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Use of proton pump inhibitors after antireflux surgery: a nationwide register-based follow-up study

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ABSTRACT

Objective Antireflux surgery (ARS) has been suggested as an alternative to lifelong use of proton pump inhibitors (PPI) in reflux disease. Data from clinical trials on PPI use after ARS have been conflicting. We investigated PPI use after ARS in the general Danish population using nationwide healthcare registries.

Design A nationwide retrospective follow-up study of all patients aged ≥18 and undergoing first-time ARS in Denmark during 1996–2010. Two outcome measures were used: redemption of first PPI prescription after ARS (index prescription) and a marker of long-term use, defined by an average PPI use of ≥180 defined daily doses (DDDs) per year. Kaplan–Meier curves and Cox proportional hazards model were used for statistics.

Results 3465 patients entered the analysis. 12.7% used no PPI in the year before surgery, while 14.2%, 13.4% and 59.7% used 1–89 DDD, 90–179 DDD and ≥180 DDD, respectively. Five-, 10- and 15-year risks of redeeming index PPI prescription were 57.5%, 72.4% and 82.6%, respectively. Similarly, 5-, 10- and 15-year risks of taking up long-term PPI use were 29.4%, 41.1% and 56.6%. Female gender, high age, ARS performed in most recent years, previous use of PPI and use of nonsteroidal anti-inflammatory drugs or antiplatelet therapy significantly increased the risk of PPI use.

Conclusions Risk of PPI use after ARS was higher than previously reported, and more than 50% of patients became long-term PPI users 10–15 years postsurgery. Patients should be made aware that long-term PPI therapy is often necessary after ARS.

Significance of this study

What is already known on this subject?

- Antireflux surgery is an established alternative to medical therapy for GORD.
- Antireflux surgery is considered in some patients, despite successful medical management, due to quality-of-life considerations.
- In clinical trial settings, the use of proton pump inhibitor (PPI) after surgery has varied considerably.

What are the new findings?

- Use of PPI after surgery was much higher than previously reported.
- More than 50% of operated patients became long-term PPI users 10–15 years after surgery.
- A high proportion of patients used PPI in insufficient doses before surgery.

How might it impact on clinical practice in the foreseeable future?

- Patients considering antireflux surgery should be informed of the high risk of long-term PPI use postsurgery.
- Surgeons should consider checking PPI compliance before deciding on antireflux surgery.

INTRODUCTION

Antireflux surgery (ARS) is an established alternative to medical treatment for severe GORD.[1] Reduction in the use of acid-suppressive medicine, notably proton pump inhibitors (PPI), is an important reason why ARS is recommended for some GORD patients. Surgery is recommended to avoid the drawbacks of polypharmacy and the reduction in quality of life that many patients associate with having to use medication.[2] Another aspect is the continuing increase in long-term use of PPI and the possible adverse effects this may lead to, such as enteric infections, fractures and nutritional deficiencies.[3–8] Finally, ARS has been reported to be more cost-effective compared with long-term PPI therapy.[9]

In clinical trials, the risk of PPI use after ARS has varied between 12% and 44% with follow-up periods from 1 to 12 years, with a tendency towards increased risk of PPI use with longer follow-up.[10–16] However, PPI use has rarely been accounted for in detail and, to our knowledge, no studies have validated the rate of PPI use seen in the trials by cross-checking with prescription databases. More importantly, use of PPI after ARS in routine care, outside the rigorous conditions of randomised trials, has not been investigated.

Denmark has a tax-supported healthcare system enabling national health-related registers to present validated data of a geographically well-defined area and not just from single hospital centres. Using these registers, we sought to describe the use of PPI after ARS in the Danish general population in the period 1996–2010. The primary aim of the study was to estimate the proportion of ARS patients who redeemed prescriptions of PPI or who took up long-term PPI use after ARS. The secondary aim was to investigate factors that might predict the use of PPI after ARS.

DESIGN

The analysis was conducted as a population-based, descriptive follow-up study of patients undergoing

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first-time ARS during the period 1 January 1996 to 31 December 2010.

