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# Aspects of Endoscopic Interventions of the Upper Gastrointestinal Tract



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*For the patients*

*Felix qui potuit rerum cognoscere tempus*  
*Fortunate is he who understands the causes of things*

## Abstract

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Interventional endoscopy of the upper gastrointestinal tract is a rapidly evolving surgical discipline that minimizes the surgical trauma. Yet, complications occur that sometimes are severe. This thesis aims to improve upper gastrointestinal endoscopic therapeutic procedures by addressing aspects of their complications in three randomised clinical trials (paper I-III) and one prospective cohort study (paper IV).

In distal oesophageal tumours the palliative placement of stent, against dysphagia, crosses the gastrooesophageal junction, thus possibly causing reflux-induced severe oesophagitis and aspiration. Therefore, in paper I, a multicentre trial was performed with the intention of improving the health-related quality of life (HRQL) by testing an anti-reflux stent after palliative stenting of patients with inoperable distal oesophageal cancer. The 65 patients included were randomised for an anti-reflux stent or a conventional stent. HRQL was measured using validated questionnaires assessing general and oesophageal-specific symptoms and functions (EORTC QLQ-C30 and QLQ-OES18) at baseline, and both one and three months after stenting. No statistically significant differences were found between the two types of stents.

Some research has indicated that the antihypertensive angiotensin II receptor blocker (ARB) losartan might prevent acute pancreatitis. Therefore, in paper II, we conducted a placebo controlled trial that tested whether losartan prevents hyperenzymemia (a marker of acute pancreatitis) as assessed 24 hours after endoscopic retrograde cholangiopancreatography (ERCP). Among 76 randomised patients, there was no evidence of any preventive effect of losartan on such hyperenzymemia.

A significant problem after insertion of nutritional percutaneous endoscopic gastrostomy (PEG) is peristomal infection. A standard antibiotic prophylaxis of 1.5 g cefuroxime (Zinacef<sup>®</sup>) given intravenously one hour before PEG insertion is generally recommended. In paper III, to develop and facilitate such prophylaxis, we tested whether antibiotic prophylaxis with 20 ml oral solution sulphamethoxazole/trimethoprim (Bactrim<sup>®</sup>) given in the newly inserted PEG catheter could replace the standard treatment. Among 234 randomised patients, 10 and 14 peristomal infections occurred in the sulphamethoxazole/trimethoprim and the cefuroxime group, respectively. The intention-to-treat and per-protocol analyses both revealed that the sulphamethoxazole/trimethoprim strategy was at least as effective as standard antibiotic prophylaxis.

The risk factors for peristomal infections and early mortality after PEG insertion are uncertain. In paper IV we therefore conducted a hospital-based prospective cohort study addressing six potential risk factors for infectious complications or 30-day mortality after PEG insertion: age  $\geq$  65 years, BMI  $<$ 18.5 kg/m<sup>2</sup>, albumin  $<$ 30 g/L, C-reactive protein (CRP)  $\geq$ 10 mg/L, indications for PEG, and co-morbidities. After adjustment for potential confounders: advanced age, low albumin and high CRP levels were followed by a statistically significantly increased risk of short-term mortality. Compared to the 2.6% risk of mortality in patients with normal albumin and CRP levels, a combination of low albumin and high CRP rendered a greater than 7-fold increased risk (OR, 7.45; 95% confidence interval, 2.62-21.19) or a mortality rate of 20.5%.

In summary, antireflux stents might not be superior to conventional stents in the palliation of dysphagia in patients with distal oesophageal cancer. Losartan does not seem to reduce hyperenzymemia after ERCP. A local solution of 20 ml sulphamethoxazole/trimethoprim can probably replace standard antibiotic prophylaxis during PEG insertion. Low albumin and high CRP are markers of increased risk of early mortality after PEG insertion.

## List of original publications

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This thesis is based on the following papers, which will be referred to in the text by their Roman numerals (I-IV).

- I** John Blomberg, Urs Wenger, Jesper Lagergren, Urban Arnelo, Torhallur Agustsson, Erik Johnsson, Ervin Toth, Pernilla Lagergren.  
Anti-reflux stent versus conventional stent in the palliation of distal esophageal cancer. A randomised, multicenter clinical trial.  
*Scandinavian Journal of Gastroenterology* 2010;45(2):208-16
- II** Tomas Sjöberg Bexelius, John Blomberg, Yunxia Lu, Hans-Olof Håkansson, Peter Möller, Carl-Eric Nordgren, Urban Arnelo, Jesper Lagergren, Mats Lindblad.  
Angiotensin II receptor blocker losartan and the prevention of hyperenzymemia after endoscopic retrograde cholangiopancreatography: a randomised clinical trial.  
Submitted manuscript.
- III** John Blomberg, Pernilla Lagergren, Lena Martin, Fredrik Mattsson, Jesper Lagergren.  
Novel approach to antibiotic prophylaxis in percutaneous endoscopic gastrostomy (PEG): randomised controlled trial.  
*British Medical Journal* 2010 Jul 2;341:c3115.
- IV** John Blomberg, Pernilla Lagergren, Lena Martin, Fredrik Mattsson, Jesper Lagergren.  
Albumin and C-reactive protein levels predict short-term mortality after percutaneous endoscopic gastrostomy (PEG) in a prospective cohort study.  
*Gastrointestinal Endoscopy (In press)*,

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## An overview of the studies

	Question	Patients and methods	Results	Conclusion
I	Are anti-reflux stents better than conventional stent regarding health related quality of life (HRQL) in palliative treatment of dysphagia in patients with inoperable distal esophageal cancer?	Double-blinded randomised multicentre trial between 2003-2007 including 72 patients. HRQL questionnaires QLQ-C30 and QLQ-OES18 were registered at baseline and at 1 and 3 months.	No differences in HRQL scores were found between the comparison groups.	No benefit in using anti-reflux stent compared to conventional stent.
II	Does 50mg losartan given 1 hour before endoscopic retrograde cholangiopancreatography (ERCP) reduce hyperenzymemia after ERCP?	Triple-blinded randomised placebo-controlled clinical trial between 2006-2008 including 76 patients. Serum levels of amylase and lipase 24 hour after ERCP were evaluated.	No reductions in amylase or lipase levels after ERCP were found.	No support for the hypothesis that 50mg losartan prevents hyperenzymemia after ERCP.
III	Is 20 ml sulphamethoxazole/trimethoprim in the catheter after percutaneous endoscopic gastrostomy (PEG) at least as effective as standard antibiotic prophylaxis in the prevention of peristomal infection?	Double-blind randomised clinical trial between 2005-2009, including 234 patients. Standard treatment was 1.5 g cefuroxime given 1 hour before PEG. Peristomal infection was assessed at follow-up within 14 days after PEG insertion.	No difference was found in infection frequency between the comparison groups.	Sulphamethoxazole/trimethoprim is at least as effective as standard treatment for antibiotic prophylaxis in PEG insertion.
IV	Which are the risk factors for short-term mortality and peristomal infection after PEG?	A prospective cohort study evaluating 484 patients receiving a PEG catheter between 2005-2009 at Karolinska University Hospital in Solna. The study assessed pre-determined potential risk factors: age, body mass index (BMI), albumin, C-reactive protein (CRP), indication for PEG and co-morbidity.	Patients aged $\geq 65$ , with albumin $< 30\text{g/L}$ and CRP $\geq 10\text{mg/L}$ had an increased risk of mortality and possibly of peristomal infection. The combination of low albumin and high CRP resulted in a 7-fold increased risk of mortality, and an absolute mortality risk of 20.5% compared to 2.6%, when both these values were normal.	Albumin and CRP levels predict short-term mortality after PEG.



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## List of abbreviations

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ACE	Angiotensin converting enzyme
ARB	Angiotensin II receptor blocker
ARS	Anti-reflux stent
BMI	Body mass index, body weight in kg/ body area in m <sup>2</sup>
CI	Confidence interval
CCD	Charge-coupled device or light sensor
CRP	C-reactive protein, an acute phase protein with immunological properties, reflecting inflammation and infection
CS	Conventional stent
CT	Computerised tomography
DIC	Disseminated intravascular coagulopathy
EORTC	European Organisation for Research and Treatment of Cancer
ERCP	Endoscopic retrograde cholangiopancreatography
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 questions
EORTC QLQ-OES18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Oesophageal 18 questions
Fr	French = Charrière (Ch), a measure of diameter, Fr or Ch/3 = millimetre
HR	Hazard ratio
HRQL	Health-related quality of life
MODS	Multi-organ dysfunction syndrome
NOTES	Natural orifice trans-luminal endoscopic surgery

OR	Odds ratio
PEG	Percutaneous endoscopic gastrostomy
PPI	Proton pump inhibitor, inhibits gastric acid secretion
SEMS	Self-expanding metal stent
SEPS	Self-expanding plastic stent
SD	Standard deviation
SI	Synergy index
SIRS	Systemic inflammatory response syndrome
WBC	White blood cell count
WHO	World Health Organization

# Introduction

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Endoscopy (endo- prefix referring to something internal, and scopy, to see; both words are of Greek origin) originally means to look inside something. Today endoscopy mainly represents the use of flexible or rigid instruments to look inside body cavities. “Interventional endoscopy” implies that the endoscopy includes some kind of surgical treatment. The instrument used for interventions in this thesis is flexible but of different designs. The development of new instruments and the gathering of new endoscopic skills allow more advanced endoscopic surgical procedures. An increasing palette of complications is therefore to be expected but, compared to the alternative surgical procedures, the number and severity of complications is probably less and, as an extra enticement, the endoscopic procedures leave no visible scars, except when specific complications occur. Identification of the different complications, of how often they occur, of risk factors for developing complications and, most importantly, of ways of avoiding them or making them less severe is of utmost clinical importance. My interest in endoscopic procedures and clinical knowledge of diagnostic and therapeutic endoscopy has given me insight into the consequences of complications. These complications could decrease patients' quality of life, lengthen their hospital stay, add costs and sometimes cause early mortality. This knowledge has stimulated my interest in finding measures to reduce complications and suffering caused by interventional endoscopy in the upper gastrointestinal tract, and in trying to make the procedures more efficient. There are many interventional procedures with different sets of complications, but I have focused in this thesis on a few common endoscopic interventions: 1/ Insertion of self-expanding metal stents (SEMS) for palliation of inoperable malignant oesophageal cancer, 2/ Endoscopic retrograde cholangiopancreatography (ERCP) used to investigate and treat problems in the bile duct or the pancreatic duct, and 3/ Insertion of percutaneous endoscopic gastrostomy (PEG) catheter, performed mainly for nutritional reasons.

The present thesis evaluates: 1/ The role of anti-reflux stents in the palliative stenting of inoperable distal oesophageal cancer regarding health-related quality of life (HRQL), 2/ The prophylactic effect of losartan on hyperenzymemia after ERCP, 3/ A new method of antibiotic prophylaxis against peristomal infection after PEG insertion, and 4/ Potential risk factors for short-term mortality and peristomal infections after PEG.

# Background

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## *Historical development of upper gastrointestinal endoscopy*

Hippocrates (460-ca 375 BC) wrote the first known description of an investigation into the anal canal and rectum, with a device using an ambient light source, a rectal speculum, in his treaty on fistula.<sup>1</sup> The problem in early attempts to perform endoscopy was to direct strong enough light into the tubes. The Arabian physician Albukasim (936-1013 AD) is said to be the first to have used reflected light to inspect the cervix.<sup>2</sup> It was not until Bozzini (1773-1808) in 1806 developed an instrument (“Lichtleiter”) with mirrors and a wax candle light source that a better view could be achieved. It allowed inspection of the urethra, urinary bladder, rectum, mouth and even vocal cords.<sup>1,2</sup> Development continued slowly with different lens systems for condensing light. For instance, Désormeaux demonstrated in 1853 the open tube endoscope with a burner, fuelled by a mixture of alcohol and turpentine, for illumination, allowing inspection of the urethra and urinary bladder.<sup>2</sup> These methods were not well accepted by the medical profession of the time, who looked upon the invention as a mere toy. The first to develop a distal light with a glowing platinum wire with water cooling was the dentist Julius Bruck,<sup>1</sup> but his strategy did not offer any possibilities for looking deeper inside the body and there was a risk of thermal injury involved.

Probably the first documented inspection into the “live” stomach of a human was reported by Dr William Beaumont in 1853. He saw a patient with an abdominal gunshot wound that subsequently developed into a 5 cm wide gastro-cutaneous fistula, which facilitated inspection of the gastric mucosa and the study of gastric physiology.<sup>3</sup> <sup>4</sup> There were not many patients with such fistulas so, in 1868, Dr Adolf Kussmaul, inspired by a sword swallower, used the Désormeaux rigid endoscope to look down into the oesophagus and the stomach, but the light was not good enough. He described the situation by saying “we looked in vain into the darkness”.<sup>5</sup>

Nitze, a general practitioner mainly interested in the urinary bladder, worked with instrument makers and opticians to develop the first cystoscope in 1877. He used a platinum wire protected by glass at the distal end of the scope and, after Edison’s invention of the filament globe in 1879, they managed to fit a miniaturised version of this to fit at the end of the cystoscope.<sup>1</sup> The next step was taken by Professor Johann von Mikulicz-Radecki in Kraków 1881. He constructed and tested a modified Nitze cystoscope, which was 650 mm long, had a diameter of 13 mm, a 130° angled tip fitted with a globe for illumination and an airway channel for insufflation, and this was used to look into the oesophagus and stomach.<sup>1,6</sup> This method of gastric inspection must have been very unpleasant for the patient, however. It was not until 1932 that the



German Dr Rudolf Schindler together with an instrument-maker and technician, Georg Wolf, improved gastroscopy sufficiently to make it less troublesome to patients and physicians. They constructed a semi-flexible, side-viewing gastroscope equipped with 48 lenses and electric light at its tip.<sup>7</sup> So far it was only possible to have a look at the mucosal surface, with no possibility to intervene other than perhaps to push down things that had got stuck in the oesophagus. To be able to do more there was a need for additional manoeuvrability, better optics and light, and separate working channels for interventional instruments.

