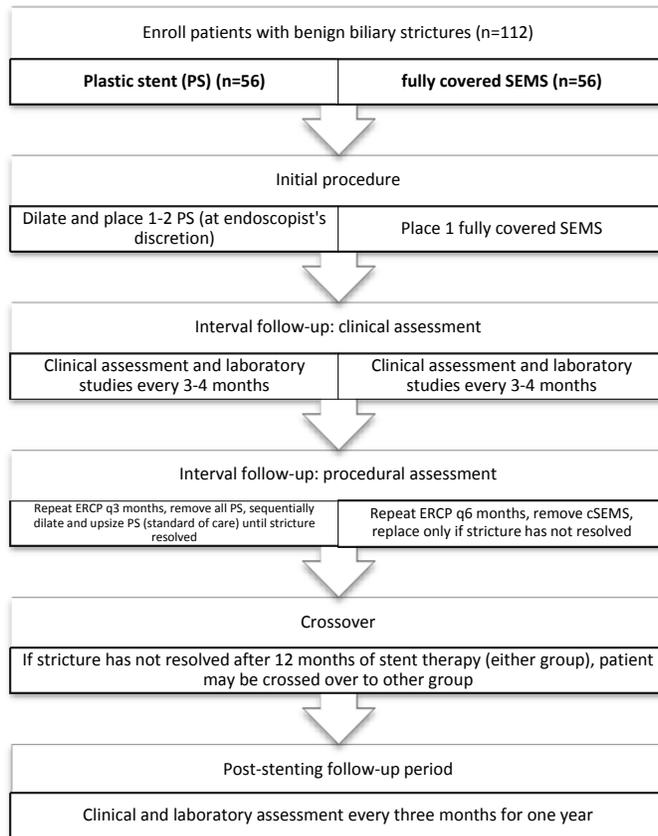
Informed consent. Each participating center will be responsible for obtaining local IRB approval. Eligible patients will be asked to sign an IRB-approved, written informed consent to verify their willingness to participate in this study. Informed consent will be obtained on the day of their scheduled ERCP and will occur at the time of consent to undergo the endoscopy (standard of care). Consent will be obtained by one of the participating endoscopists or a research assistant. Subjects will receive a copy of the signed and dated informed consent document and the original signed and dated consent form will be placed in the subject study chart. A note will be made in the subject’s hospital chart regarding participation in the research study. Original informed consent documents will be maintained on-file at each participating center. Once consented and enrolled into the trial, subjects will be issued a unique code to be used on data collection forms and other research records throughout the duration of the trial.

Pre-procedure data collection. A focused history and physical examination will be performed prior to the initial ERCP (standard of care). The Karnofsky Performance Scale Index will quantify a patient’s functional impairment, if any. This can be used to compare effectiveness of different therapies and to

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assess short-term and long-term prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses. An electronic data collection form designed by a database manager and biostatistician will be completed by the study staff before and immediately after the completion of the initial ERCP. Data collection forms will be completed after each follow-up ERCP or clinic visit (data elements listed in appendix 1).

Figure 2. Study algorithm



Randomization. Randomization will be stratified based on the participating center and underlying etiology of the benign biliary stricture: chronic pancreatitis or postoperative. Randomization will occur when a stricture has been identified which meets our predefined inclusion criteria. We will use a blocked randomization protocol to assure 1:1 randomization by center, using 4 patients per block per center.

Intraprocedural data collection. The stricture will be characterized by its length, diameter and location relative to the hepatic bifurcation prior to stent deployment. If the characteristics and location of the stricture meet our inclusion criteria, the patient will be randomized with the support of a biostatistician. Patients randomized to the PS group will be treated using a standard algorithm (figure 2). Specifically, the stricture will be dilated using a passage dilator and/or dilation balloon catheter, and one or two PS will be deployed depending on

the baseline characteristics of the stricture as well as the diameter of the proximal and distal bile duct (standard of care). The endoscopist will sequentially dilate and upsize the cumulative stent diameter on ensuing ERCPs, until the stricture has been obliterated using clinical and fluoroscopic criteria (details below).