Data sources

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

The Danish National Patient Registry contains data on all non-psychiatric hospital admissions since 1977 and data on outpatient contacts since 1995. Discharge diagnoses are coded according to the International Classification of Disease V.10 (ICD-10) since 1994, and surgical procedures are coded according to the Nordic Classification of Surgical Procedures (NCSP) since 1996.[17] In Denmark, ARS has not been a high-volume procedure in the private hospital sector and less than 0.5% of all ARS have been performed at private hospitals.[18] The Danish National Registry of Patients therefore allows true population-based study regarding ARS.

The Danish National Prescription Registry contains data on all prescription drugs redeemed by Danish citizens since 1995. Drugs are categorised according to the Anatomical Therapeutic Chemical (ATC) index. Prescription data include the date of dispensing, the substance, the brand name and the quantity expressed by the defined daily dose (DDD).[19 20]

The Danish Person Registry contains data on vital status (date of death) and migrations in and out of Denmark.[21]

All data sources were linked by use of the Central Person Registry number, a unique identifier assigned to all Danish citizens since 1968 that encodes gender and date of birth.[21] All linkage occurred within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes.

Patients and follow-up

We extracted data for all patients who had undergone ARS in the period 1996–2010. Since fundoplication is by far the most commonly used method for ARS, we restricted our analyses to this type of operation. Only patients with first-time elective ARS (index ARS) coded as either open fundoplication (JBC00) or laparoscopic fundoplication (JBC01), and who were ≥18 years at surgery, were eligible for the study. Eligible patients were followed from their index ARS to the end of follow-up (31 December 2011) or time of censoring, whichever came first. Patients were censored on day of death, day of emigration or day of repeated ARS (re-ARS) after their index ARS.

Use of PPI

Data on all redeemed prescriptions for eligible patients were extracted from 1995 to 2011. Index prescription of PPI (ATC: A02BC) was defined as the first PPI prescription redeemed more than 30 days after the index ARS. This precaution was taken because of the assumption that some patients may have been discharged after surgery with a prescription of PPI, 'just to be on the safe side'. Use of PPI in the year before index ARS was categorised as use of 0 DDD, 1–89 DDD, 90–179 DDD and ≥180 DDD.

Long-term use of PPI

Long-term use of PPI was defined as an average of at least 0.5 DDD per day (equalling an average of 180 DDD per year) from a given date until end of follow-up. The first date fulfilling this criterion was considered start of long-term use. It was not necessarily synchronous with index PPI prescription, but could occur later, whenever the criteria were fulfilled during follow-up.

STATISTICS

Simple descriptive statistics with 95% CIs were used to present proportion redeeming index PPI prescription and taking up long-term PPI use.

We constructed Kaplan–Meier curves for the cumulative risk of redeeming an index prescription of PPI and for the cumulative risk of taking up long-term PPI use. Kaplan–Meier curves were created, stratified by the year of ARS in order to account for a general increase in the use of PPI. The year of index ARS was stratified into 1996–2000, 2001–2005 and 2006–2010.

We used Cox proportional hazards model with the independent variables gender, age at surgery (10-year intervals), year of index ARS (5-year intervals), use of PPI in the year before ARS (0, 1–89, 90–179, ≥180 DDDs) and use of non-steroidal anti-inflammatory drugs (NSAIDs) or antiplatelet drugs to estimate HRs for index prescription of PPI and long-term use of PPI. Use of NSAID and antiplatelet drugs were included as time-dependent variables. Antiplatelet drugs were separated into clopidogrel and acetylsalicylic acid.

In order to assess how much our outcome was affected by the use of PPI as a prophylactic agent during NSAID or antiplatelet therapy, we performed two different sensitivity analyses. In the first analysis, patients were censored at time of redemption of an NSAID or antiplatelet prescription. In the second analysis, we excluded PPI prescriptions, which we defined as being associated with NSAID or antiplatelet prescriptions. By our definition, PPI prescription redeemed less than 7 days before prescriptions of NSAID or antiplatelet drugs were excluded, as well as PPI prescriptions redeemed during ongoing NSAID or antiplatelet therapy. Ongoing NSAID or antiplatelet therapy was defined from the prescriptions' data by assuming a daily intake of 0.8 DDD from the date of redemption. The latter analysis, by its design, could only be applied to outcomes regarding index PPI prescriptions.

