A fully covered large diameter self-expanding-metal-stent for the treatment of upper GI perforations, anastomotic leaks and fistula.

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ABSTRACT

Objective
Upper GI perforations, fistula and anastomotic leaks are severe conditions with high mortality and temporary endoscopic placement of fully covered self-expanding-metal (fSEMS) has emerged as treatment option. This study aimed to investigate the safety and efficacy of a large diameter fSEMS for treatment of these conditions.

Material and methods
Data were retrospectively collected from patients who received this stent in the Netherlands between March 2011 and August 2013. Clinical success was defined as sufficient leak closure after stent removal without surgical intervention or placement of another type of stent. Adverse events were graded according a standardized grading system.

Results
Stent placement was performed in 34 patients for the following indications: perforation (n=6), anastomotic leak (n=26) and fistula (n=2). Technical success rate was 97% (33/34). Clinical success rate was 44% (15/34) after 1 stent and 50% (17/34) after an additional stent. There were no severe adverse events and stent-related mortality. The overall adverse event rate was 50% (all graded ‘moderate’), including 14 (41%) stent migrations (complete n=8, partial n=6). Re-interventions consisted out of placement of another type of fSEMS (n=4), surgical repair (n=3) or esophagectomy (n=1). Eleven patients (32%) died in-hospital because of persisting intrathoracic sepsis (n=10) or pre-existent bowel ischemia (n=1).

Conclusion
This study suggests that temporary placement of a large diameter fSEMS for the treatment of upper GI perforations, fistula and anastomotic leaks is safe in terms of severe adverse events and stent-related mortality. The larger diameter does not seem to prevent stent migration.
INTRODUCTION

Perforations, fistula and anastomotic leaks (leaks) of the upper GI tract are severe and complex conditions with high morbidity and mortality rates.\textsuperscript{1-3} Traditional treatment consists out of conservative measures like antibiotics, nasogastric feeding tube placement and drainage of leak sites for smaller leaks which are combined with surgical treatment, including repair, diversion or esophagectomy, in case of therapy failure or in the presence of larger leaks. Unfortunately this treatment regime prolongs hospitalization and delays oral intake and despite technical improvements of surgical interventions, they are still associated with significant morbidity and mortality.\textsuperscript{4, 5}

Therefore, temporary placement of self-expanding stents is gaining popularity as a treatment modality in these patients as it is less invasive than surgical approaches and allows a quick restart of oral nutrition. Several studies have shown that temporary placement of fully covered self-expanding metal stents (fSEMS) and plastic stents (fSEPS) has the potential to sufficiently seal of the leak without any major complications, while eliminating the need for surgical re-intervention.\textsuperscript{6-13} However, one drawback of the currently used fSEMS and fSEPS designs is a relatively high migration rate ranging from 13-46%.\textsuperscript{6-8, 10, 14-16} To overcome this problem partially covered self-expanding metal stents (pSEMS) have been evaluated in several studies, because these stents allow some degree of tissue ingrowth through the uncovered part(s) which should prevent stent migration. Unfortunately severe tissue embedding might hamper safe endoscopic removal of pSEMS.\textsuperscript{13, 17}

Another option to prevent stent migration might be the use of a stent with a larger diameter. Esophageal stents were initially intended for the treatment of oesophageal stenosis and therefore their diameter is rather small and probably too small for a normal diameter esophagus. The colonic fully covered Hanarostent (CCI stent) (M.I.Tech, Seoul, South-Korea) has a larger diameter than oesophageal fSEMS and several Dutch endoscopists hypothesized that placement of this stent would be associated with a lower risk of stent-migration and sufficient closure of upper GI leaks. On the contrary, however, the large diameter of this stent might predispose towards a risk of severe adverse events like perforation, bleeding caused by stent erosion and severe retrosternal pain.\textsuperscript{18}

Therefore the aim of this study is to determine first en foremost the safety and in addition the efficacy of the placement of the Hanaro-CCI stent for the treatment of upper GI perforations, anastomotic leaks and fistula.
METHODS

Patients
This is a multicenter retrospective cohort study. All consecutive patients who received a Hanaro CCI-stent for the treatment of perforations (either spontaneous or iatrogenic), fistula or anastomotic leaks of the upper GI tract in the Netherlands between March 2011 and August 2013 were enrolled. The Hanaro CCI-stent is CE-marked for the treatment of malignant and refractory benign colonic strictures and malignant gastric outlet obstruction. Therefore placement of the Hanaro CCI-stent for the treatment of upper GI leaks was off-label. All patients gave informed consent for this off-label use prior to stent placement.