In 1956, Dr Basil Hirschowitz, a South African gastroenterologist, developed the fully flexible endoscope with glass fibre optics, and this development could be labelled the beginning of modern endoscopy.<sup>8,9</sup> Later, working channels used for interventional endoscopic instruments were added.<sup>10</sup> The videoscope, developed in 1984, made documentation easier and resolution was improved with the introduction of a Charge-Coupled Device (CCD) or electronic light sensor at the endoscopic tip.<sup>11</sup> These technical developments have made video documentation and more advanced interventions of the gastrointestinal tract possible.

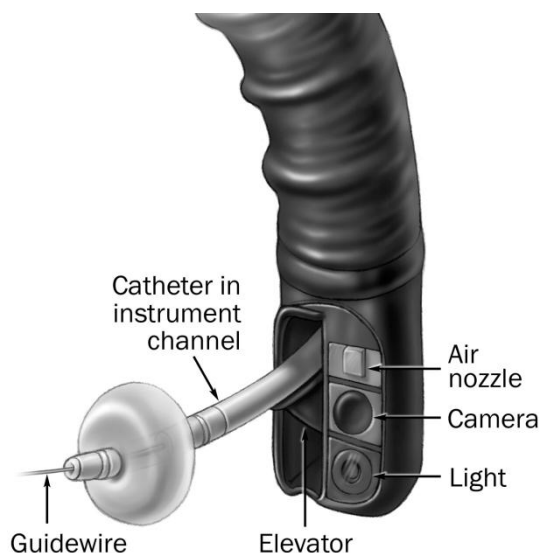
There are now a number of therapeutic possibilities, e.g. treatment of oesophageal varices, dilatation of achalasia, stenting of gastrointestinal strictures and ruptures, stopping ulcer bleeding, excision of polyps or other mucosal lesions, drainage of peri-duodenal or peri-gastric abscesses, percutaneous endoscopic gastrostomy (PEG), and interventions in the pancreatic and biliary ducts with the help of ERCP. At the beginning of the 21st century, an interesting novel technique began to develop: natural orifice transluminal endoscopic surgery (NOTES), which is supposed to allow surgery inside the abdomen or thorax by entering these cavities with flexible endoscopes through the walls of the oesophagus, stomach, colon, urinary bladder or the vagina. However, many problems remain to be solved with this technique before possibly introducing it as an alternative to laparoscopic and thoracoscopic surgery. The problem with all these more advanced endoscopic procedures is that their introduction is followed by an increased occurrence of complications that could sometimes be devastating.<sup>12-15</sup> Knowledge of these complications, how to deal with them and how they are prevented, has improved, but there is still much to be learned.

### ***Modern endoscopes***

Fully flexible video *gastrosopes* used for interventions in the adult oesophagus, stomach and duodenum, usually have a diameter of about 8-13 mm, a 0° frontal viewing CCD, one or more working channels of varying dimensions, a flushing and airflow channel, suction capabilities, and light, inside a metal coil of wire which is wrapped in a smooth rubberlike material (see the figure of a gastroscope on the front page). The endoscope could be made stiffer by rotating the metal coil in the endoscope

casings, which is used in some situations when managing sharp bends as in the first part of the duodenum. This is the current scope of choice when conducting PEG insertion and oesophageal stenting. Movements at the endoscopic tip are operated manually with two manually guided turning wheels connected to wires which bend the tip of the scope in four different directions. The movements can be augmented by twisting the instrument, allowing movements in nearly all directions, only limited by the luminal diameter of the bowel. The video image is viewed on a high resolution screen in front of the endoscopist. Programmable buttons on the scope could be used for a variety of functions, e.g. image freezing and saving.

A video *duodenoscope* is used for diagnostic and interventional procedures in the duodenum, and the bile or the pancreatic ducts. The scope, used for adults, usually has a diameter of 11-13 mm, and 90° side viewing, making manoeuvring more difficult to learn as compared to gastroscopy. Moreover, a movable elevator near the end of the endoscope is used to angulate different instruments put down through the working channel, facilitating the intubation of the bile or the pancreatic duct, see Figure 1.



**Figure 1.** The tip of a duodenoscope with a guide wire inserted through a balloon catheter which is angled by the elevator.

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It is also possible to put down a thin manoeuvrable endoscope through the working channel of the duodenoscope, to inspect the bile and pancreatic ducts for visualisation of pathologic changes, directed tissue sampling, and pulverizing big stones with laser probes or electro-hydraulic stone crushers (lithotripter). The duodenoscope is also equipped with water flushing, air or carbon dioxide (CO<sub>2</sub>, which disappears more quickly than air) flow, and suction and light capabilities. Movements at the distal end of the endoscope are otherwise regulated as in the gastroscope above.

### ***Self-expandable oesophageal metallic stents***

The word stent probably originates from the English dentist Charles Stent (1807-1885) who developed a compound which he used to make accurate impressions of the oral

cavity to make better dentures. During the first world war a Dutch plastic surgeon Dr J.F. Esser used the “Stent compound” to reconstruct war wounds of the face, using the material as a “stent mold” for skin grafts.<sup>16</sup> Later the noun stent became a word for “custom-built steel or hard plastic tubes inserted into strictured vessels or the gastrointestinal tract.

The use of an oesophageal stent was first described in 1845 by Dr. Leroy d'Étoilles using an ivory tube inserted because of an oesophageal stricture.<sup>17</sup> Early methods of stent fixation used threads from the stent knotted to the moustache, or threads taken out through the nostrils and tied around the neck.<sup>17</sup> Stiff plastic tubes were introduced during the 1950s, and one of the first descriptions came in 1983, by Frimberger, of a spiral metallic stent put in place over the scope for palliation in ten patients with inoperable oesophageal cancer.<sup>18</sup> After Domschke et al reported the use of a self-expandable mesh stent in 1990,<sup>19</sup> the development of self-expandable metallic stents (SEMS) in the oesophagus gained momentum. The dominating symptom in oesophageal cancer is dysphagia, and stent insertion has become the most frequent palliative procedure in inoperable patients, due to the technically easy insertion and the rapid effect of decreasing dysphagia.<sup>20</sup> SEMS can sometimes also be used for benign oesophageal strictures,<sup>21</sup> spontaneous or post-surgery oesophageal ruptures,<sup>22</sup> bleeding oesophageal varices,<sup>23</sup> fistulae to the airway.<sup>24</sup> The effect of endoscopic dilations on oesophageal cancer strictures is often of a very short duration, and as incurable patients with oesophageal cancer have a short life expectancy the primary use of SEMS is often the procedure of choice.<sup>25</sup> If the cancer patient is expected to live longer than 3 months, however, brachytherapy (internal radiation therapy) can be contemplated as an alternative to stents because of the reported better HRQL beyond 3 months compared to stents.<sup>26</sup>

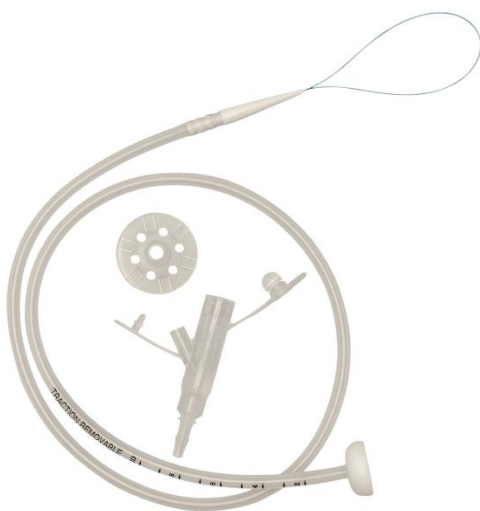
Today, there are in principle three different open metallic stent designs available. The stain-less steel zig-zag wire stent, the stain-less steel mesh stent, and the nitinol (nickel-titanium alloy) mesh stent. No randomised study has yet shown any significant differences of effect in stent design on relief of dysphagia or complications.<sup>27, 28</sup> As uncoated stents have a disturbing incidence of tumour ingrowth of 20-30%, a plastic coating of polyurethane or silicone has been added to reduce this effect.<sup>29</sup> A higher risk of stent migration might follow the use of coated stents compared to uncoated stents, especially in the region of the distal oesophagus and gastric cardia (gastrooesophageal junction). A randomised study of 62 patients with obstructing tumours at the gastrooesophageal junction showed no significant difference in migration rate between covered and uncovered Ultraflex<sup>®</sup> stents, however, while others have found a slightly elevated risk of migration when covered stents extend beyond the oesophagogastric junction.<sup>30, 31</sup> Covered stents of larger diameter seem to have a decreased risk of migration and also better patency, but maybe to the price of more complications, as compared to stents of smaller diameter.<sup>27, 32</sup>

Stents that pass the oesophagogastric junction, thus impairing the reflux-preventing mechanism, may possibly increase the risk of reflux-induced esophagitis and aspiration which could cause pneumonitis or pneumonia.<sup>29</sup> This could be an increasingly common problem for several reasons: the incidence of adenocarcinoma of the oesophagus is increasing fast and most of these tumours are located near the gastrooesophageal junction,<sup>33</sup> the majority of patients are inoperable, and nearly all develop progressive dysphagia.<sup>34</sup> Therefore, stents with an antireflux mechanism have been designed with the aim of counteracting reflux (see Figure 4, page 34). However, they have, not so far proved their efficacy in preventing these problems and are more complicated to insert than conventional SEMs.<sup>35-38</sup> Many endoscopists advocate the use of proton pump inhibitors (PPI) in patients receiving distal conventional stents to reduce the amount of refluxing acid from the stomach, although the effect on symptoms seems doubtful.<sup>39</sup>

Plastic stents (SEPS) with total silicone covering (Polyflex<sup>®</sup> Boston Scientific, Helsingborg, Sweden) or biodegradable stents (BD ELLA<sup>®</sup>, Ella-CS, Hradec Králové, Czech Republic) have been introduced mainly for the treatment of benign strictures, where multiple dilation has been unsuccessful, but SEPS are complicated to assemble and insert, and have a high migration rate.<sup>40</sup>

### **PEG catheters**

Modern gastrostomy catheters are usually made of silicone (see Figure 2), a soft pliable material, or polyurethane which is stiffer but can have thinner tube walls and thus, a slimmer design. The polyurethane catheters also seem to have better patency than silicone-based catheters.<sup>41</sup>



**Figure 2.** A Mic-PEG<sup>®</sup>. The silicone PEG catheter with its inner flange and the not yet fitted outer stopper for maintaining the position of the PEG. The stopper is slipped on the catheter after which the white plastic cone with the loop thread is cut away. Then the adapter is positioned on the catheter end.

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Latex catheters should be avoided because of short term durability and allergic reactions.<sup>42</sup> The PEG catheter flange in the stomach stops the catheter from slipping

out. It can be hard or soft, which is important to know as this determines which method to use when removing the PEG. If the stopper is soft it is easy to extract, however, if it consists of hard plastic, it perhaps should be taken out through the mouth by gastroscopy after cutting the catheter close to the skin level (“cut and push” technique), especially if there is a known history of bowel disease. Otherwise, if just dropped into the gastrointestinal tract, it has been reported to cause obstruction.<sup>43</sup> This flange can also be a fixed or a refillable balloon, usually easy to extract after deflation when catheter exchange is required, with no need for gastroscopy. Commonly used silicone PEGs in adult patients in Sweden have a diameter of 20 Fr (or Charrière). Smaller diameter catheters seem prone to a higher dysfunction frequency than large-bore catheters.

### ***Health Related Quality of Life (HRQL)***

When evaluating outcomes of different treatment options in non-curable cancer patients, HRQL plays the key role. When assessing HRQL it is important to show how it is defined, since there are many different definitions and variations in the literature with the WHO’s declaration of health from 1948 seeming to be one of the broadest: “a state of complete physical, mental and social wellbeing, and not merely the absence of disease”. Quality of life means different things to different people depending on the area of usage and is often supposed to be intuitively understood.<sup>44</sup> From a clinical trial perspective the WHO definition seems too broad because the main interest is usually “aspects affected by disease and treatment for disease”.<sup>44</sup> The definition of quality of life used in paper I has more limited scope, and is stated as being: multifactorial and including functional status, psychological and social well-being, the self-perception of general health as well as disease and treatment specific symptoms.<sup>45</sup> The instruments chosen, to assess HRQL in paper I, were developed by the European Organisation of Research and Treatment of Cancer, EORTC, founded in 1962, as an international non-profit organisation. The general cancer core questionnaire, QLQ-C30 version 3, comprises 30 questions, containing scales and items addressing five functional dimensions (physical, daily activity or role, cognitive, emotional and social function) of HRQL and three symptom scales (fatigue, pain and nausea/vomiting) as well as five single items (shortness of breath, loss of appetite, sleeping difficulties, constipation and diarrhoea) that commonly occur in patients with cancer. Moreover, the QLQ-C30 includes one question assessing the financial impact of malignant disease, and one global HRQL scale. To improve the sensitivity and specificity of disease-specific issues,<sup>46</sup> a module, QLQ-OES18, with 18 questions addressing symptoms common in patients with oesophageal cancer can be added. This questionnaire includes four symptom scales (dysphagia, eating difficulties, reflux and oesophageal pain) and six single items (trouble swallowing saliva, choking, dry mouth, taste problems, cough, and speech difficulties). These questionnaires are self-administered and easy to fill in

(it takes about 10-15 minutes) and can be completed at home without the surrounding influence of health or study personnel. The QLQ-C30 together with the QLQ-OES18 module used in paper I are well validated (measures what they are intended to measure) and show acceptable reliability (degree of random variability and reproducible results) and are recommended for use when evaluating different treatment options in oesophageal cancer patients regarding HRQL.<sup>47</sup> Since the questionnaires have been translated into several languages and have been used all over Europe for more than two decades, the results could be compared with other trials assessing HRQL in palliative oesophageal cancer patients.

The raw scores of the scales and items are usually linearly transformed, according to the recommendations of the EORTC manual, to a scale of 0-100 points.<sup>48</sup> In large studies there could be a statistically significant difference between measures of only a couple of points, which is meaningless from a clinical point of view, since such differences are not noted by the patient. Therefore, the term “clinically relevant difference” has been introduced. This represents a difference that the patient can realise as a moderate change at least and it is commonly set at  $\geq 10$  points.<sup>46, 49</sup> A common approach is to perform formal statistical tests only where clinically relevant differences are identified to avoid multiple testing and chance findings.