RESULTS

In the period 1996–2010, 3642 patients underwent ARS, of which 177 (5%) were excluded because of rare procedure techniques (72) or because of age <18 at first-time surgery (105). The study population included 3465 patients (43% female, interquartile age range 18–60), of which 308 (8.9%) were censored before the end of follow-up because of death or emigration and 267 (7.8%) were censored because of re-ARS. A total

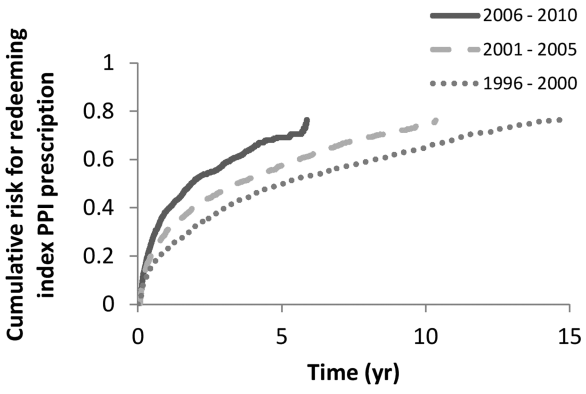

Figure 1 Cumulative risk for redeeming proton pump inhibitor (PPI) prescriptions after antireflux surgery (ARS). Kaplan–Meier curves for patients undergoing ARS in 1996–2010 stratified after period of surgery. *X*-axis: time in years. *Y*-axis: cumulative risk of redeeming index prescription of PPI.

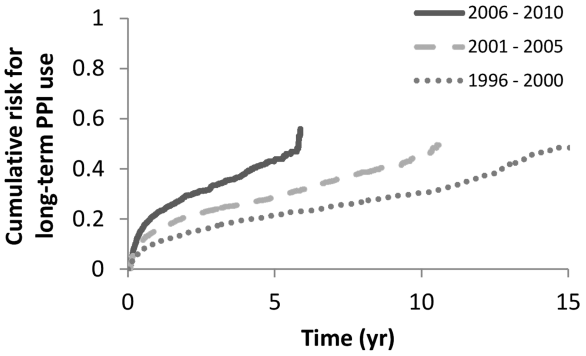

Figure 2 Cumulative risk for long-term proton pump inhibitor (PPI) use after antireflux surgery (ARS). Kaplan–Meier curves for patients undergoing ARS in 1996–2010 stratified after period of surgery. *X*-axis: time in years. *Y*-axis: cumulative risk of long-term use of PPI (defined as ≥180 defined daily dose/year).

of 1166 (33.7%) of eligible index ARS were performed in 1996–2000, 1324 (38.2%) in 2001–2005 and 975 (28.1%) in 2006–2010. Use of PPI in the year before index surgery was 0 DDD in 441 patients (12.7%), 1–89 DDD in 493 (14.2%), 90–179 DDD in 464 (13.3%) and ≥180 DDD in 2067 (59.7%).

An index prescription of PPI was redeemed by 2299 (66.4%, 95% CI 64.8 to 67.9). The 5-, 10- and 15-year cumulative risks for redeeming an index PPI prescription were 57.5% (95% CI 55.8 to 59.2), 72.4% (95% CI 70.7 to 74.2) and 82.6% (95% CI 79.9 to 85.1), respectively. Five-year risks of redeeming index PPI prescription were 49.7% (95% CI 46.8 to 52.6) for those operated in the period 1996–2000, 57.4% (95% CI 54.7 to 60.1) for those operated in the period 2001–2005 and 69.1% (95% CI 65.4 to 72.8) for those operated in the period 2006–2010. Kaplan–Meier curves for index PPI prescription, stratified after period of index ARS, are shown in figure 1.

