Title

Applying Long-term Follow-up to Improve Patient Selection in Laparoscopic Anti-reflux Surgery

Aim

The aim of this study is to use patient-reported and register-based long-term follow-up after anti-reflux surgery, to investigate treatment effect and use the results to establish a clinically applicable scoring system to ensure optimal selection of patients for surgical treatment of gastroesophageal reflux disease.

Background

Episodic reflux of gastric contests to the esophagus is physiological but is considered gastroesophageal reflux disease (GERD) when accompanied by bothersome symptoms, typically heartburn, regurgitation or retrosternal pain. Extra-esophageal symptoms such as asthma, laryngitis and chronic cough may also occur (1). GERD is a complex and multifaceted disease (2,3), affecting 10-20% of the Western population (4) and has been shown to significantly reduce the quality of life (5). Worldwide, the prevalence of GERD has been increasing (6–8).

Treatment of GERD consists of anti-secretory drugs, mainly proton pump inhibitors, or anti-reflux surgery. Laparoscopic anti-reflux surgery is considered standard of care in surgical treatment of gastro-esophageal reflux disease (9) and with careful patient selection based on thorough preoperative workup (10); symptom control and patient satisfaction are high compared to medical therapy (11,12).

Despite a tailored approach, laparoscopic anti-reflux surgery is not without risks of adverse effects, most notably disruption of the fundoplication, post-fundoplication dysphagia and gas-bloat-syndrome, in some cases leading to reoperation (13–18). Furthermore non-surgical factors such as pre-existing anxiety or depression disorders can influence postoperative satisfaction and symptom relief when compared to patients without concomitant psychological disorders (19).

Although few studies conclude that medical and surgical treatment of GERD have similar effectiveness, disease-specific quality of life generally improves after anti-reflux surgery and patient satisfaction is high. Depending on surgical procedure, the postoperative quality of life, ranges from significantly increased compared to preoperative measurements, to “normal” values as found in subjects devoid of GERD (20–33). 73-98% are satisfied with their condition after surgery and would choose surgery again (22,32–38).

Laparoscopic anti-reflux surgery is more effective than medical management with regard to short to medium length follow-up (12,34,35). Few studies provide long-term follow-up. After ten years, the benefits of surgery seem to decrease, but there is still a significant improvement in quality of life compared to preoperative measurements (36,39). Known causes of dissatisfaction are postoperative complication, redo-fundoplication and developing new bothersome symptoms such as gas-bloat and dysphagia combined with inadequate symptom relief (37,40).

Follow-up of randomized clinical trials have demonstrated, that anti-reflux surgery patients use acid suppressing drugs, primarily proton pump inhibitor (PPI) therapy at postoperative follow-up. Use have been considered minimal with <20% using PPI-therapy (35) and 27-44% using PPI at five-year follow-up (38). A recent register-based study (41), demonstrated a greater number of redeemed prescriptions of proton

pump inhibitor after primary anti-reflux surgery, than previously known. Five-, 10- and 15-year risks of long-term PPI use were 29.4%, 41.1% and 56.6%. However, this register-based study could not examine whether patients had objective recurrence of reflux disease and also did not examine indication for treatment as well as prescribing physician. From 2001 to 2011, 94,4% of PPI where prescribed in primary care (42) and it is unknown why post-fundoplication patients are prescribed PPI. It has previously been demonstrated, that the use of acid suppressing drugs after anti-reflux surgery does not necessarily correlate with abnormal acid exposure to the esophagus (43,44). In general, the use of PPI has increased rapidly in Denmark, rising 243% from 2001 to 2011 despite more restrictive guidelines and changes in reimbursement (42). As the majority of proton pump inhibitors are prescribed by general practitioners and not by the surgical centers, surgeons have very little knowledge of this aspect of life following anti-reflux surgery.

This study is part of the PhD project entitled: "Utilization, outcome and development of laparoscopic anti-reflux surgery" originating from the University of Southern Denmark (Protokol #: SDUSF-2016-115-(682)).

Methods and analysis

The study is a retrospective cohort study utilizing data from patient records and follow-up with patient-reported quality of life as well as registry-based data.

Study population

The study population consists of all adult patients (age $\geq$18) having undergone laparoscopic anti-reflux surgery (Nomesco Classification of Surgical Procedures (NCSP) (45): KJBC01) from January 1, 2002 to December 31, 2013 in The Department of Surgery, Kolding Hospital, a part of Lillebaelt Hospital Denmmark (n=557). Patients will be identified through Lillebaelt Hospital's Patient Administrative System. Day of surgery will be considered index date.