The following information was collected from their medical records: baseline demographics; indication for stent placement; leak characteristics; information on previous treatment; stent-placement and stent-removal procedure reports; adverse events including information re-interventions; information on concurrent treatment (e.g. drainage).

Stent placement and removal procedure
The Hanaro CCI-stent is a fully covered SEMS with flares at both ends as anti-migration feature and available in the lengths 5, 8, 11 and 15 cm. The diameters of the flares and body of the stent are 32 and 24mm respectively (Figure 1). The stent meshes are made of nitinol and it is fully covered with an inner silicone membrane. Gold radiopaque markers at both ends and in the middle of the stent ensure visualisation during fluoroscopic control. The stent is deployed with the help of a 24 Fr delivery device with a length a 70 cm, which enables controlled stent release.

After determining the length of the leak during upper endoscopy, a guidewire is placed into the stomach and the appropriate stent size is chosen, with the stent being at least 4 cm longer than the lesion. The delivery device is advanced over the guidewire until the distal end of the stent is at least 2 cm below the distal margin of the lesion. All stents are deployed under either constant fluoroscopic control, endoscopic control or a combination of both. In case of fluoroscopic control the upper and lower margin of the lesion are marked with a contrast agent.

Endoscopic stent removal is scheduled after approximately 6 weeks depending on clinical symptoms and local protocols. Repeat endoscopy for assessment of healing in asymptomatic patients with a stent in situ is not routinely performed. Stent removal is performed during upper endoscopy with a rat-tooth forceps grasping the loop at the proximal end of the stent (Figure 1) or by inverting the stent using the distal loop. In case of doubt about sufficient leak occlusion during stent removal, an X-ray with oral contrast is obtained. Endoscopic procedures are performed under conscious sedation with midazolam and/or fentanyl or general anaesthesia with propofol depending on the patient’s condition.
Figure 1 | A) The Hanaro CCI-stent, B) Endoscopic view of an anastomotic leak after esophagectomy, C) Endoscopic view of the Hanaro CCI-stent placed across the anastomotic leak
Additional treatment
Concurrent drainage of infected areas in the mediastinum or pleural cavity was performed when indicated, either by video-assisted thoracoscopy or radiological percutaneous drainage. Administration of antibiotics and placement of a nasoduodenal feeding tube was performed at the discretion of the treating physician and in accordance with local protocols.

Outcome measures
The following outcomes were used in this study: technical success, defined as sufficient placement and deployment of the stent at the correct location; clinical success, defined as sufficient leak closure after stent removal as confirmed by endoscopy or X-ray with oral barium contrast without the need for surgical intervention or placement of another type of stent; stent-related adverse events that were graded as mild (e.g. unplanned hospital admission or prolongation of hospital stay for ≤3 nights), moderate (e.g. repeat endoscopy for an adverse event, intensive care unit (ICU) admission for 1 night) or severe (e.g. surgery for an adverse event, ICU admission >1 night) according the severity grading system for adverse events of gastrointestinal endoscopic procedures as described by Cotton et al.;

Statistical analysis
Descriptive statistics were used for all data. For continuous data, means (± standard deviation [SD]) or medians (interquartile range (IQR)) were used depending on data distributions. All analyses were performed according the intention-to-treat principle. Statistical analyses were conducted using SPSS version 20 (SPSS Inc., Chicago, Ill. USA)

