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*,¶

*Department of Medicine, Køge University Hospital, Køge, Denmark.
†Diagnostic Center, Silkeborg Hospital, Silkeborg, Denmark.
‡Clinical Pharmacology, Department of Public Health, University of Southern Denmark, Odense, Denmark.
§Department of Clinical Chemistry & Pharmacology, Odense University Hospital, Odense, Denmark.
¶Department of Clinical Medicine, Copenhagen University, Copenhagen, Denmark.

Correspondence to:
Dr A. Lødrup, Diagnostic Center, Silkeborg Hospital, Falkevej 3, Silkeborg DK-8600, Denmark.
E-mail: loedrup.ab@gmail.com

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 H_2-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 life-long 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, al\though 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 pre-surgical 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 (H$_2$RA). 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 pre-surgical 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 H$_2$RAs 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 1 | PPIs and H$_2$RAs with marketing authorisation in Denmark during the years 2000–2012

Drug	ATC code	DDD (mg)
Omeprazole	A02BC01	20
Pantoprazole	A02BC02	40
Lansoprazole	A02BC03	30
Rabeprazole	A02BC04	20
Esomeprazole	A02BC05	30
Cimetidine	A02BA01	800
Ranitidine	A02BA02	300
Famotidine	A02BA03	40
Nizatidine	A02BA04	300

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 H$_2$RAs 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.[8] 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 laproscopically 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 H_2RA 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 H_2RA (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

Table 2 | All patients grouped according to number of defined daily dose (DDD) of redeemed of prescriptions on acid-suppressive therapy in the year before index ARS

	0 DDD 337 (11.5%)	1–89 DDD 340 (11.6%)	90–179 DDD 350 (12.0%)	≥180 DDD 1895 (64.9%)	All patients 2922 (100.0%)
Gender					
Women	146 (11.3%)	143 (11.0%)	127 (9.8%)	879 (67.9%)	1295 (44.3%)
Men	191 (11.7%)	197 (12.1%)	223 (13.7%)	1016 (62.4%)	1627 (55.7%)
Age					
18–39	112 (14.2%)	120 (15.2%)	120 (15.2%)	435 (55.3%)	787 (26.9%)
40–59	162 (10.8%)	162 (10.8%)	169 (11.3%)	1001 (67.0%)	1494 (51.1%)
≥60	63 (9.8%)	58 (9.0%)	61 (9.5%)	459 (71.6%)	641 (21.9%)
Period of ARS					
2000–2003	100 (9.6%)	158 (15.2%)	153 (14.7%)	627 (60.4%)	1067 (36.5%)
2004–2007	72 (8.0%)	112 (12.5%)	112 (12.5%)	601 (67.0%)	923 (31.6%)
2008–2012	71 (8.0%)	70 (7.8%)	85 (9.5%)	667 (74.7%)	932 (31.9%)
Procedures					
Yes man/pH/imp	233 (10.7%)	228 (10.4%)	258 (11.8%)	1465 (67.1%)	2184 (74.7%)
No man/pH/imp	104 (14.1%)	112 (15.2%)	92 (12.5%)	430 (58.3%)	738 (25.3%)
Drug use					
NSAID	118 (16.0%)	78 (10.6%)	80 (10.9%)	460 (62.5%)	736 (25.2%)
Anti-platelet	21 (9.1%)	14 (6.1%)	19 (8.3%)	176 (76.5%)	230 (7.9%)

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

Data are presented with n and horizontal percentages except for the column 'All patients', which is presented with vertical percentages. Pre-surgical procedures were performed within 3 years before index ARS. Use of NSAID or anti-platelet drugs was defined as redeeming of at least one prescription of NSAID or anti-platelet drugs within 1 year before index ARS.
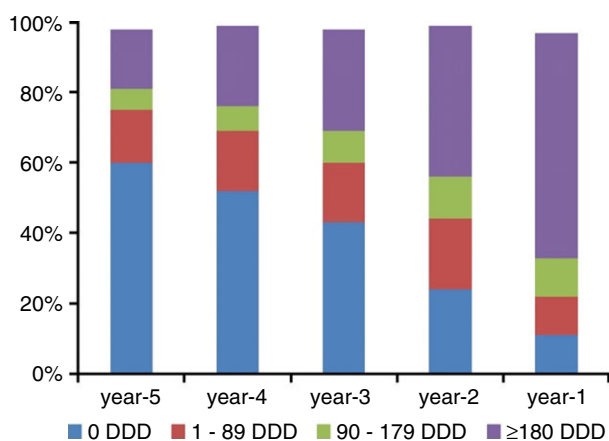
Figure 1 | Use of acid-suppressive therapy five to one year before anti-reflux surgery. Data presented as proportion redeeming 0, 1–89, 90–179 and 180 defined daily dose (DDD) of acid-suppressive therapy from 5 to 1 years before index ARS. *Y*-axis: % of patients, *X*-axis: years before index ARS.