Date of follow-up will be the date, patient filled out quality of life questionnaires as described below. For patients deceased since index date, permission to include data from electronic patient records and registry-based data will be applied for from The Danish Patient Safety Authority.

All patients will be contacted by the existing Danish national digital communication system (e-Boks) and asked to participate in the study. Patients exempt from using the system, will be contacted by letter. Only patients providing informed consent will be included in the study.

Data sources

Data for the study will consist of electronic patient records, follow-up with patient-reported quality of life measurements and registry-based data.

Electronic patient records

From the electronic patient records, the following data will be identified: age (years), sex (male/female), body mass index (kg/m^2), alcohol consumption (drinks of 12g ethanol per week), tobacco use (current, former or never-smoker), ASA-score, Charlson Comorbidity Index (CCI) (46) and previous abdominal surgery (yes/no).

Preoperative endoscopically verified occurrence of hiatal hernia (yes/no), esophagitis (yes/no) will be included as well as, from 24-hour pH-measurement and esophageal manometry, reflux-index (%), symptom correlation (%) and presence of esophageal motility disorder (hypomotility, normal motility or hypermotility). Patients preoperative reflux symptoms defined as typical symptoms (yes/no), atypical symptoms (yes/no) and dysphagia (yes/no) are included as are surgical data included duration of surgery (minutes), type of fundoplication (270° Toupet/360° Nissen), Length of hospital stay (days), per- and postoperative complications registered within 30 days as defined by Clavien-Dindo (47).

Quality of life follow-up

Patients will be contacted as described above and asked to answer validated questionnaires regarding disease-specific quality of life (GERD-HRQL) (48) and dysphagia (Dysphagia Handicap Index) (49). Patients will also be asked if they are currently taking PPI (yes/no), in what dosage (never/when needed/once daily/twice daily), which symptoms have warranted PPI-use (reflux symptoms/dysphagia/gastritis/preemptive against peptic ulcer disease/other) and which physician prescribed the drug (general practitioner/surgeon/other doctor at hospital/other specialist in private practice)

Registries

All Danish inhabitant are issued with a civil registry number at birth or at date of moving to Denmark. The civil registry number are a unique personal identifier and is used across a variety of nationwide databases with regards to health, financial and educational data. Data from the following nationwide Danish registries will be included in the study:

The National Patient Registry (NPR) on re-operative surgery (NCSP: KJBC00-02, KJBW96-98, KJBB00-01, KJBB96-97) and endoscopy (NCSP: KUJD02-05, KJCA55) during follow-up). NPR contains records of all discharge diagnosis since 1977 and all outpatient diagnosis since 1994 (50,51). All performed procedures, including endoscopies and surgeries are also registered using NCSP.

The National Patient Registry of Psychiatry (NPR-PSYK) on psychiatric diagnoses (ICD-10: F01-F99) in a two-year period before primary surgery. NPR-PSYK is a sub-registry of NPR and specifically contains records of all psychiatric discharge and outpatient diagnosis from psychiatric departments since 1995 (50,51).

The Civil Registry on marital status, 90-day mortality after primary surgery and all-cause mortality during follow-up. The Danish Civil Registry maintains complete records of births, deaths, civic status and emigration status of the entire Danish population based on civil registration number (52).

The Danish National Prescription Registry on use of anti-reflux medication (ATC: A02BA, A02BC, A02BX), anti-thrombotic treatment (ATC: B01A), non-steroid anti-inflammatory drugs (NSAID) (ATC: M01A) and selective serotonin reuptake inhibitors (SSRI) (ATC: N06AB) in a time period beginning two years before surgery and ending at end of follow-up. The Danish National Prescription Registry contains information on all sale of prescription drugs including date of sale, Anatomical Therapeutic Chemical Classification (ATC) code, civil registration number of buyer and package volume since 1994 (53).

Statistics Denmark on educational level at time of primary surgery (54) defined by ISCED (55), occupation status (employed/unemployed/retired) (56) and equivalent annual income in the year preceding primary surgery (57).

Primary outcome

Primary outcome of the study is treatment success or failure, with failure defined for each patient as at least one of the following statements being fulfilled:

1. Having undergone reoperation (NSCP: KJBC00-02, KJBW96-98, KJBB00-01, KJBB96-97) between index date and end of follow-up.
2. Having filled prescription of >60 DDD/year of PPI in any year between index date and end of follow-up.
3. Having no measure $\geq$3 on GERD-HRQL indicating symptoms being bothersome every day.
4. Having no measure $\geq$4 on Dysphagia Handicap index indicating symptoms being a moderate problem.