Long-term use of PPI was taken up by 1335 (38.5%, 95% CI 36.9 to 40.2). The 5-, 10- and 15-year risks of taking up long-term PPI use were 29.4% (95% CI 27.8 to 31.0), 41.1% (95% CI 39.2 to 43.0) and 56.6% (95% CI 53.5 to 59.7), respectively. The 5-year risks of taking up long-term use of PPI were 21.5% (95% CI 19.2 to 24.0) for those operated in the period 1996–2000, 28.6% (95% CI 26.2 to 31.2) for those operated in the period 2001–2005 and 43.3% (95% CI 39.6 to 47.4) for those operated in the period 2006–2010. Kaplan–Meier curves for long-term use of PPI, stratified after period of index ARS, are shown in figure 2.

The risks of redeeming an index PPI prescription and of long-term use of PPI were significantly affected by gender, age at operation, year of index ARS, previous use of PPI and use of NSAID or antiplatelet drugs (table 1).

In the first sensitivity analysis on how outcome was affected by PPI therapy attributed to ulcer prophylaxis, patients were censored when they redeemed a prescription of NSAID or antiplatelet drugs. This resulted in a slight drop in the 5-year risk of redeeming index PPI prescription to 57.5% (95% CI 55.8 to 59.2) and a 5-year risk of taking up long-term PPI use of 27.3% (95% CI 25.3 to 29.5). The second sensitivity analysis showed that if we excluded PPI prescriptions associated with NSAID or antiplatelet prescriptions, the 5-year risk of redeeming index PPI prescription was 51.7% (95% CI 25.3 to 29.5). Kaplan–Meier curves for index PPI prescription and long-term use of PPI according to sensitivity analyses are shown in figures 3 and 4.

Table 1 HRs (95% CI) for redemption of index PPI prescription and for long-term use of PPI (defined as ≥180 DDD/year)

Variable	N	N index PPI prescription	HR index PPI prescription	N long-term PPI use	HR long-term PPI use
Gender					
Female	1473	1094	1.00 (ref)	688	1.00 (ref)
Male	1992	1205	0.69 (0.63 to 0.75)	647	0.65 (0.58 to 0.72)
Age at operation (years)					
≤40	1100	666	1.00 (ref)	323	1.00 (ref)
41–50	889	599	1.08 (0.96 to 1.21)	336	1.19 (1.02 to 1.39)
51–60	886	627	1.16 (1.03 to 1.29)	397	1.39 (1.20 to 1.62)
61–70	445	318	1.26 (1.10 to 1.45)	213	1.58 (1.32 to 1.90)
71–80	133	81	1.37 (1.08 to 1.74)	58	1.92 (1.44 to 2.57)
≥81	12	8	2.14 (1.06 to 4.35)	8	4.76 (2.32 to 9.76)
Year of index ARS					
1996–2000	1166	819	1.00 (ref)	460	1.00 (ref)
2001–2005	1324	902	1.28 (1.16 to 1.41)	523	1.59 (1.38 to 1.82)
2006–2010	975	578	1.65 (1.47 to 1.85)	352	2.25 (1.91 to 2.64)
Prior use of PPI					
0 DDD	441	255	0.63 (0.55 to 0.72)	125	0.50 (0.41 to 0.60)
1–89 DDD	493	282	0.63 (0.55 to 0.71)	129	0.50 (0.41 to 0.60)
90–179 DDD	464	286	0.74 (0.65 to 0.84)	132	0.55 (0.46 to 0.66)
≥180 DDD	2067	1476	1.00 (ref)	949	1.00 (ref)
Use of drugs					
NSAID			1.96 (1.74 to 2.20)		1.81 (1.55 to 2.11)
ASA			1.24 (1.05 to 1.46)		1.55 (1.30 to 1.86)
Clopidogrel			3.18 (2.05 to 4.91)		1.83 (1.13 to 2.95)