# Endoscopic interventions addressed in this thesis

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Therapeutic endoscopy is usually performed after 6 hours of fasting. Local anaesthesia (1% lidocain) is sprayed on the throat mucosa after which intravenous sedation with midazolam (a benzodiazepine) or sometimes full anaesthesia with intubation and regulated respiration is used before the endoscope is introduced. Intravenous opiates are used for analgesia as required. At some centers deep sedation by using bolus injections of propofol, normally used for induction of general anaesthesia, is preferred, but under the responsibility of anaesthesiologists.

## ***Oesophageal stenting***

The stent procedure is typically done with a 0° front-viewing gastroscope often with the help of fluoroscopy to facilitate exact positioning of the stent. If the malignant stricture is too tight, dilation may enable the stricture to pass but could introduce a risk of tumour rupture. A guide wire is put down through the working channel of the endoscope and the distal end is left in place beyond the stricture, preferably down into the duodenum, to reduce the risk of gastric perforation by the stent delivery system during insertion. The endoscope is retracted leaving the guide wire in place. The stent, compressed in its delivery coating, is introduced over the guide wire usually under fluoroscopic control. After deployment, the expansion of the stent and its position is often checked by looking down again with the endoscope. It usually takes 48 or 72 hours for full stent expansion and the dysphagia almost always improves.<sup>29</sup>

## ***ERCP***

ERCP was first mentioned in 1965 by Rabinov in Boston<sup>50</sup> in a preliminary report of his experience with 8 patients, and a few years later in 1970 reports came from Japan of the continuous experience by Oi and Tagaki.<sup>51, 52</sup> The procedure is now mainly done because of stones lodged in the bile ducts or due to benign or malignant strictures both in the bile or pancreatic duct but is also effective in the treatment of ductal leaks of different origin. A 90° side-viewing duodenoscope is brought down to the duodenum where the papilla of Vater is visualised with this structure defining the end of the bile and main pancreatic duct. A catheter with a guide wire is inserted through the papilla and the sphincter of Oddi into either the bile or pancreatic duct which can sometimes be very difficult to achieve. If the guide wire cannot pass the papilla, a pre-cut papillotomy with a needle sphincterotome could be tried in order to facilitate insertion of the guide wire. The ducts are visualised either by injecting contrast medium which could reveal fluoroscopic images of any existing pathology or by direct visualisation

by a “scope through the scope” previously called “mother-and-baby” scope. After cutting the papillary circular muscle of the sphincter of Oddi (sphincterotomy/papillotomy) using electric current and/or dilation with a balloon, stones can be evacuated or stents of different designs and materials (plastic or metallic) can be inserted to relieve bile stasis. It is also possible to use tissue forceps or a brush to sample tissue for histologic diagnosis.

### **PEG insertion**

PEG was first described in a paediatric and adult population as a less traumatic procedure than open surgery for the insertion of a feeding catheter through the abdominal wall into the stomach.<sup>53, 54</sup> The main reason for using a PEG is for meeting nutritional needs when the oral route proves insufficient, but sometimes the purpose is drainage of the stomach and the gastrointestinal tract e.g. in patients with chronic bowel obstruction due to abdominal spread of various malignancies.

There are three main types of PEG procedures. The “pull” type described by Gauderer and Ponsky, technique described below, is the easiest to perform and the most commonly used.<sup>53</sup> The second type is the Sacks-Vine “push” gastrostomy where the dilator-tipped catheter is pushed down through the oesophagus over a guide wire and out through the abdominal wall.<sup>55</sup> The third type is the introducer PEG (Russell gastrostomy), sometimes wrongly referred to as the “push PEG”, where the stomach usually is attached to the abdominal wall by percutaneous sutures or suture anchors and the PEG catheter is introduced directly through the abdominal wall into the gastric lumen, guided by endoscopy, fluoroscopy, or ultrasound.<sup>56</sup> The introducer PEG has a lower reported infection rate but is technically more demanding to insert and more expensive than the pull PEG.<sup>57</sup> This procedure, as well as the other described PEG-procedures described above, could be laparoscopy assisted to reduce the risk of damaging intraabdominal organs.<sup>58, 59</sup>

When using “stay” or anchor sutures it is possible to directly insert a button-type gastrostomy (skin level design) at the first intervention which often is the norm in children needing a gastrostomy. The button gastrostomy has a refillable balloon or an expandable mushroom stopper on the inside and usually a one-way valve to stop back

flow when the button is opened for usage. See Figure 3.



**Figure 3.** A Mic-Key® “button PEG” made of silicone.

Reproduced by kind permission of MEDA AB, Solna, Stockholm, Sweden.



The PEG catheter is usually changed when it no longer functions, but due to foul smell and dark staining caused by fungal biofilm overgrowth, which also seems to be involved in making the silicone catheter brittle,<sup>41, 60</sup> the catheter is often changed every 6 to 12 months. In paper III and IV of the present thesis, a standard silicon wire-reinforced 20 Charrière (=20 Fr) Bard® FasTrac™ (Bard Norden AB, Helsingborg, Sweden) pull PEG catheter was used in all cases.

*Pull PEG technique:* This intervention is often conducted by an endoscopist involved in the gastroscopy and a surgeon performing the PEG insertion, but could be done by the endoscopist alone performing both procedures with the assistance of an endoscopy assistant. Antibiotic prophylaxis is recommended, usually as an intra-venous second generation cephalosporin (cefuroxime) given before the procedure. Insufflation of air brings the stomach wall closer to the inside of the abdominal wall and pushes the transverse colon downwards and off the stomach. Thereafter, the endoscopic light is usually seen through the abdominal wall and by pointing a finger against the abdominal wall and visualising the indentation inside the stomach, the best point for PEG-placement can be deduced. If these positioning steps are not deemed satisfactory, a safe passage to the stomach through the abdominal wall cannot be guaranteed, and the procedure should be cancelled. In such cases it is safer to perform the gastrostomy using laparoscopic assistance<sup>58</sup> or by open surgery, a modified version of the Witzel gastrostomy first performed in 1891.<sup>4</sup> If, however, the positioning steps are acceptable the pull PEG procedure continues by anaesthetising the planned introduction channel in the abdominal wall with local anaesthesia (1% lidocain) and the thin 5 cm long injection needle protruding into the stomach is visualised through the scope. A small skin incision (about 8 mm) is made adjacent to the injection needle, where also a longer, larger bore needle is inserted through which a thread is entered. This thread is captured inside the stomach by the endoscopist using a loop instrument put down through the working channel of the endoscope and the thread is thereafter pulled up together with the endoscope. The PEG-catheter (see Figure 2, page 19) is attached to the oral end of the thread and by pulling on the abdominal end, the catheter is gently pulled down through the oesophagus and out through the abdominal wall. The catheter has an inner flange and on the outside a special adapter preventing the catheter from moving inwards. The PEG-procedure usually takes 10-15 minutes to complete.<sup>57</sup> The catheter can be used for enteral feeding after 2 hours. The success rate of PEG insertion is usually  $\geq 90\%$ .<sup>61</sup>

## General endoscopic complications

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All endoscopic procedures in the upper gastrointestinal tract carry the risk of the most feared and potentially lethal complication, i.e. perforation.<sup>62</sup> When the scope is introduced into the oesophagus the first part is carried out more or less blindly and if an unsuspected anatomical abnormality or a pathological condition, e.g. a diverticulum, cancer or severe inflammation, is undiagnosed before endoscopy, a perforation might easily occur. Fortunately these perforations are very rare when diagnostic procedures are done with flexible endoscopes (0.1%), but the risk is higher when using rigid endoscopes (1.0%). This risk increases when interventional procedures in the oesophagus are performed, such as dilatation of strictures and foreign body removal.<sup>63, 64</sup>

To reduce the risk of reflux-induced aspiration during and immediately after the endoscopy, the gastric contents should preferably be emptied from the start. Cardiac arrhythmias are seldom seen but occur occasionally in patients with known cardiac disease, although lethal arrhythmias, caused by defective electrical equipment, have been reported.<sup>65</sup>

Use of intravenous sedation with midazolam during the procedure and sometimes potent opioid analgesics may introduce a risk of hypoxia when the stimulating effect of the endoscopy ends. Standardised supervision of the patient at the endoscopy department and at the wards is therefore necessary during the first hours after the procedure until the patient is fully awake.

## Procedure-specific complications

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**Oesophageal stenting:** Stenting of the oesophagus in malignant disease has been proven effective for palliating dysphagia,<sup>66</sup> but is not without risk of complications. Procedure-related mortality, mainly due to aspiration (2.3%) or oesophageal rupture (1%), has been reported.<sup>31, 66</sup> After stent deployment, a more or less severe chest pain or foreign body sensation occurs in the majority of cases during the first few days of stent expansion,<sup>31, 67</sup> and this often has to be controlled by strong analgesics, e.g. opioids.<sup>68</sup>

The rapidly increasing incidence of adenocarcinoma of the oesophagus during the last three decades contributes to the fact that a majority of oesophageal cancers are located distally.<sup>29, 69, 70</sup> This means that the stents often have to extend into the stomach, which predisposes gastrooesophageal reflux,<sup>31, 35, 36</sup> with a risk for reflux-induced severe esophagitis and aspiration pneumonia. Stent migration is another problem, especially when stents pass the oesophagogastric junction, where the distal part of the stents is much less anchored by the surrounding tissue.<sup>29, 31</sup> Stenting induces bleeding in 5-6.3% of the cases, often caused by the tumour itself,<sup>31, 68</sup> or in the gastric mucosa if the stent protrudes into the stomach.<sup>29</sup> If the stricture is very tight there is sometimes a need to dilate the tumour with e.g. a Savary-Gilliard® Dilator or a balloon dilator to pass the tumour with the stent delivery system which usually has a diameter of about 5 to 13 mm. Such dilatation introduces a risk of perforation. Stent expansion is rarely followed by perforation, but could sometimes develop into an airway fistula.<sup>31</sup> Due to the anatomic configuration of the oesophagus in the mediastinum, tumour growth near the trachea or the left main bronchus could give rise to airway compression and acute dyspnoea caused by stent expansion. If this is anticipated, e.g. on pre-stent computer tomography, the airway should be stented first.

**ERCP:** Procedure-related mortality after ERCP is  $\leq 1\%$ .<sup>71</sup> Free duodenal perforation during ERCP is rare (0-2%) but once they occur mortality rate can be high (16-18%).<sup>72</sup> A retroperitoneal perforation, most often due to the sfincterotomy, is less dangerous and could heal with conservative treatment, but if peritonitis develops, surgical treatment is necessary.<sup>73, 74</sup> The most common complication after ERCP is acute pancreatitis which occurs in about 2-7% of the cases.<sup>12, 71, 75-77</sup> The majority of these cases subside after 1-2 days, but the pancreatitis could develop into a severe form with septicaemia, systemic inflammatory response syndrome (SIRS) and perhaps multi-organ dysfunction syndrome (MODS) needing intensive care treatment. Within such severe cases the mortality rate is high (up to 67%) and the morbidity is serious.<sup>78</sup> Bleeding after papillotomy or dilatation is seen in  $<1\%$ ,<sup>12, 71</sup> but can be dangerous because of the initial absence of symptoms in the sedated patient. Ascending infections

into the biliary ducts after ERCP are reported in up to 5% ,<sup>71</sup> and antibiotic prophylaxis is therefore often used especially if there is pre-ERCP bile stasis.

**PEG:** Procedure-related mortality is low (0-2%)<sup>54, 79-81</sup> but, as the typical PEG-patient often has a heavy burden of co-morbidity apart from the reason for having PEG, a 30-day mortality of 8-28%,<sup>82-85</sup> and a 6-month mortality of 44%,<sup>86</sup> have been reported among in-hospital patients. Suggested risk factors for early mortality after PEG include hypoalbuminemia, high CRP, diabetes, chronic obstructive pulmonary disease, advanced cancer stage, severe neurological disease such as stroke, cachexia/low BMI, age, mechanical ventilation and dialysis.<sup>82, 86-88</sup> PEG is a technically an easy procedure to perform, but it is followed by a substantial risk of a number of side effects, where peristomal infection is seen in up to 32% if no antibiotic prophylaxis is used.<sup>14, 89-92</sup> These infections could cause pain, prolonged hospitalisation and increased costs,<sup>93</sup> but they also have the potential of developing into a more severe variant of necrotising fasciitis with high mortality.<sup>94</sup> Both patient-related factors (e.g. obesity, diabetes, malnourishment, smoking and cortisone medication) and surgery-related factors (e.g. inadequate aseptic technique, too short cutaneous incisions, the catheter bolster placed too tightly against the skin or low PEG-procedure surgeon volume) may contribute to the development of PEG-related infections.<sup>81, 89, 95-99</sup> Aspiration pneumonia due to reflux after initiation of feeding through the PEG is a well-known risk with a reported occurrence of 23%.<sup>100</sup> Less common problems are bleeding (<4%) from the stomal tract or ulcerations due to a mechanical effect of the PEG-catheter on the gastric mucosa, which rarely perhaps could lead to an aortogastric fistula, but the most common cause of bleeding seems to be reflux-induced esophagitis.<sup>101-105</sup> Other more or less infrequent complications are buried bumper syndrome,<sup>106</sup> peritonitis due to leakage of gastric contents alongside the PEG catheter (2.3%),<sup>90, 107, 108</sup> accidental removal of the PEG catheter,<sup>109</sup> colo-gastro-cutaneous fistula,<sup>110</sup> gastric volvulus,<sup>111</sup> subcutaneous emphysema,<sup>112</sup> and intra- or transhepatic PEG placement.<sup>113</sup> A rare but important problem is the risk of tumour seeding to the catheter tract in the abdominal wall in patients with throat cancer (up to 1% of cases).<sup>114, 115</sup> This problem is very rarely described in oesophageal cancer, perhaps because these patients have a very short survival rate due to advanced disease.<sup>116</sup> Leakage around the catheter after PEG is common (up to 78%) and is reported as “problematic” in up to 39% of patients with long-term PEG.<sup>117</sup> Gastric outlet obstruction caused by dislocation of the catheter and internal bumper into the duodenum where an occlusive effect may occur,<sup>118</sup> but it seems to be less common after PEG than after the Witzel gastrostomy, which might be explained by a better catheter fixation device included in modern PEG-sets, and perhaps by nowadays better informed patients, relatives or patient carers. Post-PEG pneumoperitoneum is found in up to 30% of patients, but is usually without clinical significance.<sup>106</sup> Long-term PEG users are also constantly reminded about their disease by the catheter, and this could negatively affect their HRQL.<sup>117</sup>