Among patients randomized to the cSEMS group, the endoscopist will deploy a cSEMS of sufficient length to traverse the papilla (figure 2). Dilation will not be performed unless the cSEMS deployment catheter cannot be advanced over a guidewire beyond the stricture. A biliary sphincterotomy may be performed at the discretion of the treating endoscopist. If the proximal or distal bile duct measures 6-8 mm in diameter, the endoscopist will use an 8 mm diameter cSEMS. All other strictures will be treated using a cSEMS with a diameter of 10 mm. The length of cSEMS (fully covered Wallflex™) will be left to the discretion of the treating endoscopist. The name, diameter and length of stent will be recorded on the data collection form.

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Early postoperative strictures. An exception to the above algorithm applies to early (defined as < 30 days) postoperative anastomotic strictures. In this subgroup, there is edema and a reactive inflammatory response to the recent surgical anastomosis. Therefore, a larger diameter cSEMS (compared to PS) may result in excessive stricture dilation and potential duct perforation during the early postoperative period. Patients with early postoperative strictures will *not* be randomized at the time of initial endoscopic evaluation. All of these patients will receive one PS at the initial endoscopy followed by a repeat ERCP 8 ±4 weeks later (standard of care). If a persistent stricture is identified, the patient will be randomized to the PS or cSEMS group. The ensuing management will be identical to other enrollees.

Follow-up data collection. All patients will be contacted via telephone 14 days (±5 days) after the index procedure to assess for adverse events post ERCP and stent placement. Subjects will then be asked to return to the ERCP clinic every 3-4 months (± 14 days) from stent placement for a clinical assessment and liver function tests (standard of care). Patients will be assessed for clinical and laboratory evidence of ongoing cholestasis. For patients who are primarily managed by a gastroenterologist in their community, a telephone call by the treating endoscopist or a research assistant at the study center will suffice. At the time of telephone contact, laboratory studies will be faxed to the participating study center for review (table 4).

PS group follow-up. Patients randomized to the PS group will undergo a repeat ERCP every 3-4 months (± 14 days) to remove all of their preexisting stents and reevaluate the stricture (standard of care). Sequential dilation and upsizing of stents will be based on the residual stricture diameter (if any). When there is fluoroscopic resolution of the stricture, all PS stents will be removed and the patient should begin a 12-month post-stenting follow-up period. *Fluoroscopic resolution* will be defined as a duct diameter of 75% or more than the unaffected proximal or distal duct. At that time, all PS will be removed and none replaced. Patients will continue to follow-up every three months for a clinical assessment and liver function tests, until they have reached one year of follow-up after their stents have been completely removed.

| Table 4. Follow-up protocol (Time is defined as time from patient enrollment and index ERCP) | |
|--|---|
| Follow-up time | Evaluation |
| 14 days (+ 5) | Clinical evaluation via telephone: assess adverse events post ERCP & stent placement (all groups) |
| 3-4 months(+ 14 days) | Clinical evaluation, laboratory evaluation (all groups) ERCP (PS group only) |
| 6 months (+ 14 days) | Clinical evaluation, laboratory evaluation, ERCP (all groups) |
| 9 months (+ 14 days) | Clinical evaluation, laboratory evaluation (all groups) ERCP (PS group only) |
| 12 months (+ 14 days) | Clinical evaluation, laboratory evaluation, ERCP (all groups) |
| Post-stenting follow-up period (after all stents removed) | |
| 3 months (+ 14 days) | Clinical evaluation, laboratory evaluation (all groups) |
| 6 months (+ 14 days) | Clinical evaluation, laboratory evaluation (all groups) |
| 9 months (+ 14 days) | Clinical evaluation, laboratory evaluation (all groups) |
| 12 months (+ 14 days) | Clinical evaluation, laboratory evaluation (all groups) |

If the patient develops objective findings to suggest recurrent biliary obstruction during the stenting period, the endoscopist should repeat the ERCP to exchange and upsize their PS as needed (standard of care). The endoscopist may cross the patient over to the cSEMS group after 12 months of endoscopic therapy, should there be a persistent stricture that requires additional endoscopic dilation. If the patient demonstrates signs or symptoms of recurrent biliary obstruction during the post-stenting follow-up period, the patient may be crossed over in anticipation of further endoscopic therapy. Informed consent for this potential crossover will be obtained at the time of enrollment in the study. If

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crossover occurs, the patient will be followed for an additional 12-month period after all stents are removed. Cross-over is at the discretion of the treating physician.

