Treatment of newly-diagnosed gastroesophageal reflux disease: A nationwide register-based cohort study
JS Ljungdalh, KH Rubin, J Durup, KC Houlin
Accepted Draft

TITLE PAGE

Title:
Treatment of newly-diagnosed gastroesophageal reflux disease: A nationwide register-based cohort study

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BACKGROUND

Gastroesophageal reflux disease (GERD) is a complex and multifaceted disease, [1,2] affecting 10-20% of the Western population [3,4] and has been shown to significantly reduce the quality of life. [5] Worldwide, the prevalence of GERD has been increasing. [6,7] In studies investigating self-reported GERD-symptoms within samples of the general Danish population, 11.2% reported symptoms of GERD according to the Montreal classification [8,9] and 21.3% of employed randomly selected respondents reported troublesome GERD-symptoms. [10] However, despite several studies concerning reflux-symptoms, no previous Danish study has used a population-based approach to investigate patients diagnosed with GERD during outpatient in-hospital evaluation. It is currently unknown how patients registered with a diagnosis of GERD after upper endoscopy are treated in Denmark, however the unique Danish health registries allows for investigation of this on a nationwide population level. There are several international and national guidelines [11,12] for the optimized treatment of GERD, however to evaluate the use of these, it must first be known how patients are treated.

Treatment of GERD consists of anti-secretory drugs, mainly proton pump inhibitors (PPI), anti-reflux surgery [13], or both. In Denmark, treatment is initiated by each citizen’s general practitioner and patients are only referred to further investigation with endoscopy if treatment is insufficient or if the patient presents with symptoms leading to a suspicion of upper gastrointestinal cancer. This further evaluation takes place in hospital, but as outpatient procedures. All contacts regarding endoscopy and further investigation are registered in nationwide registers of diagnoses and procedures.

The aim of this study was to describe treatment of GERD in patients registered with a GERD-diagnosis as part of evaluation with endoscopy using national Danish registers.
METHODS AND MATERIALS

All Danish citizens have equal access to tax-supported universal healthcare services. Use of these services are registered in nationwide registers and can be linked using the unique civil registration number (CRN) issued to each resident at birth or when moving to Denmark. This allows a unique possibility for studies to include and investigate the entire Danish population comprised of 5.78 million inhabitants by January 1, 2018. [14]

Data sources

We obtained nationwide Danish data from the following sources:

1) The National Patient Registry (NPR) on procedures (endoscopy and anti-reflux surgery) and diagnosis (GERD-related diagnosis and comorbidity). NPR contains complete records of discharge diagnosis since 1977 and all outpatient diagnosis since 1994. [15,16] Since 1995, the International Classification of Diseases and Related Health Problems 10th edition (ICD-10) has been used when registering diagnoses. All performed procedures, such as endoscopies and surgeries are also registered using The Nomensco Classification of Surgical Procedures (NCSP). [17] Each diagnosis or procedure is linked using CRN.

2) The Danish National Prescription Registry on use of anti-reflux medication, anti-thrombotic treatment and non-steroid anti-inflammatory drugs (NSAID). The Danish National Prescription Registry contains information on all sale of prescription drugs including date of sale, Anatomical Therapeutic Chemical Classification (ATC) code, CRN of buyer and package volume since 1994. [18]

3) The National Civil Registry on death and civil status. 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. [19] The CRN has been issued to the entire Danish population since 1968.

All data was linked across registers on an individual level using the CRN.

Study population

The study population was comprised of all adults (age 18+) undergoing upper gastrointestinal endoscopy (NCSP: KUJD02, KUJD05) in Denmark from 1th January 2000 to 31th December 2015, who within 90 days received a subsequent diagnosis of GERD (ICD-10: K20.9B, K21*). Patients with a prior diagnosis of GERD (ICD-10: K20.9B, K21*), Barrett’s esophagitis (K22.7), peptic ulcer disease (K25.0-26.9) or cancer of the gastrointestinal tract (ICD-10: C15*-
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26*) and patients previously undergoing upper endoscopy (NCSP: KUJD02, KUJD05) or anti-reflux surgery (NCSP: KJBC00, KJBC01, KJ8W96, KJBW97) were excluded from the study. Only patients with a valid CRN available for follow-up were included. Each patient could only be included once.