# Aspects of complications and risk factors addressed in this thesis

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## ***I. The impact of anti-reflux stenting on HRQL in patients with incurable distal oesophageal cancer:***

The main symptom in oesophageal cancer is progressive dysphagia, which affects nearly all patients. Since a majority of oesophageal cancers are situated distally, and in more than 50% of cases, are inoperable on diagnosis,<sup>119</sup> palliative stenting across the gastrooesophageal junction is common in oesophageal cancer patients. This compromises the anti-reflux function of the lower oesophageal sphincter,<sup>36</sup> and introduces a risk of gastric reflux induced esophagitis and aspiration pneumonia with possibly severe consequences in the daily lives of the patients. Therefore, stents with an anti-reflux valve have been introduced.<sup>120-122</sup> A few randomised studies comparing antireflux stents with conventional stents have shown conflicting results regarding their efficacy in counteracting reflux, but they seem to have equally good effect against dysphagia.<sup>35-38</sup> When treating incurable oesophageal cancer patients who are known to have a short survival and where different palliative procedures do not materially prolong survival, the main purpose should be to improve HRQL during the remainder of the patient's life. Thus, the results of different palliative strategies on HRQL found in randomised trials should be used in decision making.<sup>123, 124</sup> In paper I, we randomised patients with inoperable distal oesophageal cancer or cardia cancer to anti-reflux or conventional stents and assessed the effect on baseline HRQL at follow-up using self-administered questionnaires developed by EORTC.<sup>46, 47</sup>

## ***II. Prophylaxis against post-ERCP pancreatitis:***

A frequently used definition of post-ERCP pancreatitis is 1/ abdominal pain >24 hours after ERCP and 2/ pancreatic enzyme amylase or lipase levels >3 times the upper normal limit. Post-ERCP elevation of amylase in serum occurs in 25-40% of cases,<sup>75, 76, 125-127</sup> and post-ERCP pancreatitis occurs in 2-7%.<sup>12, 71, 75-77, 125</sup> The wide range between reported frequencies could be due to different patient populations, indications, procedures, endoscopic skill, and different definitions of outcome.<sup>127</sup> Risk factors for developing pancreatitis after ERCP include young age, female sex, previous pancreatitis, dysfunction of the sphincter of Oddi, and procedure-related factors, such as difficult cannulation of the bile and pancreatic ducts, experience of the endoscopist, pancreatic duct manipulation or injection of contrast media, sphincterotomy, and use

of SEMS instead of plastic stents for bile decompression.<sup>12, 71, 77, 127, 128</sup> Much effort has been devoted to identifying preventive measures against post-ERCP pancreatitis. Several clinical trials addressing many different pharmacological preparations have been conducted, but so far there is no established pharmacological prophylaxis even though some drugs have shown some promising effects.<sup>129-131</sup> Non-pharmacological means of prevention could perhaps be achieved by temporary stenting of the pancreatic duct after ERCP.<sup>132, 133</sup>

There is, however, support for the new hypothesis that angiotensin II type 1 receptor blockers (ARB) could prevent the development of pancreatitis and/or pancreatic hyperenzymemia after ERCP. Angiotensin II is the active product in the biochemically complex renin-angiotensin system which is said to regulate blood volume, electrolyte homeostasis, and vascular tone, but also to have trophic and pro-inflammatory characteristics.<sup>134</sup> Another finding is that there is not only a systemic component, but also a local tissue component which seems to modulate cell growth, cell differentiation, and intercellular communication.<sup>134</sup> Later research has found that the renin-angiotensin system comprises both a pressor and a depressor function in vascular tone regulation and cellular signalling.<sup>134</sup> Moreover, acute pancreatitis activates a local pancreatic renin-angiotensin system, mainly localised in the vascular endothelium and the pancreatic duct epithelium, as well as the systemic renin-angiotensin system.<sup>135, 136</sup> Experimental research has shown that the angiotensin II type 1 receptor and angiotensinogen are highly expressed in inflamed pancreatic tissue, leading to local vasoconstriction with hypoxia, acidosis and inflammation.<sup>137</sup> Administration of angiotensin II increases the secretion of pancreatic enzymes, and this increased secretion can in turn be blocked by the commonly used antihypertensive drug, ARB losartan (Cozaar<sup>®</sup>).<sup>137, 138</sup> Moreover, losartan can prevent experimentally induced acute pancreatitis in rats.<sup>138-140</sup> Furthermore, a recent case-control study from our group indicated a decreased risk of acute pancreatitis among patients treated with ARB.<sup>141</sup>

Paper II describes a clinical trial testing whether losartan prevents pancreatic hyperenzymemia after ERCP. As hyperenzymemia is linked to acute pancreatitis and if this increase in enzyme levels could be reduced by losartan a larger study would be conducted to see if losartan also could reduce the frequency of post ERCP pancreatitis.

### ***III. Antibiotic prophylaxis during PEG:***

Several randomised trials and meta-analyses have shown that antibiotic prophylaxis reduces the absolute risk of peristomal infection by between 14-17.5%, corresponding to 6 patients having to be treated in order to avoid one infection (number needed to treat = 6).<sup>142-145</sup> Other means of reducing the risk of peristomal infection are to use the introducer PEG technique or to pull down the PEG catheter inside a plastic covering.

These techniques bypass the bacteria in the mouth, throat, and oesophagus.<sup>57, 146, 147</sup> They are, however, more complicated to perform than the simple pull PEG technique and involve a substantially higher cost. Therefore, the pull PEG technique is still the most frequently used.

A single dose of a second generation cephalosporin (cefuroxime) is often used as antibiotic prophylaxis,<sup>148</sup> since cefuroxime has a documented good effect on the bacteria commonly found in the upper gastrointestinal tract.<sup>149, 150</sup> Normally, 1.5 grams of cefuroxime is given intravenously at the ward about 1 hour before the planned intervention, but sometimes this is forgotten or postponed which could delay the PEG procedure. Cefuroxime is also comparatively expensive, has a short biological half-life (1.5 hours), is given unnecessarily whenever the PEG procedure is unsuccessful (5-10%),<sup>61, 79</sup> and can contribute to pseudomembranous enterocolitis induced by *Clostridium difficile* bacteria after only a single dose.<sup>151, 152</sup>

We considered whether the enteral solution of sulphamethoxazole/trimethoprim, given in the PEG catheter directly after the catheter insertion, could be at least as effective as the standard treatment with cefuroxime. If this was the case there are several advantages to be gained, namely: faster, easier administration, longer biological effect (biological half-life 10 and 11 hours), avoidance of unnecessary treatment when the PEG insertion fails, reduced cost and, probably, better bacterial ecology.

In paper III we tested whether sulphamethoxazole/trimethoprim was at least as good as standard antibiotic prophylaxis.

#### ***IV. Risk factors for mortality and peristomal infections after PEG:***

Patients considered for PEG have in general an increased risk of complications, due to the malnutrition requiring PEG placement and the disease causing the malnutrition, as well as a high occurrence of co-morbidities associated with these patients, such as diabetes, cardiovascular disease and cancer. Knowledge of risk factors that are linked with a particularly increased risk of poor outcomes after PEG insertion is essential when selecting and advising patients for PEG placement.

There are alternatives to PEG, such as nasogastric and intravenous catheters for nutrition, which might be preferable if certain high-risk patients are identified.

Previous research has indicated that advanced age, low serum albumin levels, high CRP levels, low BMI, and co-morbidities might be risk factors for complications after PEG.<sup>82, 86-88, 153-156</sup> Low albumin and raised CRP seem to be strong risk factors for early mortality and post-operative infection in cancer patients.<sup>157-161</sup> High CRP is associated with inflammatory states, which in turn could contribute to cachexia.<sup>162</sup>

Thus, low albumin and high CRP are both linked with malnutrition. These potential risk factors for PEG complications have, however, not been established and are therefore not considered in the clinical decision-making.<sup>88</sup>

In paper IV we therefore evaluated potential risk factors for early mortality and peristomal infection after PEG.



## Aims of the studies

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The overall aim of this thesis was to gain knowledge of how to modify endoscopic interventions so that fewer complications and morbidities occur.

### *Specific aims:*

- To evaluate whether the anti-reflux stent Esophageal Z-stent<sup>®</sup> with a Dua Anti-reflux Valve improves the HRQL in patients with incurable distal oesophageal or cardia cancer, as compared to conventional stenting. (Paper I)
- To assess whether the antihypertensive angiotensin II receptor blocker losartan prevents pancreatic hyperenzymemia after ERCP. (Paper II)
- To estimate whether enteral sulphamethoxazole/trimethoprim antibiotic prophylaxis given in the PEG catheter after the procedure can replace standard treatment in the prevention of peristomal infections. (Paper III)
- To identify risk factors for early mortality and peristomal infection after PEG. (Paper IV)

# Patients and methods

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## Paper I

### *Design*

A randomised, single-blind, clinical, multicentre trial, comparing an anti-reflux oesophageal stent (ARS) with conventional stents (CS) in relation to measures of HRQL, was conducted at 11 centers in Sweden during the period 1 September 2003 to 31 December 2007 with follow-up until 31 March 2008. The randomisation was conducted at The Regional Oncological Center at Karolinska University Hospital, Solna. The patients were unaware of the type of stent inserted. We hypothesised that an ARS, compared to a CS in the distal oesophagus, would be followed by a better HRQL as measured by the validated HRQL questionnaires EORTC QLQ-C30 and the QLQ-OES-18.

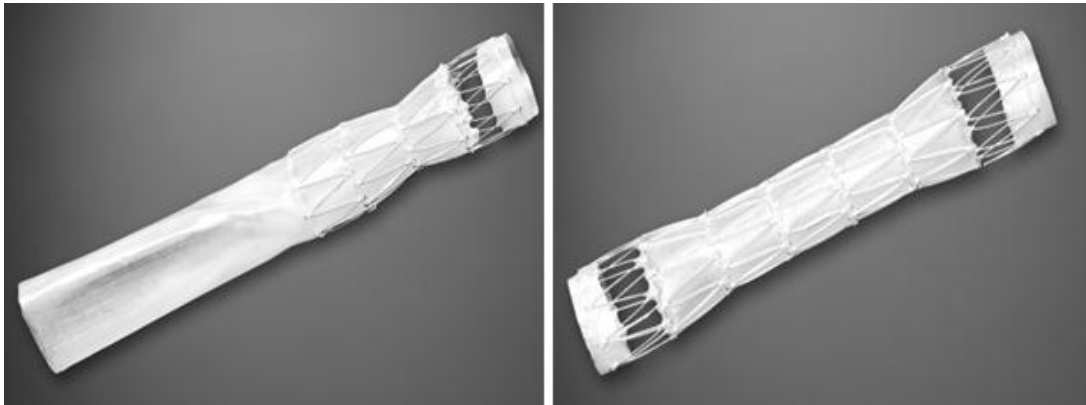
### *Patients*

Patients considered for randomisation were those with histologically verified inoperable cancer of the distal oesophagus or cardia with dysphagia (could at best eat semisolid food) with a clinical need for a stent that would be assumed to pass through the cardia. Moreover, the anticipated survival should be at least one month, and the patients should have no other malignant disease.

### *Stent types*

The test stent was a covered Oesophageal Z-stent<sup>®</sup> with a Dua Anti-reflux Valve (Wilson-Cook Medical, Winston Salem, NC, USA) which is a self-expanding, covered, stainless-steel mesh stent with an 80 mm long antireflux plastic sleeve attached to the distal part of the stent (Figure 4). The body diameter was 18 mm and there was a partly uncoated flared upper part with a diameter of 25 mm. These stents were available in lengths of 8 to 14 cm. The CSs used were of three types (chosen according to local hospital tradition): a partly covered stain-less steel Z-stent<sup>®</sup> without anti-reflux sleeve (Wilson Cook Medical Inc, Winston Salem, NC, USA) with same diameters as above (see Figure 4), an UltraFlex<sup>®</sup> single-strand nitinol (nickel titanium alloy) wire stent with a body diameter of 18 mm and flared uncovered ends of 23 mm (Boston Scientific, Natick, MA, USA), or a Wallstent<sup>®</sup> with partial silicone covering (Boston Scientific) and 18 mm shaft diameter and flared ends of 23 mm. The reasons, for the decision to accept different CSs in the trial were 1/ to get maximum inclusion,

since several centres preferred to use “their” type of CS for these patients, and 2/ studies have not shown any major differences between different covered CSs.<sup>27, 28</sup>



**Figure 4.** Oesophageal Z-Stent with Dua Anti-Reflux valve, a 80 mm long plastic collapsible sleeve connected to the distal part of the stent (left, ARS) and Oesophageal Z-Stent, (right, CS), Cook® Medical Inc.

### *Follow-up*

The patients were scheduled for revisits at one and three months after stent insertion and thereafter every third month until death or end of study period. At baseline and at these revisits the HRQL scores were assessed with the validated standardised questionnaires designed for self-administration (EORTC QLQ-C30 and QLQ-OES18), on general and oesophageal cancer specific symptoms and functions, which the patients also had completed at baseline. Adverse events were noted.

### *Statistical methods*

In the sample size calculation we assumed that patients with ARS would have 30% better results regarding HRQL, and with 80% power and alpha 0.05, we calculated a total sample size of 210 patients. All HRQL scales and single-item scores from the questionnaires were converted into a score between 0 and 100, and mean scores and their 95% confidence intervals were calculated in accordance with the EORTC manual.<sup>48</sup> Previous research has shown that a difference of at least 10 in mean scores between follow-ups or between comparison groups may be considered a clinically relevant difference.<sup>49, 163</sup> Clinically relevant mean score differences between baseline and follow up were formally tested for statistical significance with the Mann-Whitney test for continuous variables. The Chi-square test for dichotomous variables was used when comparing clinical details between the treatment groups. Kaplan-Meier estimates

were calculated to assess differences in survival between groups, and tested with the log-rank test.