cSEMS group follow-up. Patients in the cSEMS group will undergo a repeat ERCP six months (\pm 14 days) after the initial endoscopy unless there is laboratory or clinical evidence of recurrent cholestasis earlier. If stent migration prompts a repeat ERCP earlier than planned, the stent should be removed and the stricture assessed for resolution (using our predefined criteria). If the stricture has resolved, then a new stent will not be replaced and the post-stenting follow-up period commences. However, if the stricture persists, then a new stent will be deployed using the standard technique. At the six month follow-up ERCP, the endoscopist will remove the cSEMS and reevaluate the stricture by fluoroscopy. If the stricture has resolved at that time, no stents will be replaced. We will use the same definition of resolution as for the PS group. If there is evidence of a persistent stricture, a second cSEMS will be placed for another six month interval. Throughout the protocol, patients will continue to follow-up every three months for a clinical assessment and liver function tests, until they have reached one year of follow-up after their stents have been removed.

The endoscopist may cross the patient over to the PS group after 12 months of endoscopic therapy, should there be a persistent stricture that requires additional endoscopic dilation. If the patient demonstrates signs or symptoms of recurrent biliary obstruction during the post-stenting follow-up period, the patient may be crossed over in anticipation of further endoscopic therapy. Informed consent for this potential crossover will be obtained at the time of enrollment in the study. If crossover occurs, the patient will be followed for an additional 12 month period after all stents are removed. Cross-over is at the discretion of the treating physician.

Study outcomes

Primary outcome: *Late clinical success* will be defined as fluoroscopic resolution at the time of final stent(s) withdrawal as well as the absence of objective findings of stricture recurrence during the one year, post-stenting follow-up period.

Fluoroscopic resolution will be defined as a duct diameter of 75% or more than the unaffected proximal or distal duct. A persistent stricture must be confirmed with radiography (MRCP) or endoscopy (ERCP) (standard of care). If there is other clinical evidence to suggest recurrence (i.e., jaundice, pruritis, abnormal LFTs), one of these modalities will be performed to confirm the presence or absence of a recurrent stricture (standard of care). Patients who develop recurrent biliary obstruction during the stenting period will undergo more frequent ERCP for stent exchange as needed, but will not be considered clinical failures.

Secondary outcome: *Technical success* will be defined as the completion of the initial and each follow-up ERCP, including stent deployment and removal. Cases where stents cannot be deployed or removed via endoscopy will be considered *technical failures*. We will compare technical success rates in each group.

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Secondary outcome: *Early clinical success* will be defined as fluoroscopic resolution at the time all stent(s) are removed. If there is a persistent stricture after 12 months of stent therapy in either group, the patient will be classified as a *clinical failure*. We will compare early clinical success rates in each group.

Secondary outcome: Cost analysis. Among patients with malignant biliary obstruction, SEMS have been shown to be cost effective in patients whose life expectancy is greater than six months, or where the unit cost of ERCP exceeds \$1820.^{20,47,48} That is, if one additional ERCP costs more than \$1820, then placement of a SEMS would reduce overall costs. An assessment of cost effectiveness for patients with benign biliary strictures is more complex, since the etiology, location and duration of the stricture is highly variable.

For patients at the coordinating center, **costs** will be measured from multiple sources. The primary source of direct costs associated with cSEMS and PS is from the billing department of the local health system, which has agreed to provide us with the paid charges for our enrolled patients for two years from the first ERCP. We will include all care directly related to the stricture, including inpatient hospitalizations for the management of complications. Additional data on all health care utilization will be obtained from the patients' electronic records in the Indiana Network for Patient Care (INPC), which covers all of central Indiana. Therefore, the consent for each participant will include an authorization for collection of information concerning resource use and billed charges for the hospital as well as physician billings by CPT code. We will also get patients' self-reports on hospitalizations, emergency room visits, and surgical procedures at one and two years.