**Primary outcome**

Primary outcome was type of treatment of GERD within two years of primary endoscopy defined as either no treatment (no prescription anti-reflux drugs AND no anti-reflux surgery), medical treatment alone (any use of prescription anti-reflux drugs AND no anti-reflux surgery), surgical treatment alone (no prescription anti-reflux drugs AND any anti-reflux surgery) or both medical and surgical treatment (any prescription anti-reflux drugs AND any anti-reflux surgery).

Prescription anti-reflux drugs were further defined as proton pump inhibitors (ATC: A02BC), H$_2$-receptor antagonists (ATC: A02BA) and other anti-reflux drugs (ATC: A02BX). Anti-reflux surgery was defined as either open-approach anti-reflux surgery (NCSP: KJBC00, KJBW96) or laparoscopic anti-reflux surgery (NCSP: KJBC01, KJBW97)

**Secondary outcomes**

Time to pharmacological treatment was defined as time from initial endoscopy to first filled prescription of an anti-reflux drug (proton pump inhibitors (ATC: A02BC), H$_2$-receptor antagonists (ATC: A02BA) and/or other anti-reflux drugs (ATC: A02BX)). Time to surgery was defined as time from initial endoscopy to first registered surgical anti-reflux procedure (NCSP: KJBC00, KJBC01, KJBW96, KJBW97).

Intensity of pharmacological treatment was defined as number of anti-reflux drug types (proton pump inhibitors (ATC: A02BC), H$_2$-receptor antagonists (ATC: A02BA) and/or other anti-reflux drugs (ATC: A02BX)) utilized in the first two years after initial endoscopy.

Volume of filled prescriptions of proton pump inhibitors were registered in defined daily dose (DDD)/year for each of the two years before endoscopy and each of the two years following endoscopy.
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Confounders and covariates
Age were at date of endoscopy and marital status was defined as either married or unmarried at time of endoscopy.
Using diagnoses from the NPR, Charlson Comorbidity Index (CCI) was calculated for each included patient and
categorized as either having no comorbidity (CCI=0) or some comorbidity (CCI>0) with a lookback period of 5 years.
CCI was calculated using weights of comorbidity validated by Quan et al. [20] Any occurrence of previous non-
gastrointestinal cancer (C00-48 excluding C15.1-26.0) was registered.

Diagnoses of GERD were grouped as GERD with esophagitis (K20.9, K21.0) or GERD without esophagitis (K21.9,
K21.9A, K21.9B). Any use of NSAID (ATC: M01A*) or anti-thrombotic drugs (ATC: B01A*) up to two years before
endoscopy were registered.

Intensity of previous pharmacological treatment was defined as number of anti-reflux drug types (proton pump
inhibitors (ATC: A02BC), H₂-receptor antagonists (ATC: A02BA) and/or other anti-reflux drugs (ATC: A02BX)) utilized in
the last 365 days before initial endoscopy.

Statistics
Contingency tables by treatment type listing age (median), sex (male/female), marital status (married/unmarried), CCI
(0/>0), any previous non-gastrointestinal cancer (yes/no), type of GERD-diagnoses (GERD with or without esophagitis),
previous pharmacological treatment (NSAID and/or anti-thrombotic drugs), type of previous pharmacological anti-
reflux treatment (proton pump inhibitors, H₂-receptor antagonists and/or other anti-reflux drugs), intensity of
previous pharmacological anti-reflux treatment (0,1,2 or 3 drugs), occurrence of Barrett’s esophagitis during follow-up
(yes/no), peptic ulcer disease during follow-up (yes/no), cancer of the gastrointestinal tract during follow-up
(yes/no), non-gastrointestinal cancer during follow-up (yes/no), time to first filled prescription (median), time to
surgery (median), type of pharmacological anti-reflux treatment (proton pump inhibitors, H₂-receptor antagonists
and/or other anti-reflux drugs), intensity of pharmacological anti-reflux treatment (0, 1, 2 or 3 drugs) and volume of
filled prescriptions of proton pump inhibitors (Median DDD/year) for each of the two years before endoscopy and
each of the two years following endoscopy. Categorical and continuous variables were compared using Chi², Fisher’s
Exact Test and Kruskal-Wallis-test where appropriate.
Logistic regression was performed with any pharmacological anti-reflux treatment or any surgical anti-reflux treatment as dependent variables and age, sex, marital status, CCI, any previous non-gastrointestinal cancer, type of GERD-diagnoses, previous pharmacological treatment (NSAID and/or anti-thrombotic drugs), and type of previous pharmacological anti-reflux treatment.