## **Paper II**

### *Design*

A triple-blind, placebo-controlled randomised trial was performed to evaluate the effect of 50 mg of the angiotensin II receptor blocker losartan on hyperenzymemia after ERCP. Two hospitals participated and included patients during the period from 1 May 2006 to 31 October 2008. The capsule was given 1 hour before ERCP. The patients, endoscopists, and the evaluators were all blinded to the treatment given. The capsules in the different treatment groups were identical in appearance. The code identifying the capsules and patients were kept with the study administrator, who did not participate in the treatment of the patients.

### *Patients*

Patients considered for inclusion were those who were older than 18 and referred for first time ERCP or in whom >1 year had passed since the last ERCP. Patients not considered for inclusion were those with on-going acute or chronic pancreatitis, elevated amylase or lipase levels, users of any ARB or ACE inhibitor medication, kidney insufficiency, bilateral renal arterial stenosis, pregnancy, or severe predefined co-morbidity such as sepsis, disseminated intravascular coagulation, circulatory collapse, severe dehydration, hypovolemia, or liver failure.

### *ERCP procedure*

The procedure is done with the same sedation method as in other endoscopies with the patient in the left lateral position or with general anaesthesia with the patient often in the supine position. When the tip of the duodenoscope has reached the second part of the duodenum the endoscope is made stiffer by rotating it about 90° to the right and at the same time reducing the inserted length of the scope. This shortening of scope length inside the patient makes manoeuvring in the duodenum easier. Otherwise it is done as described on page 22. If needed, glucagon or butylscopolamine could be given to reduce intestinal motility and relax the sphincter muscle of Oddi, which may make it easier to intubate the papilla.

### *Post-ERCP measurements*

Blood tests for analyses of amylase, lipase and glucose were taken at baseline, and at 1, 4 and 24 hours after ERCP. Blood pressure and pulse rate were analysed at baseline,

and at every hour up to 6 hours and 24 hours after ERCP. Any abdominal pain was registered at baseline and 24 hours after ERCP.

### *Statistical methods*

The sample size calculation showed that a total of 76 patients would be needed, on the assumption that hyperenzymemia after ERCP would decrease from 40% to 10%, with 80% power and alpha 0.05. The main analysis strategy was intention-to-treat.

Categorical variables were tested with the Chi squared test or the Fishers exact test, and for continuous data we used an analysis of variance (ANOVA). To adjust for any imbalance of potentially confounding factors occurring in spite of randomisation, we used a multivariable logistic regression model with adjustment for possible confounders such as sex, age, BMI, history of pancreatitis, study centre and duration of procedure, when estimating the relative risk of hyperenzymemia.

## **Paper III**

### *Design*

A single centre, double-blind randomised clinical trial was conducted to compare standard antibiotic prophylaxis (1.5 grams cefuroxime given intravenously before PEG insertion) with a new strategy: 20 ml oral solution sulphamethoxazole/trimethoprim injected via the PEG catheter immediately after the procedure, regarding the frequency of peristomal infection. Patients and the nurses who evaluated any occurrence of complications at follow-up were blinded to the treatment given.

### *Patients*

Patients referred for PEG, at Karolinska University Hospital, without exclusion criteria and who were able to give informed consent, were included during the period from 3 June 2005 to 31 October 2009.

### *Follow-up*

Specially trained nurses evaluated whether the patients had any complications, with special focus on peristomal infection at follow-up within 14 days after PEG insertion. If there was a larger red zone around the catheter than usual, suppuration, and pain on palpation in the immediate vicinity of the PEG catheter, a clinical infection was diagnosed. Haemoglobin, CRP and white blood cell count were analysed and a bacterial culture was taken from the stoma.

## *Statistical methods*

The primary objective was to assess non-inferiority of sulphamethoxazole/trimethoprim compared to cefuroxime with a pre-specified non-inferiority limit of 15%. The difference in the proportion of infection between the groups was estimated and the corresponding two-sided 95% confidence interval (CI) was calculated. Non-inferiority of the test treatment would be achieved if the upper limit of the 95% CI was smaller than the pre-specified non-inferiority margin of 15%. The main strategy was intention-to-treat analysis, which evaluated all randomised patients regardless of whether or not they received a PEG and were followed up. Moreover, a per-protocol analysis was performed as a sensitivity test.

## **Paper IV**

### *Design*

A prospective cohort study was conducted at the Karolinska University Hospital during the period 2005-2009. Follow-up within 14 days was conducted to evaluate the importance of 6 pre-determined potential risk factors, registered at baseline, for short-term mortality and peristomal infections after PEG. The potential risk factors were: 1/ advanced age ( $\geq 65$  years or younger), 2/ low BMI ( $< 18.5 \text{ kg/m}^2$  or higher), 3/ low albumin level ( $< 30 \text{ g/L}$  or higher), 4/ high CRP level ( $\geq 10 \text{ mg/L}$  or lower), 5/ indication for PEG (cancer, stroke, neurological disease, dementia, or other), and 6/ co-morbidity (cancer, cardiovascular disease, neurological disease, diabetes, or other). Primary outcomes were mortality within 30 days and peristomal infection within 14 days after PEG insertion.

### *Patients*

All patients referred for PEG at Karolinska University Hospital in Solna were eligible for inclusion. At baseline, body height and weight were measured and BMI was calculated, blood samples (CRP and albumin) were taken, and the indications for PEG and co-morbidity were registered.

### *Follow-up*

The follow-up procedure was identical to that in paper III above.

### *Statistical methods*

We used a logistic regression model to estimate odds ratio with 95% confidence interval regarding risk of peristomal infection within 14 days after PEG. Since we did not have the exact starting dates for such infections, Cox regression was not possible. A Cox proportional hazards model was used to estimate hazards ratio with 95 %

confidence interval to evaluate the risk of mortality within 30 days after PEG. Adjustments were made for age, sex, albumin, co-morbidity index (0-3 co-morbidities), tobacco smoking, and BMI. A test for possible biological interaction between low albumin and high CRP was also performed.

### **Ethical consideration**

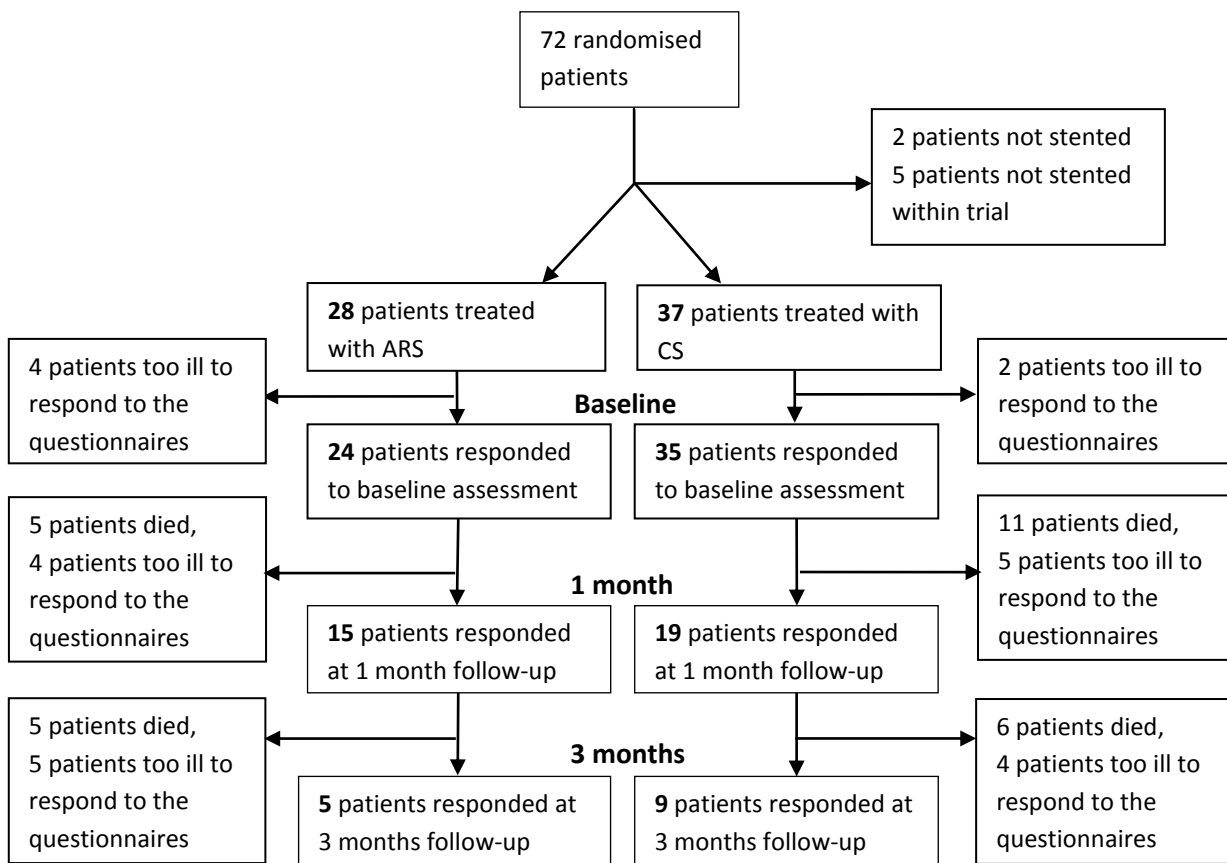
All the studies (I-IV) were approved by the local ethical committee. Study II and III were approved by the Swedish Medical Products Agency. In papers I and II, written, informed, signed consent was obtained from each participant before inclusion. In paper III the patients were given oral and written information about the study before they agreed to participate and this was documented in the journal and, in paper IV, the patients, their care givers or attending relatives were given written and oral information about the data collection and its use for research purposes.

# Results

## Paper I

### *Study participants and procedures*

A total of 72 patients were randomised, but 5 patients were excluded due to misclassification, and 2 patients were excluded due to rapidly progressive disease. These exclusions contributed to the skewness of allocation, since 6 of the 7 excluded patients had been randomised to the ARS group. A flow chart of the study is shown in Figure 5.

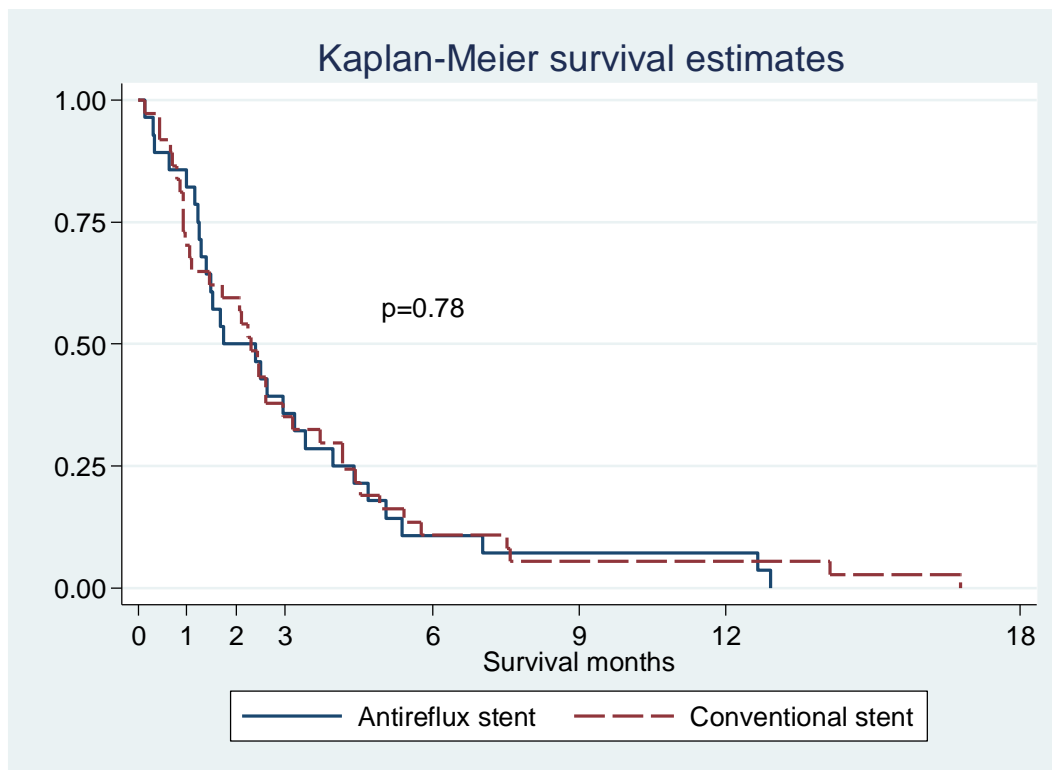


**Figure 5.** Flowchart of all randomised patients. ARS=anti-reflux stent, CS=conventional stent.

The complication rate within one month did not differ significantly between the two groups, although the total number of complications was higher in the CS group while more patients had complications in the ARS group. No procedure-related death was noted. As expected, males dominated in both groups. The median survival in the ARS



and CS group was 63 and 70 days respectively. A Kaplan-Meier curve of probability of survival is shown in Figure 6, visualising the short life expectancy, which was equal in the comparison groups.



**Figure 6.** Survival curve, after stenting, in 65 randomised patients treated with an antireflux stent or a conventional stent.

### *HRQL*

Among the 34 patients who completed the HRQL questionnaires both at baseline and at one month, there were some clinically relevant differences in HRQL between treatment groups but no statistically significant differences. Dysphagia and eating difficulties improved to a greater degree in the CS group, but unexpectedly the reflux symptoms increased in the ARS group. Oesophageal pain increased in both groups, whereas speech problems only increased in the CS group. At 3 months there were only 14 patients able to answer the questionnaires, and those in the CS group had deteriorated more in physical and social function and fatigue compared to the ARS group.

