Use of acid-suppressive therapy before anti-reflux surgery in 2922 patients: a nationwide register-based study in Denmark

A. Lødrup†, A. Pottegård‡, J. Hallas§ & P. Bytzer*†

SUMMARY

Background
Guidelines recommend that patients with gastro-oesophageal reflux disease are adequately treated with acid-suppressive therapy before undergoing anti-reflux surgery. Little is known of the use of acid-suppressive drugs before anti-reflux surgery.

Aim
This study aimed to determine the use of proton pump inhibitors and H2-receptor antagonists in the year before anti-reflux surgery.

Methods
A nationwide retrospective study of all patients aged ≥18 undergoing first-time anti-reflux surgery in Denmark during 2000–2012 using data from three different sources: the Danish National Register of Patients, the Danish National Prescription Register, and the Danish Person Register.

Results
The study population thus included 2922 patients (median age: 48 years, 55.7% male). The annual proportion of patients redeeming ≥180 DDD of acid-suppressive therapy increased from 17.0% 5 years before anti-reflux surgery to 64.9% 1 year before. The probability for inadequate dosing 1 year before surgery (<180 DDD) was significantly increased for younger patients, patients operated in the period 2000–2003, patients who had not undergone pre-surgical manometry, pH- or impedance monitoring, and patients who had not redeemed prescriptions on NSAID or anti-platelet drugs.

Conclusion
Compliance with medical therapy should be evaluated thoroughly before planning anti-reflux surgery, as a high proportion of patients receive inadequate dosing of acid-suppressive therapy prior to the operation.
INTRODUCTION

Anti-reflux surgery (ARS) is an alternative to long-term acid-suppressive medication for some patients with gastro-oesophageal reflux disease (GERD). GERD patients, who may benefit from ARS, are those who are intolerant to or are poorly controlled by proton pump inhibitors (PPI).\(^1\) It has also been suggested that GERD patients, who are otherwise responding well to medical therapy, may be selected for ARS in the interest of avoiding lifelong medical therapy and the possible side effects associated with this.\(^2\)

In a Cochrane meta-analysis comparing fundoplication with PPI therapy, three of four studies only included patients taking PPI before randomisation.\(^3\) However, although guidelines recommend acid-suppressive therapy before ARS, and most of our knowledge regarding the effect of ARS is based on clinical studies with patients already on medical therapy, little is known of the actual use of acid-suppressive drugs before ARS and which factors that may be related to inadequate presurgical use of acid-suppressive therapy.

In a recent register-based study we observed that the use of PPI 1 year before surgery was surprisingly low.\(^4\) However, these results were not the primary outcome of that study and did not include data on use of histamine-receptor-2-antagonists (H2RA). Furthermore, in that study we had no data on oesophageal manometry, pH- or impedance monitoring. These are typical diagnostic procedures preceding ARS, but to which extent this presurgical diagnostic workup is applied in a real-life nationwide setting and how it may influence awareness of adequate dosing of acid-suppressive medicine is unknown. Finally, when discussing pre-surgical acid-suppressive medicine in the context of ARS, two sub-groups of patients are also of interest: those who undergo fundoplication because of a large hiatal hernia and those who may need repeated surgery. Limited use of acid-suppressive medication before ARS would not be a surprise in the first group. In the latter group, an assessment of pre-surgical compliance to medical therapy may help to identify patients who would later need repeated ARS procedures.

The aim of this study is to give a comprehensive description of the use of PPIs and H2RAs before ARS in the Danish population.

METHOD

The analysis was conducted as a population-based descriptive study of subjects undergoing first-time ARS during the period 1 January 2000 to 31 December 2012.

We used data from three different sources: the Danish National Register of Patients, the Danish National Prescription Register, and the Danish Person Register.

The Danish National Patient Register (NPR) contains data on all secondary care contacts in Denmark since 1977, and data on out-patient contacts since 1995. The International Classification of Disease V.10 (ICD-10) has been used to code discharge diagnosis since 1994. Surgical procedures are coded according to the Nordic Classification of Surgical Procedures (NCSP) since 1996.\(^5\) As less than 0.5% of all ARS have been performed at private hospitals,\(^6\) the NPR allows for a true population-based study within this area. Also, it contains data on diagnostic procedures such as esophagogastroduodenoscopy, coded according to the Danish SKS procedure codes.