All analyses were performed using STATA15 (StataCorp, College Station, TX, USA).
RESULTS

A total of 37,897 patients were available for inclusion and 36,292 patients were available for full two-year follow-up and subsequently included in the study. The median age at endoscopy was 53 years ranging from 18-98 years (25-75% quartiles: 41-64). A majority of patients were male (52.4%, n=19,013) and 60.1% (n=17,279) were married. Of included patients, 90.0% (n=32,669) had a CCI of 0 and 10.0% (n=3,623) had a CCI>0. Only 2.0% (n=708) had a previous diagnosis of non-gastrointestinal cancer.

Endoscopies were performed without biopsies in 67.5% (n=24,479) of cases. The majority (66.3%, n=24,077) was registered as GERD with esophagitis and median time from endoscopy to diagnosis was 0 days, ranging from 0-90 days (25-75 centiles: 0-0). A total of 39.4% (n=14,294) had filled prescriptions of NSAID prior to endoscopy and 15.1% (n=5,490) had filled prescription of any anti-thrombotic treatment.

Prior to endoscopy, 78.6% (n=28,535) had filled prescriptions of PPI, 10.8% (n=3,925) had filled prescriptions of H2-blockers and 2.3% (n=850) had filled prescriptions of other anti-reflux drugs.

Regarding intensity of pharmacological treatment, 18.5% (n=6,717) received no treatment prior to endoscopy, 71.6% (n=25,995) was treated with one type of anti-reflux drugs, 9.4% (n=3,425) was treated with two types of drugs, and 0.4% (n=155) was treated with three different types of anti-reflux drugs.
TREATMENT OF NEWLY-DIAGNOSED GASTROESOPHAGEAL REFLUX DISEASE: A NATIONWIDE REGISTER-BASED COHORT STUDY

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TREATMENT

After initial endoscopy, 10.6% (n=3,862) received no pharmacological or surgical treatment for GERD within two years of follow-up, 87.5% (n=31,761) received only pharmacological treatment, 0.1% (n=50) received only surgical treatment and 1.7% (n=619) received a combination of pharmacological and surgical treatment (Table 1).

Demographic data, comorbidity, previous pharmacological treatment and intensity of previous pharmacological anti-reflux treatment are summarized in Table 1.

For patients receiving only pharmacological treatment, median time from endoscopy to first filled prescription of anti-reflux drug after endoscopy was 2 days (range: 0-730, 25-75 centiles: 0-18). For patients receiving both surgical and pharmacological treatment, median time from endoscopy to first filled prescription of anti-reflux drug was 6 days (range: 0-640, 25-75 centiles: 0-28). For patients receiving only surgical treatment, median time from endoscopy to anti-reflux surgery was 186 days (range: 1-571, 25-75 centiles: 124-268). For patients receiving a combination of pharmacological and surgical treatment, median time from endoscopy to anti-reflux surgery was 282 days (range: 10-725, 25-75 centiles: 182-401). Data on use of pharmacological anti-reflux treatment and intensity of treatment in patients treated either solely with pharmacological treatment or a combination of pharmacological and surgical treatment are summarized in Table 2.

For patients treated either solely with pharmacological treatment or a combination of pharmacological and surgical treatment, median use of PPI increased to 168 DDD/year (range: 0-3858, 25-75 centiles: 56-336) and 231 DDD/year (range: 0-1232, 25-75 centiles: 112-392) respectively, in the first year following endoscopy and then, in the second year after endoscopy, decreased to 100 DDD/year (range: 0-4326, 25-75 centiles: 0-298) and 0 DDD/year (range: 0-1000, 25-75 centiles: 0-130) respectively. Data on volume of PPI-use for all treatment groups are summarized in Table 3.
### Table 1: Characteristics of Patients Sorted by Treatment Modality

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>NONE</th>
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<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=36292</td>
<td>3862 (10.6)</td>
<td>31761 (87.5)</td>
<td>50 (0.1)</td>
<td>619 (1.7)</td>
<td></td>
</tr>
</tbody>
</table>

#### Demographic Data

<table>
<thead>
<tr>
<th>Age, median (range)</th>
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<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 (18-92)</td>
<td>54 (18-98)</td>
<td>45 (22-71)</td>
<td>46 (18-80)</td>
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<td>P&lt;0.001</td>
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</table>