Date of failure will be defined as follows: In case of 1), date of failure will be date of reoperation. In case of 2), date of failure will be date of first prescription filled in the year, where >60 DDD of PPI are filled. In case of 3) or 4), date of failure will be end of follow-up.

Secondary outcomes

Secondary outcome will be 90-day mortality after primary surgery, rate of reoperation, use of PPI in DDD/year, use of PPI at follow-up (including indication and prescribing physician) and Quality of life defined by GERD_HRQL, Dysphagia Handicap Index.

Statistical analysis

Contingency tables

Contingency tables will be created listing:

1) Patient characteristics: Age (median), sex (male/female), body mass index (kg/m^2), alcohol consumption (drinks of 12g ethanol per week), tobacco use (current, former or never-smoker), ASA-score, CCI, preoperative psychiatric diagnoses, use of anti-reflux medication (yes/no), NSAID (yes/no) and SSRI before surgery (yes/no) and previous abdominal surgery (yes/no), educational level at time of primary surgery (ISCED), occupation status (employed/unemployed/retired) and equivalent annual income in the year preceding primary surgery.
2) GERD characteristics: Symptom profile: typical symptoms (yes/no), atypical symptoms (yes/no) and dysphagia (yes/no), endoscopically verified occurrence of hiatal hernia (yes/no), esophagitis (yes/no), measures from 24-hour pH-measurement and esophageal manometry: reflux-index (%), symptom correlation (%) and presence of esophageal motility disorder (hypomotility, normal motility or hypermotility).

3) Operative characteristics: Duration of surgery (minutes), type of fundoplication (270° Toupet/360° Nissen), length of hospital stay (days), per- and postoperative complications registered within 30 days as defined by Clavien-Dindo and 90-day mortality.
4) Follow-up: Rate of reoperation (%), use of PPI in DDD/year, use of PPI at follow-up (including indication and prescribing physician), GERD-HRQL and Dysphagia Handicap Index.

Categorical and continuous variables will be compared using Chi^2, Fisher's Exact Test and Kruskal-Wallis-test where appropriate.

Cox regression

Cox regression will be performed with treatment success as dependent variable, time to end of follow-up (as defined above) and the following variables will be tested and included as independent variables where appropriate: Age (median), sex (male/female), body mass index (kg/m^2), alcohol consumption (drinks of 12g ethanol per week), tobacco use (current, former or never-smoker), ASA-score, CCI, preoperative psychiatric diagnoses, use of anti-reflux medication (yes/no), NSAID (yes/no) and SSRI before surgery (yes/no) and previous abdominal surgery (yes/no), educational level at time of primary surgery (ISCED), occupation status (employed/unemployed/retired) and equivalent annual income in the year preceding primary surgery, typical symptoms (yes/no), atypical symptoms (yes/no) and dysphagia (yes/no), endoscopically verified occurrence of hiatal hernia (yes/no), esophagitis (yes/no), measures from 24-hour pH-measurement and esophageal manometry: reflux-index (%), symptom correlation (%) and presence of esophageal motility disorder (hypomotility, normal motility or hypermotility), type of fundoplication (270° Toupet/360° Nissen).

Clinical scoring system

Using results from the Cox regression and using the methods for validation described by Steyerberg et al (58), a clinical scoring system will be developed with the purpose of identifying probability of treatment success based on preoperative known variables.

Dataflow

Data collected from electronic patient records and patient-reported quality of life follow-up will be stored using RedCAP (REDCap 7.4.23, Vanderbilt University, Nashville, TN, USA) hosted by OPEN - Odense Patient Data Explorative Network, Department of Clinical Research, University of Southern Denmark and Odense University Hospital, Denmark. Data will be transferred to Statistics Denmark and merged with registry-data. All analysis will be performed using STATA15 (StataCorp, College Station, TX, USA) on the servers of Statistics Denmark.

Ethics and dissemination

The study has been approved and registered at Lillebaelt Hospital according to current Danish Law and has previously been approved by The Danish Data Protection Agency (Permission #17/1942). Generated datasets will be stored on the servers of Statistics Denmark in compliance with Danish and EU-regulations

on personal health data and will be anonymized after merging, so that the unique personal identifier is removed.