Secondary outcome: Complication rates will be assessed by the number of procedure-related complications (table 5), including post-ERCP pancreatitis, bowel perforation, gastrointestinal bleeding, stent-associated stricture/change (see below) and stent migration. In addition, the endoscopic removability of the cSEMS will be recorded. Complications will be classified as major or minor. A major complication will be defined as any procedure-related complication that requires procedural intervention or hospitalization for > 5 days. For example, stent migration that requires a repeat ERCP earlier than planned for stent readjustment or removal. All other complications will be classified as minor.

| Table 5. Classification of procedure-related complications | |
|--|--|
| Major complications | Minor complications |
| Post-ERCP pancreatitis requiring > 5 day hospitalization | Post-ERCP pancreatitis requiring ≤ 5 day hospitalization |
| Bowel perforation | Early stent occlusion requiring repeat ERCP earlier than planned interval |
| Stent migration causing signs or symptoms of cholestasis and repeat ERCP earlier than planned interval | Stent migration incidentally found at the time of scheduled follow-up ERCP |
| Stent-associated ductal change requiring additional endoscopic therapy | Stent-associated ductal change that does not require additional endoscopic therapy |
| Post-ERCP bleeding requiring a blood transfusion or repeat ERCP for therapy | |

If a procedure-related major complication occurs, precluding further endoscopic treatment, the patient will be classified as a clinical failure. Early stent occlusion requiring repeat ERCP for stent exchange prior to the standard 3-4 (PS group) or six (cSEMS group) month interval will be classified as a complication. The patient will not be considered a clinical failure unless endoscopic therapy fails to resolve the stricture within 12 months. If a patient endures two minor complications related to stent migration or early stent occlusion, the patient will be classified as a clinical failure. Early stent occlusion

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is defined as signs or symptoms related to stent occlusion that obligate the performance of ERCP prior to the predefined study window of 3-4 months \pm 14 days.

Secondary outcome: Stent-associated ductal changes. Epithelial hyperplasia has been implicated as a reason for SEMS occlusion and a potential cause for stent-associated strictures.^{25,36} There are limited animal data to suggest the universal presence of hyperplastic change in the bile duct following a trial of stenting (plastic or metallic), though the clinical significance of this is unknown.^{49,50} To address this concern, three physicians with extensive experience in ERCP will review completion cholangiograms that are obtained at the time of final stent withdrawal. They will be masked to the patient's study group. Participating centers will be asked to send these films to the primary site for masked review. Patient data will be removed from these films prior to review. Each reviewer will assess for: 1) the presence of a persistent stricture (defined as residual duct diameter of less than 75% of the proximal or distal duct diameter) and 2) evidence of irregularity in the common hepatic duct, which would be suggestive of a stent-associated change (classified as yes/no). If either of these is present, the reviewer will note what proportion (%) of the duct diameter is narrowed. This process will also serve as an internal review to compare the agreement between the treating physician and the blinded reviewing physician with regards to stricture resolution and stent-associated change. The first 10 cases will be used for resolving any discrepancies among reviewers and a consensus conference will be conducted to resolve the differences and establish common criteria. Remaining cases will be used to estimate the interobserver agreement between reviewers and between reviewers and the treating physician.

Statistical considerations

Power and sample size estimation. We estimate our sample size based on overall clinical resolution rates (combining the CP and postoperative subgroups). Our study is designed to detect a non-inferiority margin of difference of 15% in clinical resolution rates between cSEMS as first-line treatment compared to PS. Under the null hypothesis of inferiority, we assume a clinical resolution rate of 80% in the PS group and a rate of 65% in the cSEMS group. A difference of 15% or greater would be considered clinically significant. The rate in the PS group is based on > 90% resolution in the post-operative subgroup and 65% in the CP subgroup. These assumptions are consistent with currently available data.^{14,23,33,37} Given no difference in actual rates, a sample size of 224 (112 in each group) achieves 80% power with targeted significance level of 0.025. Assuming a maximum overall dropout rate of 10%, this study will require an overall sample size of 250 patients (125 per group).

Revised sample size estimation, 9/13. After interim analysis and discussion with biostatistics and the Data Safety Monitoring Board, *early clinical success* (as defined under Study Outcomes above) has been > 90% in both study arms. Therefore, without changing the non-inferiority margin (15%), overall dropout rate of 10%, and beta error (20%), we have lowered the targeted sample size to 112 (56 in each group). The decision to revise the sample size target was approved by the DSMB after presenting interim results of *early clinical success*.

Randomization. Randomization will be stratified based on the participating center and underlying etiology of the benign biliary stricture: chronic pancreatitis or post-operative. Randomization will occur

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during the first ERCP when a stricture has been identified which meets our predefined inclusion criteria. Each center will use a random number generator with the support of a biostatistician for group assignment. We will use a blocked randomization protocol to assure 1:1 randomization by center, using 4 patients per block per center.