## **Paper II**

### *Study participants and procedures*

A large proportion of patients were disqualified (n=215) due to the exclusion criteria, leaving 76 patients for final analysis. Of these, 38 patients were randomised in each group. Most of the excluded patients were in the category “ERCP in less than a year before inclusion” (n=142). Basal characteristics showed equal distribution in the two groups, apart from men being somewhat overrepresented in the losartan group. Biliary duct sphincterotomy was used slightly more often in the losartan group (n=27) than in the placebo group (n=24). The number with cannulation difficulty was equally distributed between groups, as were radiological findings and patients requiring stents in the bile ducts. However, there were more pancreatic injections of contrast media and sphincterotomies in the losartan group than in the placebo group. The mean blood pressure at baseline was similar in both groups but, at 24 hours after ERCP the mean blood pressure was lower in the losartan group, which could be an indication of the pharmacological effect of losartan.

### *Pancreatic enzyme levels*

Hyperenzymemia was defined as more than 3 times the upper normal value of amylase or lipase at 24 hours or more after ERCP. Hyperenzymemia was registered in 9 (24%) and 7 (18%) patients in the losartan group and in the placebo group, respectively. The multivariable regression model did not reveal a decreased risk of hyperenzymemia in the losartan group as compared to the placebo group (OR, 1.6; 95% CI, 0.3 to 7.8). There were no major differences between enzyme response of amylase or lipase after ERCP. Mild acute pancreatitis (according to the Atlanta criteria)<sup>164</sup> occurred in 5 (13%) patients in the losartan group and 4 (11%) patients in the placebo group. No cases of severe acute pancreatitis were seen.

## **Paper III**

### *Study participants and procedures*

During the study period, 535 patients were referred for PEG. Of these, 301 were unable to give informed consent. Basic characteristics were evenly distributed, except for fewer women in the cefuroxime group and more oesophageal cancer patients in the sulphamethoxazole/trimethoprim group. In total, 118 patients were randomised to the cefuroxime group and 116 to the sulphamethoxazole/trimethoprim group. The PEG-procedure was impossible to accomplish for 10 % of the patients in each group. Moreover, 5 patients died before follow-up, 3 patients were lost to follow-up, 1 patient pulled out the catheter soon after insertion (without ensuing complication) and 1

patient received the wrong treatment. Thereafter, 100 patients in each group remained for the per-protocol analysis.

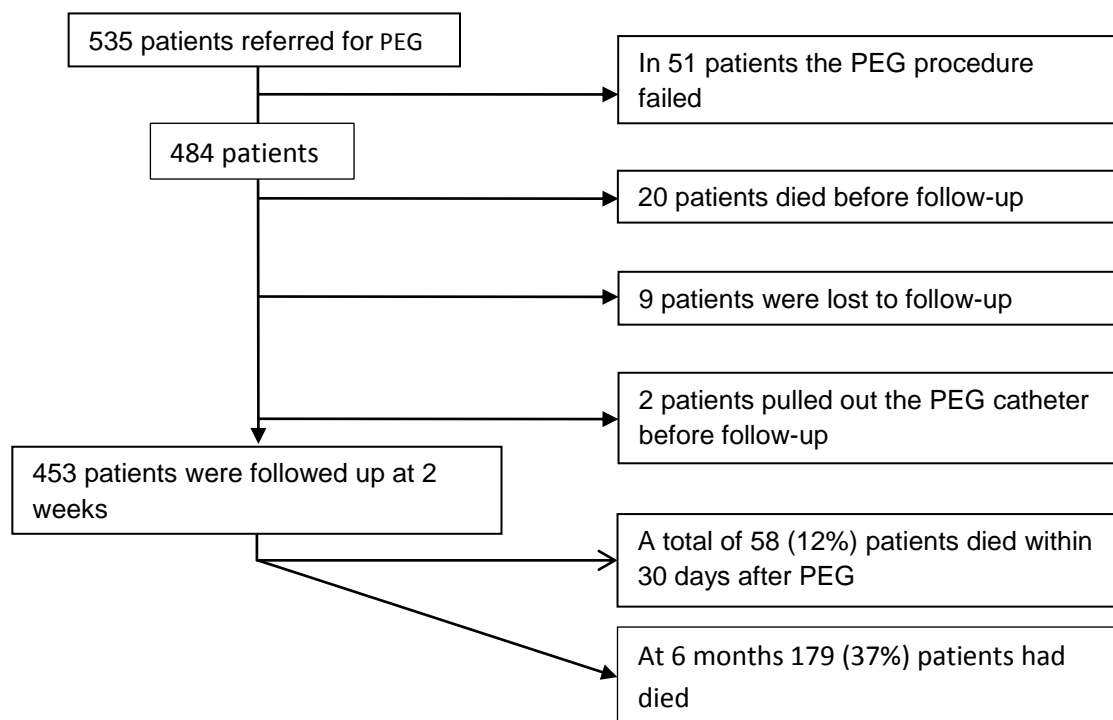
### *Complications and infection*

No statistically significant differences were noted in the pre-determined definition of complications at follow-up, but there was a numerically higher frequency of peristomal infections in the standard cefuroxime group. We detected 10 infections in the sulphamethoxazole/trimethoprim group and 14 infections in the cefuroxime group. The proportion difference in the intention to treat analysis was -3.3% (95% CI, -10.9 to 4.5%), which was well below the pre-determined non-inferiority limit of 15%. The per-protocol analysis supported the result of non-inferiority. The number of positive bacterial cultures, the white blood cell count, and CRP showed no statistical differences between the two groups. No allergic reactions were noted in either group.

## **Paper IV**

### *Study participants and procedures*

The study cohort included 535 patients, of whom 51 were excluded because the PEG insertion failed. Figure 7 shows an overview of the study flow.

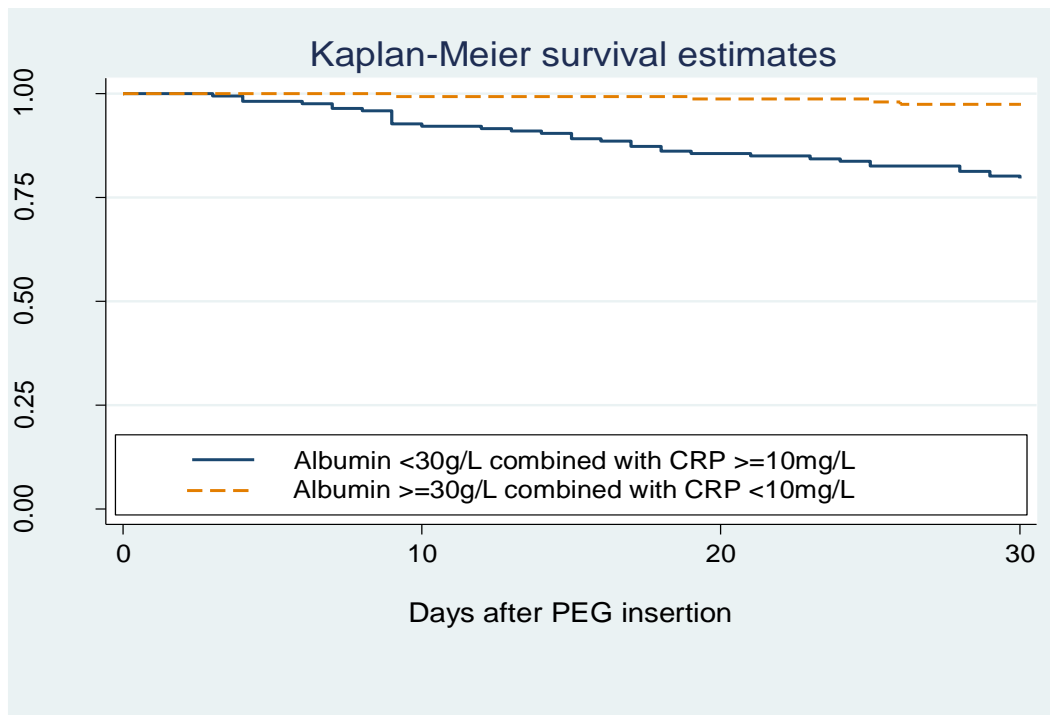


**Figure 7.** Flowchart of the PEG and risk factors prospective cohort study.

The mean age was 66 years (SD 14) and there were slightly more males than females. The main indications were cancer (44%) and neurological disease including stroke (44%).

### *Risk of early mortality*

There were 58 patients (12%) who died within 30 days after PEG insertion but there was no immediate procedure-related mortality. At 6 months 37% of the patients had died. The adjusted risk estimates for mortality within 30 days after PEG increased about 2-fold for age  $\geq 65$  years (HR, 2.26; 95% CI, 1.20 - 4.25), increased 3-fold for patients with an albumin level  $< 30$  g/L (HR, 3.46; 95% CI, 1.75 - 6.88) and 3 fold increased for patients with CRP level  $\geq 10$  mg/L (HR, 3.47; 95% CI, 1.68 - 7.18). The risk of BMI  $< 18.5$  kg/m<sup>2</sup> was possibly, but not statistically significantly, increased (HR, 2.04; 95% CI, 0.97 - 4.31). The cancer patients had a trend toward lower risk of short-term mortality than stroke patients. The risk for 30-day mortality tended to increase with a higher number of co-morbidities but this was not statistically significant. The combination of low albumin ( $< 30$  g/L) and high CRP ( $\geq 10$  mg/L) levels was followed by a 7-fold increased risk of 30-day mortality, as compared to patients with albumin  $\geq 30$  g/L combined with CRP  $< 10$  mg/L (HR, 7.45; 95% CI, 2.62 - 21.19). The absolute mortality rate in patients with this risk combination was 20.5%, compared to 2.6% in patients with normal values. A trend of biological interaction (effect modification) was noted with the combination of low albumin and high CRP, but this was non-significant. The effect of low albumin combined with high CRP on survival compared to patients with both values normal is illustrated in Figure 8.



**Figure 8.** 30-day survival curve comparing patients with combination of low albumin and high CRP with patients with combination of high albumin and low CRP.

### *Risk of peristomal infection*

As 20 patients died before follow-up, 9 were lost to follow-up and 2 patients pulled out their catheters, 453 patients remained for evaluation of peristomal infection at 14 days after PEG insertion, see Table 1. Among these, 50 patients (11%) had a clinically detected peristomal infection. Low BMI (<18.5), low albumin (<30 g/L) level, and high CRP ( $\geq 10$  mg/L) level each showed a non-statistically increased risk of infection. Co-morbidities and the number of these did not influence the risk. No biological interaction was noted for low albumin and high CRP regarding the risk of peristomal infection.

### *Complications*

Apart from peristomal infection and mortality, we pre-defined five common complications about which patients often complain after PEG insertion. These symptoms were registered at follow-up at 2 weeks and 2 months (Table 1). Leakage and diarrhoea were as common as peristomal infection at the 2-week follow-up. At 2 months, peristomal infection was reduced to nearly half the initial value (Table 1).

**Table 1.** Complications registered at follow-up after insertion of percutaneous endoscopic gastrostomy (PEG) catheter in 484 patients. One patient can have more than one complication.

	<b>2 weeks</b> n=453*	<b>2 months</b> n=370*
<b>Complications</b>	<b>Number (%)</b>	<b>Number (%)</b>
No complication	288 (64)	254 (69)
Died before follow-up	20 (4)	85 (18)
Elective extraction of PEG before follow-up	0 (0)	19 (4)
PEG pulled out by the patient	2 (0)	0 (0)
Leakage	43 (10)	30 (8)
Diarrhoea	50 (11)	34 (9)
Constipation	26 (6)	17 (5)
Abdominal pain	57 (13)	16 (4)
Fever	10 (2)	4 (1)
Peristomal infection	50 (11)	23 (6)

\* Number of patients available at follow-up. At 2 weeks and 2 months, 9 and 10 patients respectively were lost to follow-up.

# Discussion

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## *General methodological considerations*

The randomised clinical trial used in papers I-III, is considered in its best form to give the most valid data about new drugs or therapeutic procedures, but it must be designed in an ethical manner so the patients are not denied the best available treatment. The patients must also give their consent voluntarily and it is crucial that they understand the aims of the study. The trial must also be designed to assess what it is supposed to test. A superiority trial, which is the most common type, is typically conducted to show whether a new treatment is superior to the standard treatment. A non-inferiority study has the aim of proving whether the new treatment is at least as good as standard treatment (the new treatment has other benefits than better effect, e.g. lower price or easier administration).

The blinded randomisation process (allocation by chance) reduces the risk of systematic errors, including known or unknown confounding. This can further be decreased by maximum blinding (of the patient, treating personnel and evaluator) of given treatment. To further decrease contamination of unpredictable factors distorting the true association between treatment and outcome, the sample size must be large enough to provide a random distribution of confounders and allow a statistical power good enough to secure clinically meaningful findings. Sometimes this has to be achieved by a multi-centre trial which could give better sample size and possibly external validity or generalisability. On the other hand, the different centres could make it difficult for the principal investigator to control the proper equal inclusion, treatment and data registration of patients. If a large enough sample size is too difficult to achieve, a pooled analysis of a collection of several randomised studies of similar design and topic can be performed, i.e. a meta-analysis, to achieve better power. Other ways of reducing confounding are by randomised stratification of known confounding factors or by using exclusion criteria. At the analytic stage of small trials, multivariable regression models with adjustment for possible confounders can be utilised to further minimise confounding.

Randomised trials have also been said to sometimes show very conflicting results although the design is equal. This could be explained by different groups of patients and the validity and generalisability must be considered carefully.<sup>165</sup> Intention-to-treat analysis is the recommended primary analytic procedure but if compliance is low a true effect might be missed by loss of power. Therefore a per-protocol analysis could be done as a sensitivity analysis.

The cohort study design, analytical or descriptive, is an observational study in which study subjects with different exposure can be observed and followed regarding the risk

of developing an outcome over time. RCT is a type of study where the exposures are randomly assigned to the study subjects. There are, however, many exposures usually not possible to randomly designate to people, e.g. age, sex, ethnicity BMI, and smoking. The non-randomly assigned exposures age, BMI, albumin level, CRP, indication for PEG and co-morbidity studied in paper IV carry the risk of systematic bias, e.g. confounding, with regard to their association with the outcomes of mortality and peristomal infection. The statistical assessment in this type of study, therefore, has to use analyses to allow adjustments for potential confounding variables, which cannot be ignored as they can in a properly conducted randomised study of sufficient sample size where the known and unknown confounders are likely to be evenly spread across treatment groups. The number of outcomes of interest in RCTs and cohort studies are usually limited to one or two. The mortality and infection rate after PEG (paper IV), are rather common outcomes and the cohort was rather large making the interpretation more robust.