Permission to contact patient for the project will be obtained from The Danish Patient Safety Agency. Each patient must consent to inclusion in the study, including the use of electronic patient records and registry-based data as described above. For deceased patients, permission for use of electronic patient records and registry-based data will be obtained from The Danish Patient Safety Agency. Specific permission for use of registry-based data will be obtained from The Danish Health Data Authority and Statistics Denmark.

The results of the study will be published in peer-reviewed medical journals regardless of whether these are positive, negative or inconclusive. Two peer-reviewed articles are expected to come from this study: one including the primary results, and one calculating a clinical scoring system based on the results.

References

1. Madanick RD. Extraesophageal presentations of GERD: where is the science? Gastroenterol Clin North Am [Internet]. 2014;43(1):105–20. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24503362

2. Herregods TVK, Bredenoord AJ, Smout AJPM. Pathophysiology of gastroesophageal reflux disease: new understanding in a new era. Neurogastroenterol Motil [Internet]. 2015;27(9):1202–13. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=26053301

3. Boeckxstaens GE, Rohof WO. Pathophysiology of Gastroesophageal Reflux Disease. Gastroenterol Clin North Am [Internet]. 2014;43(1):15–25. Available from: http://dx.doi.org/10.1016/j.gtc.2013.11.001

4. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut [Internet]. 2005;54(5):710–7. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15831922

5. Hansen JM, Wildner-Christensen M, Schaffalitzky de Muckadell OB, de Muckadell OBS. Gastroesophageal reflux symptoms in a Danish population: a prospective follow-up analysis of symptoms, quality of life, and health-care use. Am J Gastroenterol [Internet]. 2009;104(10):2394–403. Available from: http://www.nature.com/ajg/journal/v104/n10/full/ajg2009391a.html

6. Friedenberg FK, Hanlon A, Vanar V, Nehemia D, Mekapati J, Nelson DB, et al. Trends in gastroesophageal reflux disease as measured by the National Ambulatory Medical Care Survey. Dig Dis Sci [Internet]. 2010;55(7):1911–7. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19830561

7. El-Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. Clin Gastroenterol Hepatol [Internet]. 2007;5(1):17–26. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17142109

8. Rubenstein JH, Chen JW. Epidemiology of gastroesophageal reflux disease. Gastroenterol Clin North Am [Internet]. 2014;43(1):1–14. Available from: http://dx.doi.org/10.1016/j.gtc.2013.11.006

9. Fuchs KH, Babic B, Breithaupt W, Dallemagne B, Fingerhut A, Furnee E, et al. EAES recommendations for the management of gastroesophageal reflux disease. Surg Endosc Other Interv Tech. 2014;28(6):1753–73.

10. Jobe BA, Richter JE, Hoppo T, Peters JH, Bell R, Dengler WC, et al. Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the Esophageal Diagnostic Advisory Panel. J Am Coll Surg [Internet]. 2013;217(4):586–97. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23973101

11. Rickenbacher N, Kotter T, Kochen MM, Scherer M, Blozik E. Fundoplication versus medical

management of gastroesophageal reflux disease: systematic review and meta-analysis. Surg Endosc [Internet]. 2014;28(1):143–55. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24018760

12. Wileman SM, McCann S, Grant AM, Krukowski ZH, Bruce J. Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. In: Cochrane Database of Systematic Reviews [Internet]. 2010. Available from: http://doi.wiley.com/10.1002/14651858.CD003243.pub2

13. Broeders JA, Sportel IG, Jamieson GG, Nijjar RS, Granchi N, Myers JC, et al. Impact of ineffective oesophageal motility and wrap type on dysphagia after laparoscopic fundoplication. Br J Surg [Internet]. 2011;98(10):1414–21. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21647868

14. Bunting DM, Szczebiot L, Peyser PM. Pain after laparoscopic antireflux surgery. Ann R Coll Surg Engl. 2014;96(2):95–100.