<table>
<thead>
<tr>
<th>Sex</th>
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<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
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<tbody>
<tr>
<td>- Male</td>
<td>2021 (52.3)</td>
<td>16605 (52.3)</td>
<td>30 (60.0)</td>
<td>357 (57.7)</td>
<td>P=0.041</td>
</tr>
<tr>
<td>- Female</td>
<td>1841 (47.7)</td>
<td>15156 (47.7)</td>
<td>20 (40.0)</td>
<td>262 (42.3)</td>
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<table>
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<th>Marital status</th>
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<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Unmarried</td>
<td>1583 (41.0)</td>
<td>12641 (39.8)</td>
<td>25 (50.0)</td>
<td>232 (37.5)</td>
<td>P=0.128</td>
</tr>
<tr>
<td>- Married</td>
<td>2279 (59.0)</td>
<td>19120 (60.2)</td>
<td>25 (50.0)</td>
<td>387 (62.5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Charlson Comorbidity Index</th>
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<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3588 (92.9)</td>
<td>28453 (89.6)</td>
<td>47 (94.0)</td>
<td>581 (93.9)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>=&gt;1</td>
<td>274 (7.1)</td>
<td>3308 (10.4)</td>
<td>NA*</td>
<td>38 (6.1)</td>
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</tr>
</tbody>
</table>

<table>
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<tr>
<th>Any non-GI cancer before?</th>
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<th>MEDICAL ONLY</th>
<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 (1.7)</td>
<td>640 (2.0)</td>
<td>0 (0)</td>
<td>NA*</td>
<td></td>
<td>P=0.018</td>
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#### Diagnosis

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<th>GERD with esophagitis</th>
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<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1861 (48.2)</td>
<td>21767 (68.5)</td>
<td>33 (66.0)</td>
<td>416 (67.2)</td>
<td></td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GERD without esophagitis</th>
<th>NONE</th>
<th>MEDICAL ONLY</th>
<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001 (51.8)</td>
<td>9994 (31.5)</td>
<td>17 (34.0)</td>
<td>203 (32.8)</td>
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#### Previous Pharmacological Treatment

<table>
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<tr>
<th>NSAID</th>
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<th>SURGICAL ONLY</th>
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<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1314 (34.0)</td>
<td>12694 (40.0)</td>
<td>19 (38.0)</td>
<td>267 (43.1)</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anti-thrombotic agents</th>
<th>NONE</th>
<th>MEDICAL ONLY</th>
<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>325 (8.4)</td>
<td>5118 (16.1)</td>
<td>NA*</td>
<td>44 (7.1)</td>
<td>P&lt;0.001</td>
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</table>

#### Previous Anti-reflux Treatment

<table>
<thead>
<tr>
<th>PPI</th>
<th>NONE</th>
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<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2228 (57.7)</td>
<td>25705 (80.9)</td>
<td>37 (74)</td>
<td>566 (91.4)</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>H2-blockers</th>
<th>NONE</th>
<th>MEDICAL ONLY</th>
<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>316 (8.2)</td>
<td>3504 (11.0)</td>
<td>8 (16.0)</td>
<td>97 (15.7)</td>
<td>P&lt;0.001</td>
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</table>

<table>
<thead>
<tr>
<th>Other anti-reflux medication</th>
<th>NONE</th>
<th>MEDICAL ONLY</th>
<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA*</td>
<td>803 (2.5)</td>
<td>0 (0)</td>
<td>46 (7.4)</td>
<td>P&lt;0.001</td>
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#### Intensity of Previous Anti-reflux Treatment

<table>
<thead>
<tr>
<th>Intensity</th>
<th>NONE</th>
<th>MEDICAL ONLY</th>
<th>SURGICAL ONLY</th>
<th>COMBINATION</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>1475 (38.2)</td>
<td>5189 (16.3)</td>
<td>11 (22.0)</td>
<td>42 (6.8)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Single drug</td>
<td>2129 (57.7)</td>
<td>23278 (73.3)</td>
<td>33 (66.0)</td>
<td>455 (73.5)</td>
<td></td>
</tr>
<tr>
<td>Two drugs</td>
<td>158 (4.1)</td>
<td>3149 (9.9)</td>
<td>26 (52.0)</td>
<td>112 (18.1)</td>
<td></td>
</tr>
<tr>
<td>Three drugs</td>
<td>0 (0)</td>
<td>145 (0.5)</td>
<td>0 (0)</td>
<td>10 (1.6)</td>
<td></td>
</tr>
</tbody>
</table>