(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 H$_2$RAs, 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-

Table 3 | Probability for redeeming of prescriptions for <180 DDD and 0 DDD of acid-suppressive therapy in the year before index ARS

	<180 DDD	0 DDD
Gender		
Women	1.00 (ref.)	1.00 (ref.)
Men	1.13 [0.96–1.34]	0.95 [0.72–1.25]
Age		
18–39	1.00 (ref.)	1.00 (ref.)
40–59	0.65 [0.54–0.78]	0.84 [0.62–1.15]
≥60	0.57 [0.45–0.72]	0.83 [0.56–1.23]
Period of ARS		
2000–2003	1.00 (ref.)	1.00 (ref.)
2004–2007	0.80 [0.66–0.97]	0.91 [0.66–1.25]
2008–2012	0.59 [0.48–0.72]	0.89 [0.64–1.25]
Procedures		
No man/pH/imp	1.00 (ref.)	1.00 (ref.)
Yes man/pH/imp	0.63 [0.51–0.77]	0.56 [0.41–0.77]
Use of NSAID or anti-platelet		
No	1.00 (ref.)	1.00 (ref.)
Yes	0.75 [0.62–0.90]	0.51 [0.36–0.72]

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,

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 H_2RAs constitutes only 2% of the total sale of acid-suppressive medicine in Denmark, which we consider without significance for our results.[9] Surgical procedures, such as fundoplication, are generally correctly registered (>90% of registered cases) in the National Danish Patient Register.[10] 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).[12, 13] 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).[14, 15] 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-compliant.[16, 17] 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.

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.[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.[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.[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,[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.

AUTHORSHIP

Guarantor of the article: Anders Lødrup.

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

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

1. Kahrilas PJ, Shaheen NJ, Vaezi MF. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology* 2008; **135**: 1392–413.

2. Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc* 2010; **24**: 2647–69.

3. Wileman SM, McCann S, Grant AM, Krukowski ZH, Bruce J. Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database Syst Rev* 2010; **28**: CD003243.

4. Lødrup A, Pottegård A, Hallas J, Bytzer P. Use of proton pump inhibitors after antireflux surgery: a nationwide register-based follow-up study. *Gut* 2014; **63**: 1544–9.

5. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; **39**: 30–3.

6. Private and Public Healthcare System in Denmark (Privat /offentligt samspil i sundhedsvæsenet). Published by The Danish National Institute for Research in the Municipalities and Regions. Available from www.KORA.DK. Accessed date 26 April 2015.

7. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; **39**: 38–41.

8. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; **39**: 22–5.

9. Total sale of PPI and H2RA in Denmark 1996 – 2012. Danish National Institute for Health Data and Disease Control. Available at: www.medstat.dk/en (accessed 20 February 2014).

10. Validation of the Danish Patient Register regarding obstetric research and quality assurance. The Danish Health and Medicine Authority 2003. Available at: www.sundhedsstyrelsen.dk (accessed 10 December 2014).

11. Nickelsen TN. Data validity in the Danish Patient Register. *Danish Med Assoc* 2002; **164**: 33–7.

12. Cross-National Comparison of Drug Utilisation activities. The European branch of the Special Interest Group for Drug Utilization Research (SIGDUR) Available at: www.pharmacoepi.org (accessed 10 December 2014).

13. Total sale of PPI and H2RA in Denmark, Norway and Sweden 2013. Danish National Institute for Health Data and Disease Control, Drug Consumption in Norway, The Swedish National Board of Health and Welfare. Available at: www.medstat.dk, www.legemiddelforbruk.no, www.socialstyrelsen.se (accessed 25 February 2015).

14. Dutta S, Bamehriz F, Boghossian T, Pottruff CG, Anvari M. Outcome of laparoscopic redo fundoplication. *Surg Endosc* 2004; **18**: 440–3.

15. Zhou T, Harnsberger C, Broderick R, *et al*. Reoperation rates after laparoscopic fundoplication. *Surg Endosc* 2014; **29**: 510–4.

16. Kamolz T. Analysis of medical compliance in gastro-oesophageal reflux disease patients referred to pre-surgical examination. *Dig Liver Dis* 2002; **34**: 183–9.

17. Kamolz T, Granderath FA, Pointner R. The outcome of laparoscopic antireflux surgery in relation to patients' subjective degree of compliance with former antireflux medication. *Surg Laparosc Endosc Percutan Tech* 2003; **13**: 155–60.

18. Lundell L, Miettinen P, Myrvold HE, *et al*. Long-term management of gastro-oesophageal reflux disease with omeprazole or open antireflux surgery: results of a prospective, randomized clinical trial. The Nordic GORD Study Group. *Eur J Gastroenterol Hepatol* 2000; **12**: 879–87.

19. Pessaux P, Arnaud J-P, Delattre J-F, Meyer C, Baulieux J, Mosnier H. Laparoscopic antireflux surgery: five-year results and beyond in 1340 patients. *Arch Surg* 2005; **140**: 946–51.

20. Lundell L, Attwood S, Ell C, *et al*. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. *Gut* 2008; **57**: 1207–13.

21. Grant AM, Wileman SM, Ramsay CR, *et al*. Minimal access surgery compared with medical management for chronic gastro-oesophageal reflux disease: UK collaborative randomised trial. *BMJ* 2008; **337**: a2664.

22. Anvari M, Allen C, Marshall J, *et al*. A randomized controlled trial of laparoscopic Nissen fundoplication versus proton pump inhibitors for the treatment of patients with chronic gastroesophageal reflux disease (GERD): 3-year outcomes. *Surg Endosc* 2011; **25**: 2547–54.

23. Lundell L, Miettinen P, Myrvold HE, *et al*. Seven-year follow-up of a randomized clinical trial comparing proton-pump inhibition with surgical therapy for reflux oesophagitis. *Br J Surg* 2007; **94**: 198–203.