The Danish National Prescription Register contains data on all prescription drugs redeemed by Danish citizens since 1995. Prescription data include the date of dispensing, the substance, brand name, and quantity expressed by the defined daily dose (DDD).\(^7\) The DDD is a technical measurement unit established by an expert panel in World Health Organization and defined as typical maintenance dose when the drug is used for its main indication by an adult, see Table 1. One DDD for different drugs should thus represent roughly equipotent doses.

The Danish Person Register contains data on vital status (date of death) and migrations in and out of Denmark.\(^8\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>ATC code</th>
<th>DDD (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>A02BC01</td>
<td>20</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>A02BC02</td>
<td>40</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>A02BC03</td>
<td>30</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>A02BC04</td>
<td>20</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>A02BC05</td>
<td>30</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>A02BA01</td>
<td>800</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>A02BA02</td>
<td>300</td>
</tr>
<tr>
<td>Famotidine</td>
<td>A02BA03</td>
<td>40</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>A02BA04</td>
<td>300</td>
</tr>
</tbody>
</table>

ATC, anatomical therapeutic chemical; DDD, defined daily dose.

The DDD is a technical unit for measuring drug use by quantity. It is established by an expert panel at WHO as the typical maintenance dose when the drug is used for its main indication in an adult. DDDs for PPIs are based on treatment of gastro-oesophageal reflux disease and DDDs for H2RAs are based on treatment of peptic ulcers.
All data sources were linked by use of the Central Person Register number, a unique identifier assigned to all Danish citizens since 1968 that encodes gender and date of birth. All linkage occurred within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes.

We included subjects who had undergone ARS, coded as JBC00 (Gastro-oesophageal anti-reflux operation, including fundoplication, cardiopexy and repair of sliding hiatal hernia) or JBC01 (Laparoscopic gastro-oesophageal anti-reflux operation, including fundoplication and Angelchik prosthesis), in the 13 year period 2000–2012. The date of the procedure was taken as the index date. The vast majority of surgical anti-reflux procedures have been performed by fundoplication, either laparoscopically or by open procedure, which are included in the JBC 00 and JBC 01. We excluded the minority of cases undergoing ARS coded as different techniques for the first episode of ARS and we excluded procedures coded as surgery on diaphragmatic hernia (NCSP-coded ‘JBB’), as this coding excludes surgery coded as ARS. Also, we excluded subjects who had undergone ARS prior to the study period, subjects who were <18 years at index ARS, and subjects who immigrated to Denmark less than 5 years before index ARS.

We extracted data for PPI and H2RA prescriptions within 5 years before index ARS, surgical centre where index ARS was performed and prescriptions of non-steroidal anti-inflammatory drugs (NSAID) and anti-platelet drugs for the year leading up to index ARS. NSAID and anti-platelet drug use may be the indication for acid-suppressive therapy in some patients, particularly the elderly, and use of these drugs was therefore included and adjusted for in our analyses. We also extracted data for the pre-surgical procedures upper endoscopy, oesophageal manometry, pH monitoring and impedance monitoring within 3 years before index ARS. Furthermore, we extracted data for any diagnosis of GERD (ICD-10: DK21 - DK219B) and hiatal hernia (ICD-10: DK44 - DK449) in the period of 1995–2012. For coding details, see Appendix S1.

Study objective
The main scope of the study was to determine the combined use of PPI and H2RA (hereafter denoted acid-suppressive therapy) in the year before index ARS. Additionally, use of acid-suppressive therapy 5 years before index ARS was determined as were factors associated with having used <180 DDD of acid-suppressive therapy in the year before index ARS, proportion of patients undergoing ARS, who were diagnosed with GERD and/or hiatal hernia, and the rate of repeated ARS procedures according to use of pre-surgical acid-suppressive therapy.