RESULTS
Patient characteristics
In total 34 patients (male n=23 [68%], mean age 60 [± 10.4]) were included. The majority of patients underwent stent placement for an anastomotic leak after esophagectomy with gastric tube formation for esophageal cancer (n=17), bariatric surgery (gastric sleeve [n=2], gastric bypass [n=6]) or resection of an esophageal diverticulum (n=1). Other indications were an iatrogenic perforation after pneumodilation (n=1), tumor perforation (n=2), Boerhaave’s syndrome (n=3) and a radiotherapy induced esophagobronchial fistula (n=2). Leaks were located in the cervical region in 15 patients, the intra-thoracic region in 4 and at the gastro-esophageal junction region in 15. Sixteen patients had undergone a failed previous treatment, which consisted out of fSEMS placement (n=6), surgical closure (n=4) or a combination of both (n=6). A nasoduodenal feeding tube was placed in 16 patients. Twenty-two patients were treated with simultaneous drainage of infected areas in the mediastinum or pleural cavity, either surgically (n=16) or radiologically (n=6). Most patients (n=25) were administered antibiotic treatment. All baseline characteristics and clinical details are summarized in Table 1.
Table 1 | Baseline characteristics and clinical information

| Age, years, mean (± SD) | 60 (± 10.4) |
| Male, n (%) | 23 (68%) |

**Indication for stent placement, n (%)**
- Anastomotic leak: 27 (77)
- Esophagectomy: 18 (53)
- Bariatric surgery: 8 (24)
- Resection diverticulum: 1 (3)
- Perforation: 6 (18)
- Fistula: 1 (3)

**Leak location, n (%)**
- Cervical: 15 (44)
- Intra-thoracic: 4 (12)
- Gastro-esophageal junction: 15 (44)

**Failed previous treatment, n (%)**
- Stent placement: 6 (18)
- Surgical repair: 4 (12)
- Surgical repair & stent placement: 6 (18)
- No: 18 (53)

**Concurrent nasoduodenal feeding tube, n (%)**
- Yes: 16 (47)
- No: 16 (47)
- Unknown: 2 (6)

**Concurrent drainage of infected areas, n (%)**
- Surgical: 16 (47)
- Radiological: 6 (18)
- No: 11 (32)
- Unknown: 1 (3)

**Concurrent antibiotic treatment, n (%)**
- Yes: 25 (74)
- No: 7 (21)
- Unknown: 2 (6)

Technical and clinical outcomes

Stent placement was technically successful in 33/34 patients (97%). One technical failure occurred due to an intra-procedural distal stent migration, which was treated with endoscopic removal of the migrated stent using a rat-tooth forceps and placement of a different stent during the same procedure, because the Hanaro CCI-stent was not on stock at that moment. An 8 cm stent was used in 14 patients, an 11 cm in two and a 15 cm in five.

Stent removal was successful and without adverse events in all patients who underwent stent removal (n=29). In 21 patients stents were removed according to treatment plan after a median time interval of 40 days (IQR 35-53). In 14 of these patients sufficient
leak closure was confirmed. In addition, sufficient leak closure was confirmed in 1 patient who underwent endoscopy for a migrated stent after 33 days. Therefore clinical success was achieved in 15/34 patients (44%) after treatment with 1 Hanaro CCI-stent. In 7 patients there was still a remnant leak after scheduled stent removal, which was treated with placement of an additional Hanaro CCI-stent (n=4) or another type of stent (n=3). Ultimately 3 of the patients who received an additional Hanaro CCI-stent and all 3 patients who received another type of stent died with the new stent in situ because of persisting intra-thoracic sepsis, while 1 of the patients who received an additional Hanaro CCI-stent eventually underwent surgical leak repair because of persisting intra-thoracic sepsis.

There were 7 complete stent migrations after a median of 7 days (IQR 5-13). These patients were treated with removal of the migrated stent and placement of another stent (Hanaro CCI-stent [n=4], other type of stent [n=1]), placement of an additional stent through the migrated stent (n=1) or stent removal and esophagectomy (n=1). From the patients whom received another type of stent, 1 patient died with the new stent in situ because of persisting intra-thoracic sepsis, while in the other patient the second stent was removed at the planned date and the leak was sufficiently closed. A bleeding behind the stent occurred in 1 of the 4 patients who received a second Hanaro CCI-stent, which was treated with stent removal and placement of an endo-SPONGE® (B. Braun Aesculap AG, Germany), while the new Hanaro CCI-stent migrated in another patient, which was removed endoscopically and the patient was referred for surgical leak repair. In the remaining 2 patients who received a new Hanaro CCI-stent the second stent was removed at the scheduled date and the leak was sufficiently closed. Therefore, overall clinical success was achieved in 17/34 patients (50%).