*NA*: Reporting of results with n<5 not allowed according to Danish law concerning registry-based research
TABLE 2: PHARMACOLOGICAL ANTI-REFLUX TREATMENT AFTER ENDOSCOPY

<table>
<thead>
<tr>
<th></th>
<th>MEDICAL ONLY N (%)</th>
<th>COMBINATION N (%)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>PPI</td>
<td>31429 (99.0)</td>
<td>611 (98.7)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>H2-blocker</td>
<td>1669 (5.3)</td>
<td>44 (7.1)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Other anti-reflux medication</td>
<td>802 (2.5)</td>
<td>46 (7.4)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Intensity of anti-reflux treatment
- No treatment
- Single drug
- Two drugs
- Three drugs

TABLE 3: USE OF PPI BEFORE AND AFTER ENDOSCOPY BY TREATMENT MODALITY, DDD/year

<table>
<thead>
<tr>
<th></th>
<th>NONE N (%)</th>
<th>MEDICAL ONLY N (%)</th>
<th>SURGICAL ONLY N (%)</th>
<th>COMBINATION N (%)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>N=36292</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years before endoscopy, median ( range)</td>
<td>0 (0-672)</td>
<td>0 (0-3662)</td>
<td>0 (0-362)</td>
<td>0 (0-1008)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>1 year before endoscopy, median ( range)</td>
<td>14 (0-644)</td>
<td>46 (0-3503)</td>
<td>18 (0-398)</td>
<td>93 (0-952)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>1 year after endoscopy, median ( range)</td>
<td>-</td>
<td>168.0 (0-3858)</td>
<td>-</td>
<td>231.0 (0-1232)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>2 year after endoscopy, median ( range)</td>
<td>-</td>
<td>100.0 (0-4326)</td>
<td>-</td>
<td>0 (0-1000)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>
Regression analysis

Logistic regression demonstrated statistically significantly increased probability of receiving pharmacological treatment with increasing age (OR 1.03, 95% CI 1.03-1.03 per incremental year), with increasing CCI (OR 1.28, 95% CI 1.11-1.48), with previous use of NSAID (OR 1.18, 95% CI 1.10-1.27) or anti-thrombotic medication (OR 1.27, 95% CI 1.12-1.44) and with previous use of PPI (OR 3.70, 95% CI 3.44-3.98), H₂-blockers (OR 1.64, 95% CI 1.45-1.85) or other anti-reflux medication (OR 91.03, 95% CI 12.79-648.10). Statistically significant lower probability of receiving pharmacological treatment was demonstrated in patients with previous non-gastrointestinal cancer (OR 0.70, 95% CI 0.53-0.94) and patients with a diagnosis of GERD without esophagitis (OR 0.42, 95% CI 0.39-0.45).

Logistic regression demonstrated statistically significantly increased probability of receiving surgical treatment with previous use of NSAID (OR 1.19, 95% CI 1.02-1.39) and with previous use of PPI (OR 2.41, 95% CI 1.86-3.12), H₂-blockers (OR 1.42, 95% CI 1.15-1.76) or other anti-reflux medication (OR 3.14, 95% CI 2.30-4.28). Statistically significantly lower probability of receiving surgical treatment was demonstrated in patients with increasing age (OR 0.98, 95% CI 0.97-0.98 per incremental year), for females (OR 0.79, 95% CI 0.68-0.93) and for patients with previous use of anti-thrombotic medication (OR 0.64, 95% CI 0.47-0.87).