Analysis
Simple descriptive statistics were used to present proportion of patients redeeming prescriptions on 0, 1–89, 90–179, ≥180 DDD of acid-suppressive therapy in the year before index ARS. We defined inadequate dosing as <180 DDD of acid-suppressive therapy in the year before index ARS and factors associated with inadequate dosing was analysed using logistic regression and presented as odds ratio (OR) with 95% confidence intervals (CI). For logistic regression we included the co-variates gender, age (in categories of 20 years), year of index ARS (in categories of 4–5 years), surgical centre, pre-surgical diagnostic procedures (oesophageal manometry, pH- or impedance monitoring) within 3 years before index ARS and redeeming of at least one prescription of either NSAID or anti-platelet drugs within 1 year before index ARS. We repeated the logistic regression for probability of redeeming 0 DDD of acid-suppressive therapy. Lastly, the rate of repeated ARS procedures was estimated within 3 years following index ARS (limited to those operated in 2000–2009).

RESULTS
In the period 2000–2012, 3206 patients underwent ARS, whereof 284 (8.9%) were excluded because of previous anti-reflux surgery (n = 56), rare procedure-techniques (n = 71), age <18 at first-time surgery (n = 87) and recent immigration (n = 70). The study population thus included 2922 patients with a median age of 48 years (interquartile range: 39–58 years), whereof 55.7% were male. In total, 18 106 prescriptions on acid-suppressive therapy were redeemed in the year before ARS by the study population and esomeprazole was the most frequently redeemed acid-suppressive drug (34.2% of all prescriptions), for details see Appendix S2. Data on redeeming of prescriptions on acid-suppressive therapy in the year before index surgery is presented in Table 2. The number of ARS procedures performed for each period was fairly equally distributed (range: 31.6–36.5% of all procedures) with seven surgical centres performing 87.3% of all procedures (range: 7.3–17.2% of all procedures). The annual proportion of patients redeeming ≥180 DDD of acid-suppressive therapy increased from 17.0% 5 years before index ARS to 64.9% 1 year before
Figure 1). Of the 1895 patients redeeming ≥180 DDD in the year before ARS, 1121 (59.2%) redeemed ≥360 DDD. Of the 1027 patients redeeming <180 DDD 1 year before ARS, 839 (81.7%) redeemed <180 DDD every year in the 5 years leading up to surgery. The proportion of patients, who only redeemed prescriptions on PPIs and H2RAs, rose from 84.2% in 2000–2003 to 89.2% and 94.5% in 2004–2007 and 2008–2012, respectively.

Within 3 years before index ARS 2623 (89.8%) patients underwent upper endoscopy; manometry was performed on 2080 (71.2%), pH monitoring on 1954 (66.9%) and impedance monitoring on 117 (4.0%). In all, 738 (25.3%) had no manometry, pH- or impedance monitoring registered within 3 years before index ARS. NSAIDs or anti-platelet drugs were redeemed by 890 patients (30.5%) 1 year before index ARS.

The relative probability of redeeming <180 DDD of acid-suppressive therapy in the year before index ARS, expressed as OR by multiple logistic regression, is presented in Table 3. The probability was significantly increased for younger patients, patients operated in the period 2000–2003 and patients, who had not redeemed prescriptions on NSAIDs or anti-platelet drugs. Furthermore, patients, who had not undergone pre-surgical manometry, pH- or impedance monitoring, also had an increased probability of redeeming <180 DDD.

According to the register, 792 of 1895 (41.8%) ARS patients redeeming ≥180 DDD were diagnosed with only GERD before index ARS, 73 (3.9%) with only hiatal her-
Acid-suppressive therapy before anti-reflux surgery
given the potential for complications and known side effects to this surgical intervention.

By drawing the study population from our nationwide registers and thereby include all patients undergoing standard ARS in Denmark over a period of 13 years, we were able to present an estimate of the pre-operative use of acid-suppressive therapy based on redeemed prescriptions, instead of relying on patient-reported compliance. This is the major strength of the study.