It has been said that cohort studies have a tendency to overestimate treatment effects but this seems to be related to the design and it has been suggested that well designed cohort or case-control studies do not overestimate the association between exposure and outcome as compared to randomised studies.<sup>166</sup> Many cohort studies are conducted in retrospectively making control of confounding factors less accurate as compared to a more labour-intensive, time-consuming, prospective design. In paper IV we used a prospective cohort study design.

### *Specific methodological considerations*

#### **Paper I**

This is a randomised, single-blind, multicentre, superiority study comparing two different oesophageal stents. The population from which recruitment was made had been thoroughly defined regarding tumour localisation, stage, histology, operability, dysphagia grade and the clinical need for an oesophageal stent. The patients were blinded to which stent they received, but the endoscopist could not be kept blinded due to obvious differences in the stent delivery system and the need for assembling the ARS immediately prior to stenting. The calculated number of patients needed for inclusion over 3 years was far higher than the number of participants finally included, although as many as 11 centres were involved in an effort to maximise inclusion. Thus, the statistical power was less than expected. This could contribute to a risk of rejecting a true difference, i.e. of accepting a false null hypothesis (type 2 error). The inclusion rate declined significantly over time, probably partly due to a change in the indication for surgery to a more aggressive approach, competing trials regarding chemoradiotherapy, and due to recent publications, indicating no positive effect of the



more complex and time-consuming insertion of the ARS. All this led presumably to a decreased willingness to include patients in the study. Other explanations were that, due to the rapidly deteriorating health status of the inoperable oesophageal cancer patients, they often had difficulties in answering HRQL questionnaires, and their survival was much shorter than expected.<sup>66</sup>

Multiple testing is a risk in HRQL research where many measures are assessed. To limit this source of false positive findings (type I error), we only tested differences of more than 10 points between measured time points.<sup>49, 163</sup> We used the EORTC QLQ C-30 and QLQ OES-18 questionnaires which are well validated and have shown acceptable reliability.<sup>46, 167</sup> The questionnaires are used internationally, making comparisons possible, and they are also reliably translated, back and forth for testing of the validity of the translation, into different languages including Swedish. The evaluation of stent effects on HRQL was made by the patients filling in the EORTC questionnaires, without external interference by study and health personnel, in the ward or at home. The patients did not know what kind of stent they had received, making the results less flawed. Finally, the conclusions could have been distorted by the imbalance of patient inclusion from different participating centres, but the site distribution was even in comparison groups and nearly 80% of the stented patients came from three large-volume hospitals, counteracting the influence of such imbalance.

Advantages of the study are the randomised design, the blinding of the patients to the inserted stent, and the use of validated and reliable instruments for measurement of HRQL.

## **Paper II**

This study was triple-blinded (to patients, endoscopists, and evaluators), randomised, two centre, placebo controlled, superiority trial evaluating the effect of losartan on pancreatic enzyme levels 24 hours after ERCP. Since the study aimed at first time ERCP patients, an arbitrary limit of one year since last ERCP was chosen. This criterion excluded many patients, which contributed to the slow inclusion pace. The hypothetical gain was set at the assumption that the maximum noted rate in the literature of patients with post ERCP hyperenzymemia, i.e. 40%,<sup>126</sup> would be reduced to 10% of hyperenzymemia in the treatment group. Any weak association would therefore not be detected. However, hyperenzymemia in this study was less common than expected, contributing to a limited statistical power. The rate of acute pancreatitis was, however, more common than expected, probably due to detection bias or perhaps to chance. The predefined dose of 50 mg losartan, which is a common starting dose in treatment of hypertension, was calculated from animal studies where a protective dose of losartan was found to be 0.2mg/kg.<sup>138</sup> For practical and predetermined reasons,

losartan was given 1 hour before ERCP, while the peak concentration is about 3-4 hours after administration, and perhaps 1 or 2 hours more for the more potent active metabolite of losartan. Speculatively, a longer latency interval between administration and ERCP could have given other results, but on the other hand, pancreatitis develops over the course of several hours. The blood pressure was lower at 24 hours after ERCP in losartan-treated patients, showing that the losartan dose had some pharmacological effect.

Obvious strengths of the study were the maximum blinding, the identical capsules with active drug or placebo, the objective measurements of pancreatic enzymes, and the short follow-up.

### **Paper III**

This was a double-blinded, randomised, single centre, non-inferiority clinical study with active controls including 234 patients, to elucidate whether sulphamethoxazole/trimethoprim is at least as good as cefuroxime in infection prophylaxis during the PEG procedure. Findings in the literature on the effect of antibiotic prophylaxis during PEG on peristomal infection frequency made us decide on clinical grounds on a non-inferiority level of 15%. In practical terms this means that <15% more infected patients in the co-methoxazole group could be accepted and still be labelled non-inferior to standard treatment. The primary outcome, peristomal infection was detected on clinical grounds using predefined clinical signs of infection at follow-up, by specially trained nurses who were unaware of the antibiotic prophylaxis given. This subjectiveness could introduce bias, but any such error ought to be evenly distributed due to the rather large sample size and the randomised double-blinded design of the study. Moreover, the objective measures of infection (culture and blood tests) supported the findings. The patients included had to be able to give informed consent and perhaps this included a healthier group of patients compared to those who were unable to give consent. This could perhaps influence the generalisability of the study, but not its internal validity. Moreover, the infection frequency in both groups was comparable to the whole cohort of 484 patients (paper IV) as well as other PEG patients with antibiotic prophylaxis described in other trials.<sup>168, 169</sup>

Advantages of the study are the randomised design, the blind administration of antibiotic prophylaxis to patients, follow-up by nurses without knowledge of given treatment, the objective markers of infection (bacterial cultures and blood chemistry), and the large sample size.

## Paper IV

This large cohort study comprised virtually all patients receiving PEG over the course of 4 years at one endoscopy centre, which included 484 patients with nearly complete follow-up. The study was prospective and the potential risk factors and their categorisations were pre-determined, which should reduce the risk for bias. We wanted to analyse the two primary outcomes, 30-day mortality and peristomal infection at follow-up, in the best possible way. Since mortality was specified in time, but not the peristomal infections, we chose the Cox proportional hazard regression model regarding risk for short-term mortality and the logistic regression model regarding risk for peristomal infection. The trial gave access to a rich number of potential confounding variables, for which adjustments was made, thus limiting the risk of bias from confounding. There was a high proportion of missing data concerning tobacco smoking (25%) and BMI (31%), but they did not alter the risk estimates and were therefore excluded in the final analyses. Another issue regarding smoking is that many PEG patients had stroke and neurological disease, and were therefore unable to continue to smoke and many cancer patients may have stopped smoking after diagnosis of throat cancer where smoking is known to be a major risk factor. Because of such smoking cessation, the risk of post-operative infection due to the smoking effect might already have been reduced.<sup>170, 171</sup> A test for biological interaction looking for departure from additivity was conducted between low albumin and high CRP, but was without statistical significance.

The cut-off values for CRP and albumin were chosen before analyses and after studying the literature of comparable studies. Loss to follow-up (31 patients of whom 20 died before follow-up) weakens the conclusions regarding risk of peristomal infections, especially since these patients were over-represented regarding low albumin and high CRP.

Strengths of the study are the prospective design with a large number of participants, the complete follow-up with objective measures, and the abundance of data, allowing for adjustment for potential confounding.

# Findings and implications

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## Paper I

This trial did not identify any obvious HRQL benefit from using ARS instead of CS. There were no statistically significant differences in HRQL score changes between baseline and 1 month between the ARS and the CS group, but the proportion of patients who completed the questionnaires at baseline and first follow-up at 1 month was reduced because of rapidly progressing disease and short survival. Some patients who were stented were not even able to fill in the baseline forms, which emphasises the importance of making the interval between randomisation and stent procedure as short as possible. This loss of patients contributed to a reduced statistical power. Nevertheless, this is hitherto the largest study addressing the issue of ARS in these patients. The decreasing inclusion rate indicates that larger studies on the subject could be very difficult to perform in the future, but the available trials may be useful in a meta-analysis.<sup>172</sup> The ARS tested in this study was technically more difficult to insert and the procedure more time-consuming and, as the complication rate did not significantly differ between this and earlier studies, there is no significant reason to recommend the Esophageal Z-stent<sup>®</sup> with a Dua Anti-reflux Valve instead of CS. The risk of reflux after stenting should, however, be stressed and any symptoms of reflux should be counteracted by a raised body position, especially immediately after a meal and medication could be tried for reduction of acid production even if the effect is uncertain in this category of patients.<sup>39</sup> In case of future improvements in ARS design and delivery system, ARS could be considered but, if ARS are to be used in clinical practice, proof of their superiority over CS is essential.<sup>26</sup>

## Paper II

This trial demonstrated no benefit from using losartan prophylactically during ERCP against post-procedural hyperenzymemia and pancreatitis. The hypothesis was based on experimental work among animals and the finding of a preventive effect of ARB on acute pancreatitis in general in a large case-control study.<sup>135-141</sup> The reasons for a possibly true preventive effect not being shown could be due to limited sample size, inappropriate timing of the drug administration, low dose, the test drug perhaps not being the ARB with the best potency, or unknown confounding. So the question is whether or not we are missing a true effect (type 2 error)? There are some practical difficulties to solve if another trial is to be performed. For maximum effect, losartan

should be given 3-4 hours before ERCP, but since many patients arrive the same day as the investigation, this time limit would be difficult to achieve. Another difficulty is that more patients might need general anaesthesia during ERCP, because of the more advanced and time-consuming investigations done. The anaesthetists, in many cases, might not accept ARB taken the same day as general anaesthesia because of the risk of serious hypotension.<sup>173</sup> All this also applies to higher dosage and more potent ARBs. Therefore, it seems difficult to propose a larger randomised study using ARB as proposed prevention of post-ERCP pancreatitis. If the present study had shown a reduced risk of hyperenzymemia, we had planned a much larger study, using the same design, but evaluating a much larger sample size at several centres and addressing the risk of pancreatitis rather than hyperenzymemia alone.

### **Paper III**

This clinical trial indicates that an oral solution of co-methoxazole administered in the PEG catheter after the PEG procedure is at least as good as standard antibiotic prophylaxis given intravenously before the PEG insertion. The literature has indicated that antibiotic prophylaxis is of value during the PEG procedure,<sup>145</sup> but the present standard treatment with cefuroxime has many disadvantages, i.e. high costs, time-consuming administration, the need to be given intravenously before the procedure which means unnecessary treatment whenever the PEG procedure fails, short biological effect, and ecological disadvantages.<sup>151, 152</sup> These problems could all be solved by using the alternative sulphamethoxazole/trimethoprim, which also seems to have a local effect<sup>174</sup>. Since this study provides scientifically robust evidence supporting the use of local sulphamethoxazole/trimethoprim and since it has several practical advantages, we can recommend this strategy in clinical practice.

### **Paper IV**

The present cohort study regarding risk factors for short-term mortality within 30 days and peristomal infection at follow-up within 14 days indicates that low albumin and high CRP levels increase the risk of short term mortality more than 3-fold. Being older than 65 also involved an increased risk, while low BMI possibly could involve an added risk of mortality within 30 days. The corresponding parameters in relation to risk of peristomal infection within 14 days were weaker. The combination of low albumin and high CRP had a high relative risk for short-term mortality and this could perhaps be used as an indicator of patients that the PEG insertion should be postponed

until the patient is stronger. It is important to inform the patient, caring relatives or referring doctor about the high risk of early mortality. Low albumin and high CRP might be an indication of severe disease that in itself might lead to early mortality where the additional risk of a PEG might not be that important. A patient with a very short life expectancy might therefore not benefit at all of a PEG which only might introduce pain and an added risk of complications. Instead it could be of value trying to optimise the patient e.g. antibiotics against infection, anti-inflammatory medication, and nutrition by other means of delivery. If the patient survives a couple of weeks and hopefully is less diseased, a new attempt at PEG may be contemplated.

## Conclusions

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- The use of an anti-reflux stent in the palliation of inoperable distal oesophageal cancer might not be superior to conventional open stent from a HRQL perspective.
- The angiotensin II receptor blocker losartan might not have any strong preventive effect against hyperenzymemia after ERCP.
- Injection of 20 ml sulphamethoxazole/trimethoprim solution into the newly inserted PEG catheter seems to be at least as good in preventing peristomal infection as standard treatment of 1.5 grams cefuroxime administered intravenously before the PEG. This new method could therefore be recommended as prophylaxis instead of standard treatment because of its positive clinical implications.
- Low albumin combined with high CRP seems to predict a high risk of mortality within 30 days after PEG insertion. Such measures could be used to give the patient better information about the potential risks after PEG insertion and used in better decision-making regarding the timing of the PEG procedure.

## Future perspective

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Endoscopic procedures will continue on the market for a long time and developments will probably bloom exponentially as new and better instruments are designed. Lateral thinking will help to find new ideas, new methods and new interventions. This will lead to the need for new, properly executed randomised trials in order to evaluate their suggested better effects. To assess unwanted side effects and risks, large cohort studies are needed. NOTES is the latest example of a new endoscopic field being investigated.

Stenting of the gastrointestinal tract will require further improvement such as use of bio compatible materials with better design and properties. The antireflux stent for the distal oesophagus in palliative treatments of cancer may not be the stent of choice today but, with improved design and a more smoothly operated delivery system that might change. If other palliative treatments, such as new oncological therapies, prolong the survival of oesophageal cancer patients, the anti-reflux stent might be picked up again making new studies of their efficacy important. Comparing new stents with brachytherapy will then also be necessary.