Logistic regressions are summarized in Table 4.
Treatment of newly-diagnosed gastroesophageal reflux disease: A nationwide register-based cohort study
JS Ljungdalh, KH Rubin, J Durup, KC Houlin
Accepted Draft

<table>
<thead>
<tr>
<th>TABLE 4: LOGISTIC REGRESSION</th>
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<td>N=36292</td>
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<table>
<thead>
<tr>
<th>Demographic data</th>
<th>MEDICAL TREATMENT</th>
<th>SURGICAL TREATMENT</th>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
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<td>Age</td>
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</tr>
<tr>
<td>Sex</td>
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<tr>
<td>- Male</td>
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<tr>
<td>- Female</td>
<td>0.97 (0.91-1.04)</td>
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<td>Marital status</td>
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<tr>
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<tr>
<td>- Married</td>
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<td>Charlson Comorbidity Index</td>
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<td>- 0</td>
<td>1.00</td>
<td>-</td>
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<tr>
<td>- &gt;=1</td>
<td>1.28 (1.11-1.48)</td>
<td>P=0.001</td>
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<tr>
<td>Any non-GI cancer before?</td>
<td>0.70 (0.53-0.94)</td>
<td>P=0.017</td>
</tr>
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<td>Diagnosis</td>
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<tr>
<td>- GERD with esophagitis</td>
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<tr>
<td>- GERD without esophagitis</td>
<td>0.42 (0.39-0.45)</td>
<td>P&lt;0.001</td>
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<td>Previous pharmacological treatment</td>
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<tr>
<td>Use of NSAID</td>
<td>1.18 (1.10-1.27)</td>
<td>P&lt;0.001</td>
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<td>Use of anti-thrombotic medication</td>
<td>1.27 (1.12-1.44)</td>
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<td>Previous anti-reflux treatment</td>
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<td>Use of PPI</td>
<td>3.70 (3.44-3.98)</td>
<td>P&lt;0.001</td>
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<td>Use of H2-blockers</td>
<td>1.64 (1.45-1.85)</td>
<td>P&lt;0.001</td>
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<tr>
<td>Use of other anti-reflux medication</td>
<td>91.03 (12.79-648.10)</td>
<td>P&lt;0.001</td>
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DISCUSSION

This study showed that from 2000-2015, treatment in Denmark for newly diagnosed GERD after endoscopy was primarily pharmacological with 89.2% of patients receiving some form of prescription anti-reflux medication within two years. Only 1.8% are treated surgically. Pharmacological treatment was intensified after endoscopy with PPI being the primary agent.

For patients receiving pharmacological treatment either as only treatment or with concomitant surgical treatment, median time from endoscopy to first filled prescription of anti-reflux drug was 2 and 6 days respectively, illustrating that existing pharmacological treatment is reevaluated at endoscopy. Median time from endoscopy to anti-reflux surgery was 186 days and 286 days respectively for patients receiving solely surgical treatment and patients receiving both pharmacological and surgical treatment. This indicates that patients go through further examination and most likely evaluate efficiency of pharmacological treatment before proceeding to anti-reflux surgery.

In the group receiving neither surgical nor pharmacological treatment, GERD without esophagitis was the dominating diagnosis whereas GERD with esophagitis was more predominant in patients receiving any type of treatment. This may be because esophagitis indicates more severe disease. However, it is worrying that 1861 patients were diagnosed with GERD with esophagitis without receiving any pharmacological or surgical treatment. The reason for this lack of treatment may be that these patients had a lower grade of esophagitis, but the Danish register does not allow for differentiating this as grading systems are not part of the ICD-10 coding practice. Patients with oesophagitis were more likely to receive any treatment compared to patients without oesophagitis (92.3% (n=22216) vs 83.6% (n=10214). However, they were no more likely to receive surgical therapy (1.9% n=449 vs 1.8% n=220). Patients with oesophagitis were also less likely to have received pharmacological treatment of GERD prior to endoscopy (20.0% n=4826 vs 15.5% n=1891) and were more likely to receive PPIs in the first two years after diagnosis (91.3% n=21993 vs 82.3% n=10047). As such, a diagnosis of oesophagitis in our study, does in general lead to a more intense course of treatment compared to other GERD-patients, but does not result in a higher rate of anti-reflux surgery.

Patients could have been buying anti-reflux drugs without prescription, however this is unlikely as sale of PPIs are prescription-based in 98% of sales and PPI are the predominant pharmacological anti-reflux agent. [21] Sale of H2-blockers and other anti-reflux drugs are however primarily sold without prescriptions with only 17% and 14% of sales...
being prescription-based. [21] Some of the patients receiving no treatment in our study, may very well be self-medicating, but as drug-cost are reimbursed only when using a prescription, long-term treatment should result in each patient receiving a prescription.