Age is categorised in intervals of 10 years, and year of index ARS is categorised in intervals of 5 years. Prior use of PPI, expressed in DDD in the year before index surgery, is categorised in four intervals. Use of NSAID, clopidogrel and acetylsalicylic acid (ASA) are time-dependent variables.
ARS, antireflux surgery; DDD, defined daily dose; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

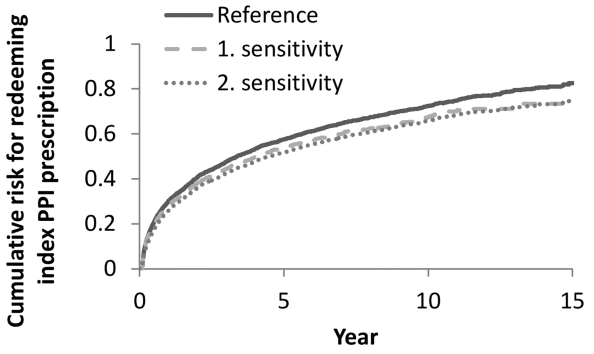

Figure 3 Cumulative risk for redeeming proton pump inhibitor (PPI) prescriptions, censored for presumed use as ulcer prophylaxis. Kaplan–Meier curves for patients undergoing antireflux surgery in 1996–2010. Data presented without sensitivity analyses (reference), censored at redemption of nonsteroidal anti-inflammatory drugs (NSAID) or antiplatelet prescription (1, sensitivity) and after exclusion of PPI prescriptions associated with NSAID or antiplatelet prescription (2, sensitivity). *X*-axis: time in years. *Y*-axis: cumulative risk of redeeming index prescription of PPI.

DISCUSSION

In this nationwide register-based study, risk of redeeming a PPI prescription after ARS was surprisingly high and more than half of the patients took up long-term PPI use within 10–15 years after the operation, which is substantially more than reported by clinical trials. Furthermore, a high proportion of patients used little or no PPI in the year before surgery.

The use of validated registers has allowed us to make precise estimates of the PPI use in a population that includes all patients undergoing ARS in Denmark from 1996 to 2010. It is a major strength of our study that we provide valid data from a population perspective reflecting clinical practice outside the rigid frameworks of a clinical trial. On the other hand, there are some limitations to our study: the rate of antireflux procedures in Denmark has traditionally been rather low. In the year 2000, six procedures were performed per 100 000 inhabitants, which was half the rate compared with Sweden ($13/10^5$) and the USA ($12/10^5$).[22–24] It is possible that our results are not fully representative for countries or regions with a higher rate of ARS procedures. Redeeming a prescription is not the same as taking the medicine,[25] and a minority of those, who redeemed an index PPI prescription, may not have taken the PPI, but we believe this would be the rare exception rather than the rule. Use of histamine 2-receptor antagonist (HR2A) was not accounted for in this study, nor was over-the-counter PPI. The vast majority of patients undergoing ARS in Denmark from 1996 to 2010 have been prescribed PPI rather than H2RA, as suggested by the sales figures[26] and in line with recommendations from expert reviews and guidelines.[27 28] However, since the sale of H2RAs has decreased during the study period, any effect of H2RA use on our outcome would be greatest in the beginning of the follow-up period, and this may contribute slightly to the differences we have found between rates of PPI use in the beginning and the end of follow-up. As for over-the-counter PPI, which has been available in Denmark since 2006 in small, non-reimbursed packages with below-standard doses that do not require a prescription, 98% of the total PPI sale in Denmark from 2009 to 2012 has been related to prescriptions.[29] Thus, any potential effect of over-the-counter PPI on our outcome would be minor—and would only add to the total PPI use. One major indication for ARS is volume reflux, where gastric contents reflux into the oesophagus or mouth, often without significant heartburn. Some of these patients have no effect of acid-suppressive medicine, and this may partly explain some of our findings regarding inadequate PPI therapy before surgery. Our data did not contain information regarding indication for surgery, such as symptoms and complications to acid reflux, so we were unable to determine the proportion of operations performed because of volume reflux. However, the low use of PPI therapy before surgery does not explain why so many redeemed PPI prescriptions after surgery.