The internal validity of the data is high, especially regarding demographics, prescriptions of medicine and surgical procedures. Details of drugs redeemed by the patients instead of drugs prescribed gave us a more realistic view on the use of medicine. Over-the-counter sale of PPIs and H2RAs constitutes only 2% of the total sale of acid-suppressive medicine in Denmark, which we consider without significance for our results. Surgical procedures, such as fundoplication, are generally correctly registered (>90% of registered cases) in the National Danish Patient Register. Diagnostic procedures, such as endoscopy, manometry, pH- or impedance monitoring, are probably somewhat less well accounted for, which is reflected in the 10.2% of patients who underwent ARS without a prior upper endoscopy being registered. Gastrointestinal diseases, in general, have been shown to be correctly registered in the majority of cases within the National Danish Patient Register.11 Regarding the external validity of the data, the use of acid-suppressive therapy in Denmark has been close to the median use in Europe and similar to that seen in the other Scandinavian countries (range 53–60 DDD/1000 inhabitants/day in 2013). The rate of ARS procedures has been low compared to countries like Sweden and USA (the rate of re-surgery is, however, similar to that seen in the US). It is possible, that countries with a higher rate of ARS may have different attitudes towards pre-surgical acid-suppressive therapy in patients opting for ARS.

Kamolz and co-workers analysed compliance to acid-suppressive therapy before ARS in a single centre setting and found that 22% were non-compliant16. We considered taking less than standard dose every other day as inadequate, and found an even larger group of patients (35.1%) that may have been insufficiently treated before choosing surgery. Furthermore, our data do not suggest that patients had already tried and given up on daily acid-suppressive therapy in the years before considering ARS, as more than 85% of those on inadequate dosing in the year before surgery had not used acid-suppressive therapy in doses ≥180 DDD per year in the past 5 years.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Probability for redeeming of prescriptions for &lt;180 DDD and 0 DDD of acid-suppressive therapy in the year before index ARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>&lt;180 DDD</td>
</tr>
<tr>
<td>Women</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Men</td>
<td>1.13 [0.96–1.34]</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>18–39</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>40–59</td>
<td>0.65 [0.54–0.78]</td>
</tr>
<tr>
<td>≥60</td>
<td>0.57 [0.45–0.72]</td>
</tr>
<tr>
<td>Period of ARS</td>
<td></td>
</tr>
<tr>
<td>2000–2003</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>2004–2007</td>
<td>0.80 [0.66–0.97]</td>
</tr>
<tr>
<td>2008–2012</td>
<td>0.59 [0.48–0.72]</td>
</tr>
<tr>
<td>Procedures</td>
<td></td>
</tr>
<tr>
<td>No man/pH/imp</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Yes man/pH/imp</td>
<td>0.63 [0.51–0.77]</td>
</tr>
<tr>
<td>Use of NSAID or anti-platelet</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Yes</td>
<td>0.75 [0.62–0.90]</td>
</tr>
</tbody>
</table>

DDD, defined daily dose; Man/pH/imp, manometry, pH- or impedance monitoring; NSAID, non-steroidal anti-inflammatory drugs.

ORs are adjusted for gender, age, period, procedure, use of NSAID/antiplatelet and surgical centre. Data presented as odds ratios [95% confidence interval]. Pre-surgical procedures are performed within 3 years before index ARS. Use of NSAID or anti-platelet drugs is defined as redeeming of at least one prescription of NSAID or anti-platelet drugs within 1 year before index ARS.

nia and both diagnosis were given to 1030 (54.4%). Of those, who redeemed 0 DDD in the year before index ARS (n = 337), 89 (26.4%) were diagnosed with only GERD, 38 (11.3%) with only hiatal hernia, both diagnosis were given to 116 (34.4%) and none of them were given to 94 (27.9%).

Of patients undergoing ARS in 2000–2009 (n = 2239), 111 (5.0%) underwent repeated ARS procedures within 3 years following index ARS. Of these, 76 (68.5%) had redeemed ≥180 DDD of acid-suppressive therapy in the year before surgery and 79 (71.2%) had undergone pre-surgical manometry, pH- or impedance monitoring.