Patients undergoing surgery, either as sole treatment or in combination with pharmacological treatment, were more likely to be male and had significantly less comorbidity including previous non-gastrointestinal cancer. These patients were also less likely to be treated with anti-thrombotic drugs, probably reflecting the smaller burden of comorbidity. They were also younger than patients receiving only pharmacological treatment. All of this probably reflects selection of the fittest patients for anti-reflux surgery by surgeons.

The pre-endoscopy use of NSAID was significant in all treatment groups (up to 43.1%). This is surprisingly high, as general use of NSAID for patients 45-64 years of age during the study period peaked at 24.6%. [21] Use may even be higher as only up to 82% of sales in Denmark are by prescription – the remaining 18% are sold over the counter. [21] The high usage of NSAID is particularly problematic as symptoms of GERD can be exuberated by NSAID. [22]

Up to 91.6% of patients had used PPI before endoscopy. The development in use of PPI per year before endoscopy, illustrates that patients received treatment through their general practitioner and treatment intensified before referral to endoscopy. After endoscopy, treatment further intensified but in the second year after endoscopy, use again decreased, as an indication that symptom-control is better or that patients have undergone surgery and therefore should not need PPI. We choose to include patients with previous PPI-treatment as the course of illness warrants initial contact and treatment with a general practitioner, before referral to further treatment in the secondary sector. It is disturbing that the upper range of volume of PPI-use are considerably higher than recommended by international or Danish guidelines. [11,12] We used volume of PPI-use as PPI represents by far the most used type of pharmacological anti-reflux treatment (92.7% of all prescriptions in this study). PPI accounted for 96.8% of total sales within pharmacological anti-reflux treatment in 2011 and use of PPI increased 243% from 2001 to 2011 with 94.4% prescribed in the primary sector. [23] In a large Danish survey, 13.6% of the study population reported PPI-use [24] and using national data, the point prevalence of PPI-use in the Danish population was 7.4% of all
adults in 2014 with up to 45% of users using at least one ulcerogenic drug concomitantly. [25] This indicates that patients referred for endoscopy have a higher burden of reflux symptoms compared to the background population.

The logistic regression models demonstrated that patients with higher age, higher burden of comorbidity, previous use of anti-reflux medication, and use of NSAID or anti-thrombotic drugs had higher probability of receiving pharmacological anti-reflux treatment after endoscopy. This reflects that pharmacological treatment is considered relatively safe with few side effects for those suffering from a considerable burden of disease and comorbidity. When investigating probability of receiving surgical treatment, patients with previous use of pharmacological anti-reflux treatment or NSAID had a higher probability of surgical treatment, while increasing age and use of anti-thrombotic drugs lowered probability of surgical treatment. This probably reflects, that patients selected for surgery have a lower burden of comorbidity but still a significant burden of reflux symptoms. A bit surprisingly, females were less likely to be treated surgically as well. When comparing course of treatment between females and males, there were no significant difference in the use of PPI within the first year of diagnoses (female: median 140 DDD/year, male: median 133.33 DDD/year). However, in the second year after diagnosis, volume of PPI was significantly higher in females compared to males (65.33 DDD/year vs. 56.00 DDD/year, p<0.005). This could further indicate a deficit of surgical treatment in female GERD-patients or a milder course of treatment on PPIs that results in not being referred to surgery. In description of the Nordic Antireflux Surgery Cohort, including data from the Scandinavian countries, 43.9% of patients undergoing anti-reflux surgery were female despite the fact, that 51% of registered GERD-patients were female. [26] This corresponds to our results.

In Denmark, ambulatory pH-testing is primarily used as part of preoperative examination prior to anti-reflux surgery. Requiring patients to undergo pH-testing would lead to possible selection bias in the study population. GERD-diagnoses alone are also used as secondary diagnoses at discharge in the case of many other illnesses. Using the combination of endoscopy and GERD-diagnosis is therefore the pragmatic way of validating GERD-diagnoses and at least ensuring that they are given as part of examination at an endoscopy ward by a surgeon or gastroenterologist. A median of 0 days from endoscopy to diagnosis illustrates this point. We did not access to data detailing the use of pH-testing in this study, but even if we did, only the execution of the study, not the results, would be available. However, we recognize this as a weakness of our study.
The strengths of the study are the use of national Danish health registries with high validity and possibility of a long study period leading to high statistical power. In The NPR, surgical diagnoses have a positive predictive value of 77-89% depending on the use of secondary diagnoses. [16] No studies specifically validating GERD-diagnoses in The National Patient Registry have been conducted, however studies regarding peptic ulcer disease show a positive predictive value of 72.7-98%. [27,28] We choose to define anti-reflux surgery as NCSP: KJBC00, KJBC01, KJBW96, KJBW97 and there is a possibility that some patients undergoing surgery for GERD may be misclassified as having undergone surgery for hiatal hernia (NCSP: KJBB00, KJBB01, KJBB10, KJBB11, KJBB96, KJBB97). A total of 68 patients in our study population underwent surgery for hiatal hernia and 16 patients underwent both anti-reflux surgery and surgery for hiatal hernia. A sensitivity analysis yielded no significant difference if the 52 remaining patients were classified as having undergone anti-reflux surgery (data not shown).