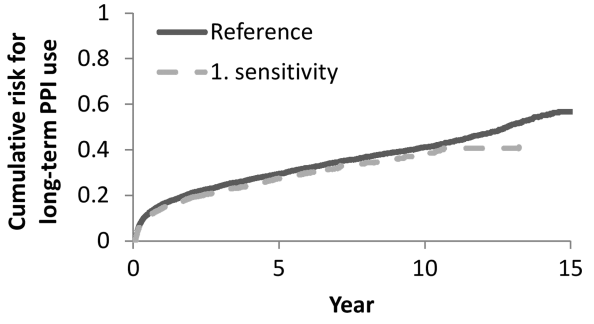

Figure 4 Cumulative risk for long-term proton pump inhibitor (PPI) use after antireflux surgery (ARS), censored for presumed use as ulcer prophylaxis. Kaplan–Meier curves for patients undergoing ARS in 1996–2010. Data presented without sensitivity analyses (reference) and after censoring at redemption of nonsteroidal anti-inflammatory drugs or antiplatelet prescription (1, sensitivity). *X*-axis: time in years. *Y*-axis: cumulative risk of long-term use of PPI (defined as ≥180 defined daily dose/year).

Use of PPI after surgery

We found the extent of the PPI use after ARS to be greater than previously shown in clinical trials,[10–16] of which the study with the longest follow-up of 12 years reported PPI use in 36% of patients.[15] Clinical trials regarding ARS have mostly monitored use of PPI at monthly or annual hospital visits, and, in the light of our findings, it is possible that undocumented use of PPI between hospital visits may have occurred. Furthermore, being part of a cohort in a clinical trial, where use of PPI is regarded as treatment failure, may make patients less liable to start PPI therapy—or to report it. Finally, in our study, the 5-year risk of long-term PPI use doubled from the beginning to the end of the follow-up period: from 22% in those operated from 1996 to 2000 to 43% in patients operated from 2006 to 2010. To our knowledge, the fundoplication procedure has not changed in a way that can explain this increase over time. The increase may be a reflection of a general trend among physicians towards prescribing more PPI,[30] for example, as routine refilling of prescriptions.

The high number of long-time PPI users found in our study challenges the results from clinical trials regarding the long-term effects of surgery compared with PPI, of which the majority has favoured surgery. More than 80% of patients undergoing ARS in the LOTUS trial reported control of heartburn and acid regurgitation at 5-year follow-up and this included no need for acid-suppressive medicine.[31] Five-year data from the REFLUX trial showed a mean score for reflux-related symptoms of ≥80 (out of 100; the higher the better), and use of PPI was seen in 27–44%.[13] Treatment failure at 12-year follow-up was seen in 47% of the patients undergoing ARS in the SOPRAN trial, which defined failure as a composite endpoint involving symptom severity, change in treatment (including use of PPI)

and need for re-surgery.[15] ARS was found to be equal to PPI therapy in the LOTUS trial, whereas both the REFLUX trial and the SOPRAN trial found ARS to be superior to PPI therapy in controlling symptoms. Furthermore, a cost–benefit analysis of the REFLUX trial data favoured ARS above PPI therapy.[32] Besides the individual clinical trials, one Cochrane meta-analysis[33] and one systematic review with meta-analysis[34] have found ARS to be superior to PPI therapy in controlling reflux-related symptoms, at least in the short to medium term. The PPI use after ARS found in our study may indicate that the risk of treatment failure after ARS is higher than the results from clinical trials might suggest, especially those studies where PPI use was a part of the definition of treatment failure. Another explanation could be that the results from studies performed on high-expertise centres may not be transferred directly to a broader clinical reality.

Admittedly, the use of PPI can only serve as a proxy for inadequate symptom relief after ARS. The vast majority of the postoperative PPI use seen in our study can probably be attributed to the same acid reflux symptoms that led to ARS to begin with. But a proportion of the PPI use may have been prescribed for symptoms with a less established association to acid reflux, for example, nausea, cough and meal-related discomfort. Some patients may even have been prescribed PPI for symptoms related to the surgery itself, for example, dysphagia. This kind of PPI therapy would not be considered as treatment failure. Furthermore, we were not able to identify the minority of patients who underwent ARS because of Barrett's oesophagus. Some of these patients may have been prescribed PPI after ARS, regardless of the presence of reflux symptoms.