Participating centers will contact the primary site (Indiana University) when an enrolled patient has completed their first endoscopy. Data from each procedure, clinic visit or telephone contact (including laboratory results) will be forwarded to the primary center after all personal identifiers have been removed. Data compilation and analysis will be performed at the primary site. All data collection will occur through the participating centers.

Statistical analysis. Statistical analysis will include all patients who are randomized, consistent with an intent-to-treat protocol. Descriptive statistics will be performed for all continuous variables (mean \pm standard deviation for normally distributed variables and median \pm interquartile range for nonnormal variables) and categorical variables (count and proportion). Categorical outcomes will be analyzed using χ^2 test or Fisher's test for small samples. Comparison of group outcomes will be analyzed using Student's t test for normally distributed data and nonparametric Wilcoxon-Mann-Whitney test for data that violate the normality assumption. All tests will be conducted as two-sided at the $\alpha=0.05$ level of significance. Univariate logistic regression analysis will be used to identify predictors of interest and multiple predictor analysis will estimate effects adjusted for covariates.

Feasibility, study duration. We estimate an enrollment period of two years, with an additional one year to obtain follow-up data and perform the final statistical analysis (study duration = 4 years). We perform close to 3,000 ERCPs at IU medical center annually. With a robust chronic pancreatitis and liver transplant patient population, we estimate 30 patients per year will meet the eligibility criteria and participate in this study. The other participating centers have comparable patient populations and are expected to contribute the additional 190 patients, requiring the recruitment of 12 patients per year, per center.

Patient safety issues

Data safety monitoring. A data safety monitoring committee (DSMC) will review the patient data every six months from the onset of enrollment to study completion, in June and December. The PI will review study progress and all adverse events with the DSMC members. This will be followed by a closed session of only the DSMC members so they can discuss their concerns frankly and be willing to stop the study if necessary. Data quality, subject recruitment (accrual and retention), procedure outcomes, adverse events, assessment of scientific reports, therapeutic developments, results of related studies that impact subject safety, and procedures designed to protect the privacy of subjects will all be monitored. The DSMC will be chaired by an experienced gastroenterologist (Debra Helper, MD). Other members will include a senior ERCP nurse (Lois Bucksot, RN, not a co-investigator) and a pancreatobiliary endoscopist from an outside institution, Dr. Robert Hawes. Dr. Hawes is a world-renowned pancreatobiliary endoscopist and has agreed to be a voting member of the DSMC. He will participate in DSMC meetings via conference call. Cases will be reviewed for accuracy of data collection, compliance

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with follow-up and procedure-related complications. An adverse event will be classified as a complication thought to be specific to the stent(s) used for stricture therapy. Specifically, these will include stent migration, re-occlusion, perforation, bleeding, and stent-induced changes to the bile duct on completion cholangiograms. Each stent-associated adverse event will be reported to the IRB on a per-event basis. Subjects will be terminated from the study if the duct stricture is later determined to be cancerous. Information that will be reported to the IRB include frequency and dates of monitoring, summary of cumulative adverse events, assessments of scientific reports, therapeutic developments, results of related studies that impact the safety of subjects, summary of subject privacy and research data confidentiality outcomes, and any changes to the risk-benefit ratio.

Stopping rules. The primary stopping rule will be if a change to the perceived risk-benefit ratio of one modality is perceived during interim analyses of complication rates. In addition, we will terminate the study early if a statistically significant difference in efficacy (defined as clinical resolution, the primary endpoint) between the two groups is identified at the time of formal interim analysis (after 50% recruitment). Finally, if the frequency of major complications in one group is > 10% after a minimum of 20 patients have been randomized to each group, the study will be terminated early.

Privacy/Confidentiality issues. We will remove all identifiable data from the research database and each subject will be assigned a unique study number. Study material will be kept on a limited number of password protected computer stations, and paper records will be kept in locked cabinets/offices in areas with limited public access. Study material will be retained until seven years after study closure, at which point records will be destroyed, and hard drives containing study data will be erased.

Follow-up and record retention. We anticipate a 24-month enrollment period to achieve our estimated sample size. The post-stenting follow-up period will be one year for all patients. Assuming a one year stenting period, we expect a four year period from the onset of patient enrollment to completion of follow-up. This does not include final statistical analysis and interpretation. Data collected for research purposes will be retained for seven years after the study is closed. At that time, all paper and electronic records pertaining to this study will be destroyed.

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