15. Furnée EJB, Draaisma WA, Broeders IAMJ, Gooszen HG, Furnee EJ, Draaisma WA, et al. Surgical reintervention after failed antireflux surgery: a systematic review of the literature. J Gastrointest Surg [Internet]. 2009;13(8):1539–49. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19347410

16. Hunter JG, Swanstrom L, Waring JP. Dysphagia after laparoscopic antireflux surgery. The impact of operative technique. Ann Surg [Internet]. 1996;224(1):51–7. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8678618

17. Iqbal A, Awad Z, Simkins J, Shah R, Haider M, Salinas V, et al. Repair of 104 failed anti-reflux operations. Ann Surg [Internet]. 2006;244(1):42–51. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16794388

18. Patterson EJ, Herron DM, Hansen PD, Ramzi N, Standage BA, Swanstrom LL. Effect of an esophageal bougie on the incidence of dysphagia following nissen fundoplication: a prospective, blinded, randomized clinical trial. Arch Surg [Internet]. 2000;135(9):1052–5. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10982510

19. Velanovich V, Karmy-Jones R. Psychiatric disorders affect outcomes of antireflux operations for gastroesophageal reflux disease. Surg Endosc [Internet]. 2001;15(2):171–5. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11285962

20. Anvari M, Allen C, Marshall J, Armstrong D, Goeree R, Ungar W, 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 [Internet]. 2011;25(8):2547–54. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21512887

21. Blazejczyk K, Hoene A, Glitsch A, Busemann A, Heidecke CD, Patrzyk M. Evaluation of short-term and long-term results after laparoscopic antireflux surgery: esophageal manometry and 24-h pH monitoring versus quality of life index. Langenbecks Arch Surg [Internet]. 2013;398(8):1107–14. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24037312

22. Streets CG, DeMeester SR, DeMeester TR, Peters JH, Hagen JA, Crookes PF, et al. Excellent quality of life after Nissen fundoplication depends on successful elimination of reflux symptoms and not the invasiveness of the surgical approach. Ann Thorac Surg [Internet]. 2002;74(4):1015–9. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12400739

23. Youssef YK, Shekar N, Lutfi R, Richards WO, Torquati A. Long-term evaluation of patient satisfaction and reflux symptoms after laparoscopic fundoplication with Collis gastroplasty. Surg Endosc [Internet]. 2006;20(11):1702–5. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16960664

24. Kamolz T, Granderath FA, Bammer T, Pasiut M, Pointner R. Dysphagia and quality of life after laparoscopic Nissen fundoplication in patients with and without prosthetic reinforcement of the hiatal crura. Surg Endosc [Internet]. 2002;16(4):572–7. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11972190

25. Kamolz T, Granderath PA, Bammer T, Pasiut M, Wykypiel HJ, Herrmann R, et al. Mid- and long-term quality of life assessments after laparoscopic fundoplication and refundoplication: a single unit review of more than 500 antireflux procedures. Dig Liver Dis [Internet]. 2002;34(7):470–6. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12236479

26. Fernando HC, Luketich JD, Christie NA, Ikramuddin S, Schauer PR. Outcomes of laparoscopic Toupet compared to laparoscopic Nissen fundoplication. Surg Endosc [Internet]. 2002;16(6):905–8. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12163952

27. Granderath FA, Kamolz T, Schweiger UM, Pasiut M, Wykypiel HJ, Pointner R. Quality of life and symptomatic outcome three to five years after laparoscopic Toupet fundoplication in gastroesophageal reflux disease patients with impaired esophageal motility. Am J Surg [Internet]. 2002;183(2):110–6. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11918872

28. Granderath FA, Kamolz T, Schweiger UM, Pointner R. Quality of life, surgical outcome, and patient satisfaction three years after laparoscopic Nissen fundoplication. World J Surg [Internet]. 2002;26(10):1234–8. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12181605

29. Granderath FA, Kamolz T, Granderath UM, Pointner R. Gas-related symptoms after laparoscopic 360 degrees Nissen or 270 degrees Toupet fundoplication in gastrooesophageal reflux disease patients with aerophagia as comorbidity. Dig Liver Dis [Internet]. 2007;39(4):312–8. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17306636

30. Kamolz T, Granderath FA, Schweiger UM, Pointner R. Laparoscopic Nissen fundoplication in patients with nonerosive reflux disease. Long-term quality-of-life assessment and surgical outcome. Surg Endosc [Internet]. 2005;19(4):494–500. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15959712

31. Pessaux P, Arnaud JP, Delattre JF, Meyer C, Baulieux J, Mosnier H. Laparoscopic antireflux surgery: five-year results and beyond in 1340 patients. Arch Surg [Internet]. 2005;140(10):946–51. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16230543

32. Rosenthal R, Peterli R, Guenin MO, von Flue M, Ackermann C. Laparoscopic antireflux surgery: long-term outcomes and quality of life. J Laparoendosc Adv Surg Tech A [Internet]. 2006;16(6):557–61. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17243869