This study allows for the combination of diagnoses, procedures and data on prescription drugs. It also allows for information on comorbidity illustrated by the use of CCI. [27] Our method eliminates patients with previous contacts to the secondary sector and allows for investigation of newly-diagnosed GERD and description of treatment.

The potential weakness of this study is that we could only examine patients with a burden of disease significant enough to warrant referral to further investigation from their general practitioner. This underestimates the occurrence of GERD and is the reason, we do not present calculated incidences of GERD based on this study. When using the Danish Prescription Registry, we can only investigate prescriptions that are actually being filled, but we have no way of knowing whether the drugs are actually being consumed by the patients. However, the Danish Prescription Registry has a high validity with <1% wrong and missing data. [29,30] Furthermore, we are dependent on ICD-10 diagnoses and cannot estimate patient symptoms further. Especially disease-specific quality of life could be a strong addition to this study. For the evaluation of somatic comorbidity, we utilized the Charlson Comorbidity Index. This index it is updated form is comprised of 12 comorbidities, none of which is obesity. Data on obesity is not routinely registered in the Danish National Patient Registry and was not available for this study. Obesity is the leading comorbidity in GERD, and the lack of data on obesity is a major weakness of this study.

A further knowledge of symptom severity, obesity, oesophagitis-grading and pH-testing could be important covariates and could help further differentiate between treatment groups.
Of the available 37,897 patients, 1,605 died before completing two-year follow-up, yielding a 2-year all-cause mortality of 4.24%. This is significantly higher than the reported numbers for the general Danish population (1.16% 1-year all-cause mortality by 2014 [14]). However, this study was not designed to investigate mortality and the apparent difference in mortality could disappear when conducting a proper matched study including causes of death.

In a British registry-based study, investigating patients affiliated with 1500 general practitioners in 1996, 11% of patients with a suspicion of GERD were referred for evaluation with endoscopy. [31] Of the patients undergoing endoscopy, 29.1-35.1% had previously been treated with H2-receptor antagonists and 21.7%-33.1% had previously been treated with PPI. This use of drugs compared to the results in our study, probably reflects that PPI-use has increased since 1996, most likely as a consequence of changed pricing. Of the patients undergoing endoscopy in the British study, 67% had esophagitis which is comparable with the degree of esophagitis in our study (66.3%). In the Olmsted County Cohort, only 5.4% of subjects reporting heartburn reported a visit at their general practitioner for that reason within the last year and 14.8% of these subjects, were referred to endoscopy. [32] 9% of subjects experiencing heartburn or acid regurgitation reported daily use of antacids and 18% reported at least weekly use. PPI was not the prevalent pharmacological treatment, most likely because the study was published in 1997. Finally, the HUNT study reported increasing prevalence of GERD, but did not include data on pharmacological or surgical treatment. [33] In general, not many registry-based studies on treatment of GERD are available and to our knowledge, no other study investigates the disease within a nationwide population-based perspective.

CONCLUSION

In conclusion, patients referred to investigation with endoscopy and diagnosed with GERD in Denmark from 2000-2015 were primarily treated with pharmacological anti-reflux treatment within the first two years with PPI being the primary agent. Only a small number of patients were treated surgically. Clinicians should focus on using guidelines in treatment, including particular attention to dosage and indication of treatment with PPI.
ETHICAL CONSIDERATIONS

Registry-based studies do not require approval from included patients according to Danish law. The study was registered with the Danish Data Protection Agency (# 17/1942) and data access and handling were approved and stored at The Danish Health Data Authority (FSEID-00003575).

COMPETING INTERESTS

None of the authors of have any competing interests to disclose

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