Finally, 4 patients died in the hospital with the first stent in situ after a median (range) of 19 days (11-50) because of persisting intra-thoracic sepsis (n=3) and pre-existing bowel ischemia respectively (n=1) without any further interventions.

**Adverse events**

There were no severe adverse events associated with the stent, stent placement or stent removal and there was no stent-related mortality. In addition to the 8 complete stent migrations as described above there were 6 partial stent migrations that could be treated with endoscopic repositioning of the stent and therefore the overall stent migration rate was 14/34 (41%). In addition to the bleeding as described above there was 1 patient who suffered from a bleeding due to mucosal pressure erosion at the proximal margin of the stent which was treated with transfusion of two units of packed cells. Furthermore 1 patient developed aspiration pneumonia within 1 day following stent placement requiring intensive care unit admission for one night. According to the severity grading system as defined by Cotton et al. all these adverse events were classified as ‘moderate’. All study outcomes and adverse events are listed in Table 2.
### Table 2 | Overview of study outcomes

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<table>
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<tr>
<td><strong>Technical success, n (%)</strong></td>
<td>33 (97)</td>
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<tr>
<td><strong>Clinical success, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>1 stent</td>
<td>15 (44)</td>
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<tr>
<td>2 stents</td>
<td>2 (6)</td>
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<tr>
<td><strong>Cause of clinical failure, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Technical failure</td>
<td>1 (3)</td>
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<tr>
<td>Stent migration</td>
<td>5 (15)</td>
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<tr>
<td>Insufficient leak occlusion</td>
<td>7 (21)</td>
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<tr>
<td>Premature death</td>
<td>4 (12)</td>
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<tr>
<td><em><em>Reason for stent removal</em>, n (%)</em>*</td>
<td></td>
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<tr>
<td>Scheduled</td>
<td>22 (65)</td>
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<tr>
<td>Stent migration</td>
<td>7 (21)</td>
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<tr>
<td>Technical failure</td>
<td>1 (3)</td>
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<tr>
<td><strong>Adverse events, n (%)</strong></td>
<td></td>
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<tr>
<td>Total</td>
<td>17 (50)</td>
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<tr>
<td>Severe</td>
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<tr>
<td>Moderate</td>
<td></td>
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<tr>
<td>Complete stent migration</td>
<td>8 (24)</td>
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<tr>
<td>Partial stent migration</td>
<td>6 (18)</td>
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<tr>
<td>Aspiration pneumonia</td>
<td>1 (3)</td>
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<tr>
<td>Bleeding</td>
<td>2 (6)</td>
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<tr>
<td>Mild</td>
<td>0</td>
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*Regarding removal of first stent.
DISCUSSION

In recent years temporary stent placement has emerged as a treatment option for anastomotic leaks, perforations and fistula of the upper GI tract. Although this endoscopic technique appears to be safe in the majority of patients, efficacy is hampered by a relatively high stent migration rate. In this retrospective multicenter study we aimed to evaluate the safety and efficacy of temporary placement of a large diameter fSEMS in order to prevent migration. Our study suggests that placement and removal of this specific fSEMS is safe in terms of severe adverse events and stent-related mortality. However, the overall stent migration rate was still 41% and clinical success was only achieved in half of patients.

To our knowledge there are two studies that investigated a relationship between stent diameter and adverse events. The authors concluded that a larger stent diameter is associated with an increased risk of severe adverse events in patients with esophageal strictures. One might expect that a larger stent diameter increases the pressure to the esophageal wall and therefore the absence of stent-related adverse events like perforation, severe retrosternal pain or severe bleeding could be explained by the fact that there were no patients with strictures included in the present study. However, our migration rate was at the high end of the range of 13-46% as reported in the literature. Although 6 stent migrations could be treated by endoscopic repositioning without the need for an additional stent, this is a disappointing finding as it appears that increasing the stent diameter does not provide better anchoring of fSEMS in these patients.