Combating post-ERCP pancreatitis is still a challenge, mainly because of its potential danger to the patient. The angiotensin II receptor blocker track might not be totally closed as yet. Newer agents of the same family with higher potency, longer biological half-life, faster absorption, and unique properties regarding oxidative stress and inflammatory response (e.g. telmisartan) might be useful. The chosen dose in our study might have been too low, as other studies suggest a higher dose could have better effect. The timing of drug intake is also of pharmacological importance for maximum effect. The hypotensive risk during general anaesthesia is probably not too difficult to resolve by perhaps using deep sedation (propofol) instead of general anaesthesia, better monitoring, proper counter measures, and interested anaesthetists.

Better PEG catheter materials with effective antibacterial properties could perhaps be developed. The infection prophylactic introducer technique for PEG insertion will probably be developed to allow easier handling and to give better results regarding complications as compared to the pull PEG technique. Pre-PEG pharmacological treatments of chronic inflammation and acute infections in high-risk patients might have an impact on the survival after PEG but have to be properly tested.



# Populärvetenskaplig sammanfattning på svenska

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**Bakgrund:** Endoskopi innebär att med hjälp av ett böjligt och styrbart optiskt instrument titta in i något av kroppens hålrum och när kirurgiska ingrepp görs med hjälp av endoskopi är det bland annat för att minska de risker som vanlig kirurgi för med sig. Under min tid som kirurg och endoskopist har jag mött patienter som tyvärr har drabbats av allvarliga biverkningar med svåra symtom efter endoskopiska ingrepp. Detta kan mer eller mindre helt förstöra den effekt ingreppet var tänkt att ha och även försämra patientens livskvalitet avsevärt och till och med leda till döden. Jag har därför blivit intresserad av att hitta metoder för att i möjligaste mån minska det lidande som endoskopiska biverkningar kan innebära. Det har gjort att jag engagerat mig i arbeten med syfte att testa vägar för att minska komplikationer och hitta faktorer som kan förutsäga en ökad risk för biverkningar vid ett antal specifika endoskopiska ingrepp i övre magtarmkanalen.

De olika endoskopiska ingreppen för med sig biverkningar eller komplikationer som kan minskas med hjälp av ökad erfarenhet hos undersökaren, utveckling av bättre instrument och klokheten av att inte utföra ingreppen när risken för komplikationer verkar vara för stor. De här riskerna är trots allt mindre än när samma eller liknande ingrepp görs med hjälp av vanlig operation. För att göra de endoskopiska ingreppen ännu mindre riskfyllda måste man känna till det spektrum av biverkningar som kan ske vid de olika undersökningarna och de riskfaktorer som pekar mot ett sämre resultat. Det räcker inte med den enskilde undersökarens eller kirurgens erfarenheter utan kunskapen måste inhämtas från välplanerade och systematiskt utförda stora forskningsstudier.

I den här avhandlingen ingår följande arbeten:

*Arbete 1:* Behandling av patienter med obotbar matstrupscancer och sväljsvårigheter jämförande 2 olika typer av självexpanderande metallrör.

*Arbete 2:* Ett försök att på medicinsk väg försöka minska risken för bukspottkörtelinflammation efter endoskopisk undersökning av gallgångar och bukspottkörtelgång.

*Arbete 3:* Testning av en ny metod att ge antibiotika som infektionsskydd vid inläggning av en matningsslang direkt till magsäcken via bukväggen (inom vården ofta kallad PEG= perkutan endoskopisk gastrostomi).

*Arbete 4:* Hitta faktorer som kan tala för ökad risk till tidig död och infektion efter PEG.

**Arbete I:** Matstrupscancer har uppvisat en kraftig ökning de senaste 30 åren men tyvärr kan större delen av patienterna inte botas eftersom sjukdomen upptäckts för sent eller på grund av att patienten är för svag för att tåla påfrestningen av en stor operation. Tyvärr drabbas nästa alla patienter med matstrupscancer av besvärande sväljssvårigheter och behöver därför ofta behandlas för det. Den vanligaste och snabbast verkande hjälpen till patienter som inte kan opereras är att med hjälp av ett självexpanderande metallrör på plats vidga förträngningen, vilket ofta har bra och snabb effekt på sväljningsbesvären. En annan sak att ta hänsyn till är att patienterna ofta inte överlever mer än några månader efter att diagnosen har ställts och därför behöver en hjälp fungerar snabbt och har bra effekt mot symtomen. En större del av matstrupstumörerna utvecklas nedtill i matstrupen vilket gör att de rör som placeras där, sträcker sig ned i magsäcken. Det här kan göra att magsäckens syra och övriga innehåll kan rinna upp i matstrupen (reflux) och ibland spilla över till luftrören. Det finns då risk för utveckling av svår inflammation i matstrupen och lungorna vilket kan ge besvärliga symtom som kan försämra patientens hälsoberoende livskvalitet avsevärt. Därför har metallrör med en envägs ventil (antirefluxventil) utvecklats som ska förhindra det här återflödet men flera studier har inte kunna påvisa någon säker förbättring jämfört de vanliga rören utan ventil.

Den här studien testade om ett rör med antirefluxventil kunde förbättra den hälsoberoende livskvaliteten i förhållande till de patienter som fick ett standardrör utan ventil. Livskvalitet betyder olika saker för olika människor och kan omfatta väldigt många aspekter. Vi begränsade oss i den här studien till att mäta den påverkan som sjukdomen och behandlingen ger på patientens förmåga att leva sitt dagliga liv och på de symtom som patienten känner av på grund av sin sjukdom. Den här hälsoberoende livskvaliteten mättes med hjälp av frågeformulär, som analyserar symtom och dagliga funktioner både generellt vid cancer och specifikt vid matstrupscancer. Studien omfattar 65 patienter, vilket är fler än i tidigare studier men mindre än det antal som planerades. Patienterna i båda grupperna dog efter ca 2 månader (median) efter att röret lagts på plats, vilket var tidigare än förväntat. Vid analys av frågeformulären fann vi ingen statistisk skillnad mellan grupperna avseende livskvaliteten men konstigt nog sågs en poängmässig skillnad avseende symtom på reflux till det vanliga rörets fördel. Effekten mot sväljningssvårigheterna var likvärdig, men röret med ventil var tekniskt mer svårhanterat jämfört med standardröret.

Således kunde vi inte med ledning av den här undersökningen se några säkra fördelar med det nya ventilförsedda röret jämfört med standardröret.

**Arbete II:** Vid undersökning av gallgångarna och bukspottkörtelgången med ett endoskop (endoskopisk retrograd cholangiopankreatikografi=ERCP) för att t.ex. ta bort stenar eller lägga dit rör i gångarna för att avlasta förträngningar, finns risk för att

utlösa en inflammation i bukspottkörteln (pankreatit). Vanligen är det inte en allvarlig åkomma men risken finns att det kan utvecklas till en mycket svår form med hög dödlighet. Bukspottkörtelinflammation konstateras genom att mäta speciella äggviteämnen i blodet (enzym) efter ERCP och är dessa förhöjda mer än 3 gånger av det övre normalvärdet och patienten samtidigt känner smärta i magen kan man vara ganska övertygad om diagnosen. Enbart en höjning av enzymerna utan buksmärta efter ERCP är dock mycket vanligare. Eftersom de här enzymerna är förknippade med utveckling av bukspottkörtelinflammation ville vi i en första studie se om enzymstegringen påtagligt kunde dämpas av ett vanligt blodtryckssänkande läkemedel som losartan. Idén hade vi fått från tidigare utförda undersökningar där man hade påvisat en skyddande effekt av losartan både mot enzymstegring och mot bukspottkörtelinflammation.

I vår studie med slumpartad fördelning av losartan eller overksam substans (placebo) till patienter som gjorde ERCP så mätte vi enzymnivåerna efter undersökningen i upp till 24 timmar. Skulle vi se en hämmande effekt på enzymnivåerna hade vi tänkt oss en mycket större studie där vi ville se om det också finns en skyddande effekt mot bukspottkörtelinflammation efter ERCP.

Analysen av studien visade att losartan, i den här studien, inte skyddar mot en stegring av enzymerna.

### ***Arbete III***

Patienter med svårigheter att svälja, ofta orsakat av stroke eller strål- och cellgiftbehandling av öron-näsa-halscancer, är ofta i behov av hjälp för att få i sig tillräckligt med näring. Att då lägga in en slang utifrån direkt in i magsäcken (PEG) med hjälp av endoskop kan vara till nytta för att kunna ge extra näring. Det är enkelt att göra men för med sig en hel del bekymmer oftast i form av infektioner längs kanalen genom bukväggen. Flera undersökningar har visat en bra effekt mot infektion när antibiotika används under ingreppet. Trots detta uppstår infektioner kring PEG slangen i upp till 10-15%. De är oftast lindriga men kan ändå ge problem med ökad smärta och förlängd vårdtid vilket leder till ökade kostnader. Ibland kan en utveckling ske till en mer allvarlig och riskfylld infektion med hög dödlighet. Ett vanligt använt antibiotikum är cefuroxim (Zinacef<sup>®</sup>) vilket har en hel del nackdelar. Det måste ges intravenöst innan operationen, vilket tyvärr kan glömmas bort och då leda till att PEG inläggningen kanske skjuts upp. Cefuroxim har dessutom kort verkningstid, hög kostnad och ges i onödan när PEG ingreppet misslyckas (5-10%). Det finns också en risk för en ogynnsam effekt på tarmens bakterier med risk för tjocktarmsinfektion orsakad av kraftig tillväxt av sjukdomsframkallande bakterier (*clostridium difficile*) vilket kan utlösas av bara en enda antibiotika dos. Ett alternativt antibiotikum skulle kunna vara sulfametoxazol/trimetoprim (Bactrim<sup>®</sup>) som ges i PEG katetern efter

ingreppet och skulle kunna lösa alla ovanstående nackdelar. Det här förutsätter då att det har minst lika bra effekt mot infektion som standardbehandlingen. Därför tilldelades något av dessa två antibiotika helt slumpartat i samband med PEG inläggning till de 234 patienter som deltog i studien.

Vi kunde konstatera 10 infektioner hos patienterna som fick Bactrim<sup>®</sup> och 14 infektioner i Zinacef<sup>®</sup> gruppen.

En statistisk analys visade att Bactrim<sup>®</sup> som ges på det här nya sättet är minst lika bra som Zinacef<sup>®</sup> och därför på grund av sina övriga fördelar verkligen kan rekommenderas som infektionsskydd under PEG inläggningen.

#### ***Arbete IV***

PEG är ett enkelt och snabbt genomfört ingrepp och man kan därför lätt luras att tro att det är ofarligt. Tyvärr kan patienterna drabbas av många olika komplikationer, vanligen infektion runt PEG slangen i 10-15% men patienterna, har det också visat sig, riskerar att avlida i en hög frekvens (8-28%) inom 30 dagar efter PEG inläggningen. Det rör ju sig ofta om patienter med svåra sjukdomar och då skulle kunskap om vilka riskfaktorer det finns för de här allvarliga komplikationerna vara av stort värde. Skulle man kunna förutse en stor risk hos en enskild patient, kanske man borde avråda patienten från att få PEG för tillfället eftersom det finns alternativa sätt att ge patienten näring. Under tiden kunde man kanske prova medicinsk behandling för att försöka få patienten i bättre form inför ett eventuellt nytt PEG-inläggningsförsök.

Eftersom tidigare studier inte entydigt klarlagt riskfaktorer för dessa komplikationer, utförde vi en stor undersökning bland alla patienter som fick PEG mellan 2005 och 2009 för att försöka hitta viktiga riskfaktorer för infektion eller tidig död efter PEG. De 484 som deltog följdes upp efter 2 veckor och dödsfall upp till 30 dagar efter PEG registrerades. Med ledning av tidigare undersökningar valde vi att titta på 6 riskfaktorer: 1/  $\geq 65$  års ålder, 2/ lågt albumin värde ( $< 30$  g/L), 3/ högt C-reaktivt protein (CRP)  $\geq 10$  mg/L, 4/ BMI  $< 18,5$  kg/m<sup>2</sup>, 5/ orsaken för PEG behovet, samt 6/ ytterligare sjukdomar hos patienten.

Statistisk analys visade att patienter med ålder  $\geq 65$  år, lågt albumin och högt CRP hade 2-3 gånger ökad risk att dö inom 30 dagar efter PEG. Möjligen fanns även denna risk hos patienter med BMI  $< 18,5$ . Hos patienter med både lågt albumin och högt CRP avled 20,5 %, inom 30 dagar, jämfört 2,6 % hos de patienter som hade normala värden. Lågt albumin ses ofta vid undernäring men förekommer också vid inflammatoriska tillstånd. CRP stegring ses vid akuta och kroniska inflammationer som kan orsakas av både bakterieinfektioner och andra svåra sjukdomar som t.ex. cancer.

**Slutsatser:** Hela det här avhandlingsarbetet har syftat till att försöka göra endoskopiska ingrepp mindre riskfyllda och ge mindre symtom och till att hitta riskfaktorer som skulle kunna ge patienten bättre information om vad som kan hända efter ingreppet och att det kanske kan göras vid en bättre tidpunkt:

- Vi hittade inga säkra fördelar avseende hälsoberoende symtom och dagliga funktioner med att använda ett rör med inbyggd antirefluxventil, jämfört med standardröret utan ventil vid behandling av obotbar matstrupscancer.
- Inte heller verkar risken för utveckling av ERCP-utlöst bukspottkörtelinflammation kunna minskas genom medicinsk förbehandling med det blodtryckssänkande läkemedlet losartan.
- Däremot verkar en ny metod att ge antibiotika som skydd mot infektioner efter inlagd PEG vara minst lika bra jämfört standard behandling men har då istället stora fördelar genom att vara snabbare att ge, säkrare, billigare och leder inte till överbehandling om ingreppet misslyckas jämfört standardbehandlingen.
- Patienter som får PEG och har låga albuminvärden kombinerat med höga CRP nivåer har stor risk att avlida inom 30 dagar efter ingreppet, vilket är viktig information att ge till patienten. Om en patient har dessa riskfaktorer så kan man kanske erbjuda en mindre riskfylld behandling genom att skjuta upp ingreppet och försöka behandla näringsbristen på annat sätt och samtidigt kanske dämpa inflammationen genom medicinsk behandling. Eventuellt kan patienten då hämta sig så att en PEG kan sättas dit vid ett senare tillfälle och då kanske med mindre risk, om då PEG behovet fortfarande finns kvar.

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