DISCUSSION

In this nationwide register-based study, the use of acid-suppressive therapy before anti-reflux surgery was deemed insufficient in one-third of the patients. Thus, only 65% had used acid-suppressive therapy equalling standard dosing at least every other day in the year before surgery. It is surprising that so many patients had not tried adequate medical therapy before choosing ARS,
The high number of patients not using acid-suppressive therapy in adequate doses in our study may raise concern for several reasons. Patients opting for surgery are recommended to first try to manage their symptoms with medical therapy, as it has been an important inclusion criteria for most trials comparing ARS with acid-suppressive medicine.\textsuperscript{18–22} In fact, most of these trials have only included patients with a satisfactory response to acid-suppressive therapy. Also, side effects to ARS, although often mild, are common: Dysphagia, impaired ability to belch and rectal flatulence have been shown to persist for several years after surgery.\textsuperscript{23} Add to this the rare, but serious, complications to surgery such as infection, bleeding and perforations. Whether patients on low pre-surgical dosing may experience a lesser effect of ARS cannot be determined from our results, but in general non-compliance to acid-suppressive drugs makes it difficult to weigh the pros and cons of a surgical intervention, intended to be an alternative to failed medical therapy. Previously, we have shown that 25% of the Danish ARS patients, who were not using any PPI in the year before ARS, went on to take up long-term PPI use (≥180 DDD per year) following surgery.\textsuperscript{4} Many of these patients could possibly have been managed on medical therapy alone and thereby avoided surgery.

Several factors were associated with inadequate dosing of acid-suppressive therapy in our logistic regression analysis. The higher probability for patients undergoing ARS in the earlier years (2000–2003) could be explained by the general increase in PPI use throughout the study period, its lower price in recent years and, finally, the recently emerged possibility of crosschecking the patient’s pharmacy dispensings. Some of the younger patients in our population may have been offered ARS in order to avoid long-term medical therapy, although their symptoms were sufficiently controlled on medication. In these patients, total compliance to medical therapy may have been considered less important and this may contribute to the increased probability for inadequate dosing in this age group. In Denmark, no national guideline for ARS is available, but most surgical centres recommend manometry in all patients and pH monitoring in patients with non-erosive reflux disease. Still, the number of patients, who did not undergo manometry, pH- or impedance monitoring in our study was high compared to some previous clinical trials,\textsuperscript{20, 22} highlighting the well-known differences between everyday clinical practice and the rigid frameworks in a clinical trial setting. Whether the proportion of patients, who underwent pre-surgical diagnostic procedures, is satisfactory cannot be estimated from register-based data only. Particularly, we had no detailed data regarding the findings on endoscopy (e.g. erosive esophagitis), which could otherwise qualify the need for pH monitoring on an individual level. However, if we assume that the majority of patients, who did not use any acid-suppressive therapy before surgery, were without erosive erosions on endoscopy, it is remarkable that only half of these (146/284; 51.4%) underwent pH monitoring before surgery. In general, we found an association between inadequate dosing of acid-suppressive therapy and not undergoing pre-surgical manometry, pH- or impedance monitoring. No obvious explanation can be given for this finding.

A diagnosis of GERD was not registered in 39.2% (132/337) of the patients, not using any pre-surgical acid-suppressive therapy, and 11.3% (38/337) were registered as having only hiatal hernia. A minority of these patients, although registered as undergoing ARS, may have been operated because of a large hiatal hernia without troublesome GERD necessitating acid-suppressive therapy. Our data did not allow us to identify patients undergoing ARS primarily because of regurgitation without other reflux-related symptoms or findings, such as erosive esophagitis. These patients may not benefit sufficiently from acid-suppressive therapy, which may contribute to the high proportion of patients not using adequate dosing. Finally, our data did not suggest that pre-surgical compliance to acid-suppressive therapy was related to the need for repeated ARS procedures, as the proportion of patients using ≥180 DDD of acid-suppressive therapy did not differ notably between the entire study population and the sub-sample, who underwent repeated ARS.

In conclusion, using nationwide registered data, we have found that the number of patients on inadequate dosing of acid-suppressive therapy before anti-reflux surgery was much higher than previously shown, although the number decreased in more recent years. Young age and lack of pre-surgical manometry, pH- or impedance monitoring were associated with inadequate dosing. Compliance to acid-suppressive therapy should be evaluated thoroughly before planning anti-reflux surgery in order to select the patients that may benefit the most from this procedure.

\textbf{AUTHORSHIP}

\textbf{Guarantor of the article:} Anders Lødrup.

\textbf{Author contributions:} All authors participated in planning the study, interpreting the data and drafting the manuscript. Anton Pottegaard collected and analysed the data. Anders Lodrup, Anton Pottegaard, Jesper Hallas and Peter Bytzer have all approved the final draft submitted including the authorship list.
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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Details of coding in health related registers.

Appendix S2. Number of prescriptions for the different acid-suppressive drugs redeemed in the year before ARS by the study population.

References