In the present study no additional measures were undertaken to anchor the stent. However, several interesting methods for fixation of fSEMS have been described in small feasibility and case studies. External fixation of the stent with a polypectomy snare that is drawn out through the nose and attached to the patient’s earlobe has been proposed, but this is associated with patient discomfort and might therefore not be widely accepted. Furthermore, Blackmon et al. described a transcervical neck-pexy of stents entailing percutaneous suturing under ultrasonic guidance. This technique is, however, invasive and not applicable in the thoracic and lower esophagus, making it less attractive than endoscopic fixation methods. Vanbiervliet et al. demonstrated that endoscopic fixation of the proximal flare of the stent using through-the-scope clips significantly reduced the migration risk, while a Dutch study showed no beneficial effect of clipping. Another recent study investigated the use of an over-the-scope clip to prevent further dislocation of partially migrated SEMS and found a migration rate of 15% after clipping. In addition, multiple studies evaluated the use of a new endoscopic suturing device to secure the fSEMS to the esophageal wall in order to prevent migration. Unfortunately the largest of these studies showed a migration rate of 33% in 18 patients. All in all it is still unclear whether fixating fSEMS really reduces the migration risk and, if so, which of the fixation techniques is superior. Still, in our opinion, the use of fSEMS is preferred over pSEMS because they are easier and safer to remove, which is also confirmed by our results.

However the clinical success rate of 50% in our study was relatively low when compared to pooled rates of some 85% in systematic reviews. Though, previous treatment,
including surgical closure and placement of another stent, had already failed in 16 of 34 patients and the Hanaro CCI-stent was used as last salvation option. In-hospital mortality occurred in 8 of these patients and 2 patients ultimately underwent esophagectomy. Possibly these patients would have benefited more from direct placement of the Hanaro CCI-stent. On the contrary, 3 patients died in-hospital and 2 patients underwent surgical repair after primary treatment with the Hanaro-CCI stent. Several studies have indicated that a delay in treatment confers worse prognosis as the likelihood of septic complications increases.\(^7\), \(^30\) Therefore it seems of utmost importance to determine the best suitable treatment (i.e. stent placement, conservative treatment, surgery) for specific patient sub-groups, based on patient and leak characteristics, in order to quickly establish the optimal treatment modality in each patient.

Still, traditional treatment options carry considerable disadvantages. Surgical treatment is associated with failure rates of about 25% and 22% for repair of anastomotic leaks after esophagectomy and bariatric surgery respectively.\(^31\), \(^32\) Moreover, surgery-related mortality rates in the treatment of esophageal perforations have been reported to range between 12-50%.\(^1\), \(^4\), \(^5\), \(^33\) In addition, one study found that when surgical diversion is performed, GI-tract continuity is only re-established after an average of 7.7 months and revision surgery is associated with a complication rate of approximately 70%.\(^34\) On the other hand conservative treatment with nil per mouth, percutaneous drainage and antibiotic treatment is sufficient in some selected patients with small leaks. However this treatment regime precludes oral intake while no measures are taken to seal the leak and up to 90% of patients treated in this manner ultimately require surgery.\(^31\) Therefore temporary stent placement remains the most attractive treatment modality and further research should focus on optimizing covered stent designs and stent fixation techniques.

We are aware of the limitations of this study because of the retrospective design, the relatively small study population, heterogeneity in indications for stent placement and lack of a control group. Because of the retrospective character of this study we were unable to collect reliable information on the size of leaks and the interval between diagnosis and stent placement. Moreover, in a substantial number of patients another type of SEMS was placed in case of insufficient leak occlusion or complete stent migration because the Hanaro CCI-stent was not available. This has negatively affected clinical success rate and could also have influenced adverse event rates. Finally, selection bias cannot be excluded since there is still no guideline that clearly defines which patient benefits from stenting and which patient from conservative or surgical treatment.

In conclusion, this study suggests that temporary placement of the fully covered large diameter Hanaro CCI-stent for the treatment of upper GI anastomotic leaks, perforations and fistula is safe in terms of severe adverse events and stent-related mortality. The larger diameter does not seem to prevent stent migration. Further prospective studies are needed to define optimal stent design and stent fixation technique.
Chapter 4

REFERENCE LIST


Large diameter stent for treatment of upper GI leaks