Predicting PPI use after ARS

We found that female gender and high age increased the risk of PPI use after ARS. This is in agreement with previous findings regarding long-term use of PPI in the general population.[30]

Patients who did not use PPI in the year before surgery had a lower risk of any PPI use after surgery. However, 28% (125/441) of these patients took up long-term PPI use during follow-up, indicating that a proportion of these patients could have benefitted from PPI therapy before ARS and maybe even have been managed without surgery.

PPI is recommended as ulcer prophylaxis in some patients, who are prescribed NSAID or antiplatelet drugs,[35] and both NSAID and acetylsalicylic acid are known to cause dyspepsia, which might lead to PPI therapy.[36] This relationship was confirmed in our study, where use of NSAID, acetylsalicylic acid and clopidogrel all significantly increased the risk of PPI use after ARS. Monotherapy with clopidogrel is not strongly associated with upper gastrointestinal bleeding,[37] and it may have been preferred in patients in need of antithrombotic therapy with concomitant dyspeptic symptoms. These patients would also have a high risk of being prescribed a PPI, and this may, in part, explain the relationship between clopidogrel and PPI seen in our study.

We applied two models to test how our outcome was affected by PPI therapy, which could be attributed to ulcer prophylaxis: one conservative model, where all patients who redeemed a prescription of an NSAID or antiplatelet drug were censored. The other model was less conservative and only excluded patients whose prescription of NSAID or antiplatelet drugs was believed, owing to the temporal relationship, to be associated with a PPI prescription. Both sensitivity analyses showed 5-year risk rates and Kaplan–Meier curves very similar to the original results, and we conclude that the extensive use of PPI after ARS cannot be explained by the use of PPI as ulcer prophylaxis.

Use of PPI before surgery

Surprisingly, 40% of the patients used less than standard dose PPI every other day in the year leading up to surgery. Adequate PPI therapy is recommend before ARS in international guidelines,[27 38] and most of the trials that have tested the effect of ARS on reflux disease have only included patients who showed at least some response to PPI therapy. Most likely, our finding is explained by low compliance to medical therapy, which has previously been shown in GORD patients.[39] Especially patients with predominant regurgitation/volume reflux might have low compliance to PPI therapy since PPI is less effective in treating symptoms of regurgitation than heartburn.[40]

Implications of the study

Based on the findings from our study, we believe that patients considering ARS should be informed of the high risk of postsurgical long-term PPI use. Especially those who, according to the 2010 guidelines from American Gastrointestinal and Endoscopic Surgeons, "opt for surgery despite successful medical management (e.g., due to quality-of-life considerations, lifelong need for medication intake, expense of medications)".[38] If long-term PPI use after ARS is regarded as treatment failure, that is, as a proxy for inadequate symptom control, our study suggests that ARS may not be as effective as suggested by the outcomes from clinical trials. This does not necessarily mean that these patients will not benefit from ARS, but rather that ARS patients often need supplemental PPI therapy to achieve adequate symptom relief.

As for the lack of PPI use before ARS, one practical implication could be that surgeons might consider checking PPI compliance by pill count, enquire about prescription data or apply other measures before performing ARS.

CONCLUSION

In a population-based register study, we found that risk of using PPI 5 year after ARS was greater than 50% and increased to more than 80% during follow-up. The risk of becoming a long-term PPI user was more than 50%. The extent of PPI use was much greater than previously shown in clinical trials and suggested that the effect of ARS on reflux symptoms should be interpreted with caution. Patients should be made aware that long-term PPI therapy is often necessary after ARS.

Contributors All authors contributed to the development of the study concept, the study design, statistical analyses, interpretation of data, critical revision of the manuscript and final approval of the version to be published. AP and JH were responsible for data acquisition. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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