33. Sgromo B, Irvine LA, Cuschieri A, Shimi SM. Long-term comparative outcome between laparoscopic total Nissen and Toupet fundoplication: Symptomatic relief, patient satisfaction and quality of life. Surg Endosc [Internet]. 2008;22(4):1048–53. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18027031

34. Ciovica R, Gadenstatter M, Klingler A, Lechner W, Riedl O, Schwab GP. Quality of life in GERD patients: medical treatment versus antireflux surgery. J Gastrointest Surg [Internet]. 2006;10(7):934–9. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16843863

35. Grant AM, Cotton SC, Boachie C, Ramsay CR, Krukowski ZH, Heading RC, et al. Minimal access surgery compared with medical management for gastro-oesophageal reflux disease: five year follow-up of a randomised controlled trial (REFLUX). BMJ [Internet]. 2013;346:f1908. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23599318

36. Dallemagne B, Weerts J, Markiewicz S, Dewandre JM, Wahlen C, Monami B, et al. Clinical results of laparoscopic fundoplication at ten years after surgery. Surg Endosc [Internet]. 2006;20(1):159–65. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16333553

37. Neuvonen P, Iivonen M, Sintonen H, Rantanen T. Health-related quality of life 10 years after laparoscopic nissen fundoplication-results of a community-based hospital. J Laparoendosc Adv Surg Tech A [Internet]. 2014;24(3):134–8. Available from: http://online.liebertpub.com/doi/abs/10.1089/lap.2013.0479

38. Galmiche J-P, Hatlebakk J, Attwood S, Ell C, Fiocca R, Eklund S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. JAMA [Internet]. 2011 May 18;305(19):1969–77. Available from: http://archotol.jamanetwork.com/article.aspx?articleid=1161863

39. Kellokumpu I, Voutilainen M, Haglund C, Farkkila M, Roberts PJ, Kautiainen H. Quality of life following laparoscopic Nissen fundoplication: assessing short-term and long-term outcomes. World J Gastroenterol [Internet]. 2013;19(24):3810–8. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23840119

40. Humphries LA, Hernandez JM, Clark W, Luberice K, Ross SB, Rosemurgy AS. Causes of dissatisfaction after laparoscopic fundoplication: the impact of new symptoms, recurrent symptoms, and the patient experience. Surg Endosc [Internet]. 2013;27(5):1537–45. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23508812

41. 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(10):1544–9.

42. Haastrup P, Paulsen MS, Zwisler JE, Begtrup LM, Hansen JM, Rasmussen S, et al. Rapidly increasing prescribing of proton pump inhibitors in primary care despite interventions: a nationwide observational study. Eur J Gen Pr [Internet]. 2014;20(4):290–3. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24779533

43. Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg [Internet]. 2006;244(1):34–41. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16794387

44. Lord R V, Kaminski A, Oberg S, Bowrey DJ, Hagen JA, DeMeester SR, et al. Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after Nissen fundoplication. J Gastrointest Surg [Internet]. 2002;6(1):3–9; discussion 10. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11986011

45. Nomesco NM-SC, Nordic Medico-Statistical Committee. NOMESCO Classification of Surgical Procedures (NCSP), version 1.16. Copenhagen: NOMESCO; 2011. 1–295 p.

46. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676–82.

47. Clavien PA, Barkun J, De Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The clavien-dindo classification of surgical complications: Five-year experience. Ann Surg. 2009;250(2):187–96.

48. Velanovich V. The development of the GERD-HRQL symptom severity instrument. Dis Esophagus [Internet]. 2007;20(2):130–4. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17439596

49. Silbergleit AK, Schultz L, Jacobson BH, Beardsley T, Johnson AF. The Dysphagia handicap index: development and validation. Dysphagia [Internet]. 2012;27(1):46–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21424584?dopt=Citation

50. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National patient registry: A review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449–90.

51. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. Scand J Public Health. 2011;39(7):30–3.

52. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):541–9.

53. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: The Danish national prescription registry. Int J Epidemiol. 2017;46(3):798.

54. Jensen VM, Rasmussen AW. Danish education registers. Scand J Public Health. 2011;39(7):91–4.

55. UNESCO Institute for Statistics. International Standard Classification of Education (ISCED 2011) [Internet]. 2011. 1–86 p. Available from: http://uis.unesco.org/en/topic/international-standard-classification-education-isced

56. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. Scand J Public Health [Internet]. 2011 Jul;39(7 Suppl):95–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21775363

57. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. Scand J Public Health. 2011;39(7):103–5.

58. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: Seven steps for development and an ABCD for validation. Eur Heart J. 2014;35(29):1925–31.